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Research paper

Mechanical characterization of pharmaceutical solids: A comparison between rheological tests performed under static and dynamic porosity conditions

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Abstract

The aim of this work was to verify how and to what extent rheological tests, carried out under dynamic (Heckel) and static (creep, stress/strain) porosity conditions, may serve as a valuable complement to the classic Heckel tests in the characterization of viscoelastic and densification properties of solid materials for pharmaceutical use.

Six different modified (pregelatinized) starches were compressed in a rotary tablet machine equipped to measure force and punch displacement. Tablets were obtained using flat-faced 6 mm diameter punches at different compression pressures. Compression cycles performed at the maximal pressure of 200 MPa were used to build the Heckel plots. Ejected tablets at the 10%, 20%, 30%, and 40% porosity levels were used for the stress/strain and creep tests.

Parameters obtained with both types of tests were consistent with each other. In particular, among the six starches, lower viscosity values corresponded to lower P_Y values, and lower elastic modulus values corresponded to lower elastic recovery of the tablet.

Mechanical properties of materials can be better characterized if viscoelastic tests performed under dynamic porosity conditions (Heckel analysis) are supported by classical viscoelastic tests carried out under conditions of static porosity.

Keywords: Mechanical properties; Rheology; Viscosity; Elasticity; Retardation time; Compression

1. Introduction

The study of the phenomena occurring inside the die of a tablet machine when a powdered material is compressed for tablet preparation has always received great attention. Some methods of analysis [1,2] have been proposed and a considerable number of materials have been characterized using force/displacement, initially proposed in 1955 [3], or the more widely used Heckel plots [4,5], both derived from the stress/strain data of a single compression cycle.

In particular, the latter analysis technique has become the most widely used because it allows one to know the dynamics of powder densification in the die.

The Heckel equation (1) is:

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

where D is the relative density and $(1 - D)$ denotes the pore fraction, 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 of the prolonged linear portion of the plot with the Y axis, and is the sum of two densification terms:

$$A = \ln[1/(1-D_0)] + B \tag{2}$$

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

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

At the same time, the decrease of relative density due to the immediate elastic recovery (E_R) can be evaluated.

In addition, a distinction between densification due to the movement of the original particles and densification due to brittle fracture can be made. In fact, another parameter, usually called D'_0 [6], can be calculated by using the last relative density before the appearance of a pressure or even a little precompression pressure. As a consequence, a D'_B parameter (3) can be calculated as follows:

$$D'_B = D_A - D'_0 \quad (3)$$

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

In this way, the extent of the different phenomena (rearrangement, fragmentation, plastic deformation, and elastic deformation) occurring during densification inside the die can be quantified, though the P_Y value cannot distinguish between plastic and elastic deformation, but is only indicative of the material's ductility. This is because the viscoelasticity of a solid material depends on its porosity while the stress/strain test represented by a compression cycle is carried out under a variable porosity regime. Thus the viscosity and the elasticity of the material change instant by instant during the test.

In addition, the increase of relative density due to plastic deformation is surely overestimated, unless the porosity of the ejected tablet is considered. At the same time, the viscoelastic moduli cannot be determined; an exception could be the apparent Young modulus, which could be calculated through the use of the Sprigg equation [7]. Unfortunately, this theory was proposed for some specific materials, and is not always valid.

As an alternative to these tests, other works have reported classic viscoelastic tests, such as creep, stress/strain and dynamic mechanical analysis, carried out in non-variable porosity regime [8–17]. These tests can provide material parameters such as immediate and retarded elastic moduli, viscosity, retardation, or relaxation times.

The aim of this work was to verify how and to what extent these two types of tests, carried out under dynamic (Heckel) and static (creep, stress/strain) porosity conditions, can be considered as mutually complementary in the characterizing viscoelastic and densification properties of solid materials for pharmaceutical use. Thus, in this work, materials characterization is indirect and no specific attention has been paid to the parameters determining the observed differences among the materials used.

For this reason, we have compressed six different modified (pregelatinized) starches using a rotary tablet machine equipped to measure both force and punch displacement [18]. Ejected tablets were used to carry out stress/strain and creep viscoelastic tests.

In the stress/strain test, the stress is gradually increased at a constant speed until an upper limit is reached, and then immediately decreased at the same speed. In creep, stress is applied very quickly (in theory, immediately), and then maintained for a certain period of time.

2. Materials and methods

All starches were used as received. The values of mean particle size are reported in Table 1 as declared by the respective companies (light scattering technique).

Moisture content was determined as the loss in weight of the samples, dried to constant weight at 105 °C using a balance (Scaltec) equipped with a heating system.

The apparent particle densities of the six starches, which are also reported in Table 1, were calculated using a helium pycnometer (AccuPic 1330, Micromeritics).

2.1. Tablet preparation

Tablets of six different types of starches (Table 1) were obtained using flat-faced 6 mm diameter punches at different compression pressures by manually placing the powder in the prelubricated die. Compression cycles performed at the pressure of 200 MPa were used to build the Heckel plots. Ejected tablets at 10%, 20%, 30%, and 40% porosity levels were used for the stress/strain and creep tests.

Porosity (4) was calculated from the following expression:

$$\text{Porosity} = 1 - (D_{app}/D_{true}) \quad (4)$$

where the apparent density (D_{app}) was calculated from the weight and volume of the ejected tablet and the true density was previously obtained from the helium pycnometer analysis.

Table 1
Source and type of starches

Starch	Company	Type	Moisture (%)	Density (g/ml)	Mean diameter (μm)
Pregeflo CH 20	Roquette	Adipate acetate starch	6.73 ± 0.38	1.506 ± 0.002	60 ± 8
Pregeflo C 100	Roquette	Maize starch	8.74 ± 0.54	1.519 ± 0.006	62 ± 6
Pregeflo P 100	Roquette	Potato starch	6.42 ± 0.29	1.515 ± 0.008	68 ± 6
Pregeflo M	Roquette	Maize starch	9.02 ± 0.48	1.495 ± 0.005	85 ± 8
Cosmogel 10	Midwest grain	Wheat starch	10.07 ± 0.52	1.478 ± 0.002	94 ± 10
Cosmogel 40	Midwest grain	Hydroxypropyl starch phosphate	10.57 ± 0.47	1.479 ± 0.002	95 ± 12

2.2. Stress/strain test

Tablets of different porosity (10%, 20%, 30%, and 40%) were placed and centred in the lower flat platen (stainless steel) of a texture analyser Instron 5543 (Instron, Milan, Italy) operating with a 500N load cell. The upper probe (stainless steel) was then moved downwards until it reached the flat surface of the tablet, but without increasing the load. The diameter of both the platen and the probe was 15 mm. The test was started and the upper probe moved downwards at 0.5 mm/min. until a compression pressure of 2 MPa was reached, and then returned to the initial position at the same speed. Stress (MPa)/strain ($\Delta l/l$) linear plots were obtained from data of the test and the apparent Young modulus (G) was calculated according to Hooke's law.

2.3. Creep test

Tablets were set as previously described on the same texture analyser. A stress (4 MPa) was applied to the sample at 5 mm/min. velocity and then held constant while the strain was recorded as a function of time. The creep compliance (J_t) was plotted against time. Compliance (5) is defined as the strain at time t divided by the applied constant stress.

$$J_t = \varepsilon_t/\sigma_0 \quad (5)$$

where ε_t is the strain and σ_0 is the applied stress.

An example of creep curve is shown in Fig. 1. This curve can be represented by the generalized Voigt model, a Maxwell element in series with n Voigt elements.

The AB region of instantaneous elastic deformation with compliance J_0 is associated with the spring of the Maxwell element. The elastic modulus G_0 can be calculated from J_0 ($G_0 = 1/J_0$).

The linear CD region represents the non-recoverable viscous flow. The reciprocal of the slope (K) of this linear region gives the viscosity (η) of the material. This part of the curve is associated with the dashpot of the Maxwell unit.

The viscoelastic region BC is associated with the in series n Voigt elements. In fact, this part of the curve is determined by a combination of viscous and elastic phenomena. The elasticity of each spring is retarded according to the viscosity of the corresponding dashpot, and a retardation time τ_n can be calculated ($\tau_n = \eta_n/G_n$). The single elastic moduli can be summed and the retarded elasticity ($G_R = 1/J_R$) of the material can be calculated. At the same time, retardation times cannot be summed, but instead form a continuous spectrum, because each time corresponds to the breakage and reformation of a single secondary bond in the system.

In our case, a model with at least $n = 3$ Voigt elements describes the experimental data well, offering a good fit, and thus this model was chosen for calculating the viscoelastic parameters such as the immediate (G_0) and retarded (G_R) elastic moduli, viscosity (η), and retardation times (τ).

Indeed the three retardation times were too few to represent a spectrum, and no real differences could be distinguished among the six starches, and thus only a symbolic retardation time was calculated, assuming an approximation. It was then possible to make a comparison. The approximation entailed condensing the n Voigt elements into just one. At this point, the retardation time τ was calculated as the time necessary to reach the same deformation that the system would immediately reach if no retardation viscous phenomena were present: $\varepsilon(t) = (1 - 1/e)\ \varepsilon_{BC} = 0.631\ \varepsilon_{BC}$.

The rheological parameters were also extrapolated at zero porosity by fitting the experimental values, which were obtained at 10–40% of tablet porosity (five replicates for each porosity level), with a linear or polynomial regression according to the type of curves obtained. So, the obtained values may be considered indicative, and not absolute. All these virtual values are recapitulated in Table 2. The rheological parameters were then plotted as a function of tablet porosity. All the tests were performed in five replicates.

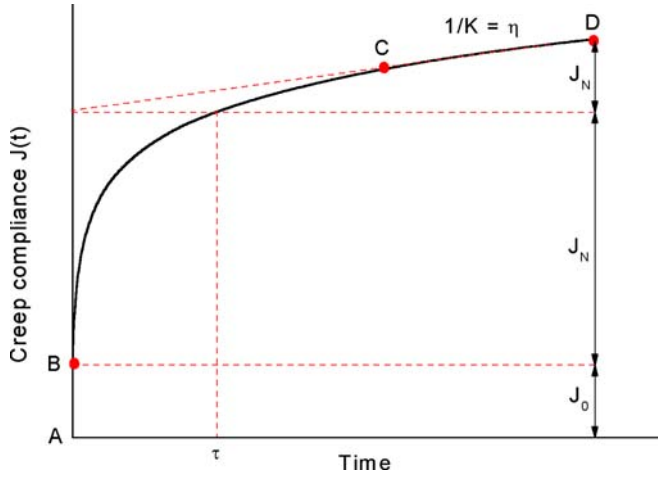

Fig. 1. Creep plot.

2.4. Heckel analysis

The six starches were compressed with an instrumented 10 station Ronchi rotary tablet machine (Ronchi, Cinisello Balsamo, Italy) equipped with 6 mm flat-faced punches, by manually introducing the powder into the prelubricated die

Table 2
Apparent parameters extrapolated at 0 porosity

Starch	G (MPa)	G_0 (MPa)	G_R (MPa)	η (MPa s) $\times 10^6$
Pregeflo CH 20	341	255	4027	10.06
Pregeflo C 100	210	186	3419	7.81
Pregeflo P 100	312	229	3864	11.13
Pregeflo M	279	214	2615	8.68
Cosmogel 10	262	201	2416	3.70
Cosmogel 40	163	149	798	2.32

(magnesium stearate slurry in acetone), after having blinded nine stations and adjusted the weight of the samples in order to obtain the desired pressures (or final porosity for the creep test). Five replicate cycles were performed for the six substances at maximal punch pressure of 200 MPa and compression speed of 25 rpm. For a single compression cycle, the compression pressure and the displacement of the upper and lower punches were measured and recorded at a frequency of 400 Hz. Correction of the displacement transducer data for machine looseness was not necessary, due to the fact that the transducer position in the turrets permitted automatic detection of machine deflection [17]. The correction of punch deformation (6) was carried out point by point according to the following equation:

$$D = F\ L/E\ S \tag{6}$$

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 higher than the pressures used to perform the analyses.

In addition, for a more precise correction, the punch length was divided into two parts: punch stem (20 mm diameter) and punch neck (6 mm diameter).

Heckel profiles (in die method) were generated from single compression cycles. D_A, D'_0, D'_B were calculated at a precompression pressure of 1.5 MPa and P_Y was calculated from the right portion of the plots (50–150 MPa). 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. Each value further presented is the mean of five measurements.

3. Results and discussion

3.1. Stress/strain test

Fig. 2 shows an example of the stress/strain plots. The linearity of the plots confirmed that the linear viscoelastic regime is present. Fig. 3 shows the Young moduli of the six starches plotted against tablet porosity.

As expected, a reverse ratio exists between elastic modulus and porosity. The elastic modulus increases as the porosity decreases. Except for Cosmogel 40, which possesses the lowest Young modulus, the other plots are not linear and present a negative deviation from linearity.

The same rank of immediate elasticity among the six starches is maintained at all porosities, with the exception of the 40% of tablet porosity, which corresponds to a scarcely structured solid block. In decreasing elasticity order: Pregeflo CH 20 > Pregeflo P 100 > Pregeflo M > Cosmogel 10 > Pregeflo C 100 > Cosmogel 40.

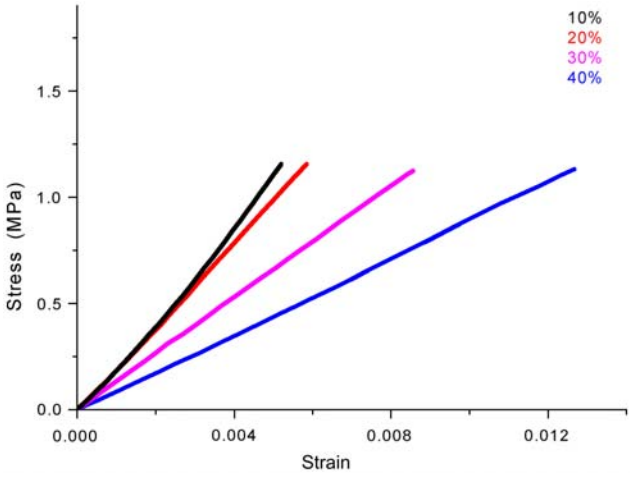

Fig. 2. Normalized stress/strain plots of Cosmogel 40 tablets at 10%, 20%, 30%, and 40% porosity level.

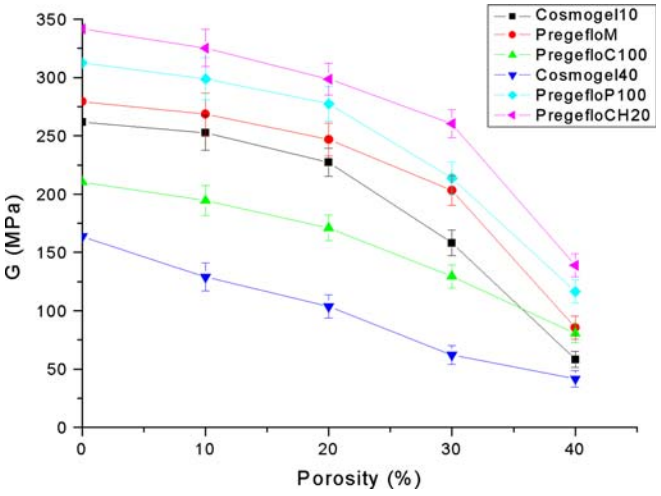

Fig. 3. Evolution of the apparent Young modulus as a function of tablet porosity for the different six starches.

3.2. Creep test

Fig. 4 shows the values of the immediate elastic modulus (G_0) obtained from the creep test at the different porosities for the six starches.

In this case, as well, the same trend already described for the stress/strain test can be observed. As the porosity decreases, the G_0 increases, but not linearly.

Despite light differences in the moduli values between G and G_0 (different tests or techniques rarely give exactly the same results), the sequence of immediate elasticity among the six starches matches perfectly at all porosities with those previously reported: Pregeflo CH 20 > Pregeflo P 100 > Pregeflo M > Cosmogel 10 > Pregeflo C 100 > Cosmogel 40.

On the other hand, plots of retarded elasticity (G_R) show a different trend (Fig. 5). G_R also increases as the porosity decreases, but this increase is exponential. This result points out that exaggerating compression pressure during

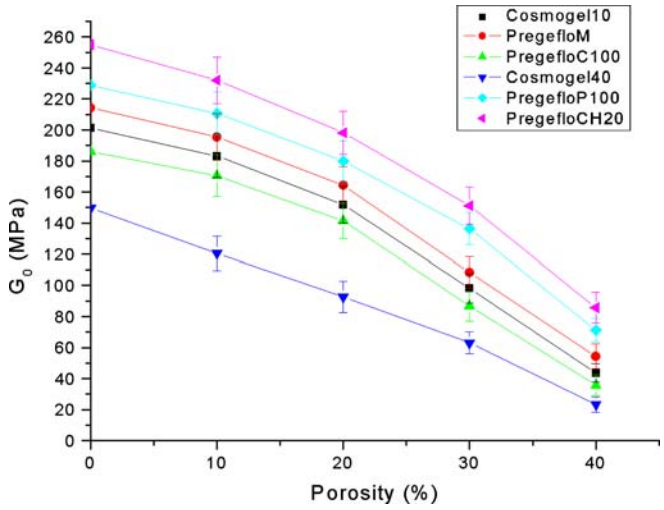

Fig. 4. Evolution of the immediate elastic modulus (G_0) with tablet porosity.

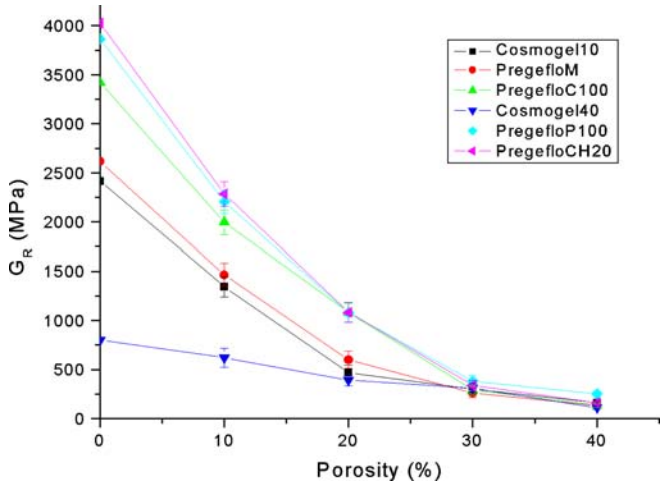

Fig. 5. Evolution of the retarded elastic modulus (G_R) with tablet porosity.

tablet production in the rotary machine, with the goal of obtaining less porous and more resistant tablets, may actually reduce tablet tensile strength, rather than improve it. The attempt to reduce tablet porosity increases elasticity markedly, particularly the retarded elasticity. In addition, at higher porosities, there is no difference in the G_R value among the six starches. Differences become visible at low porosity values (20%), but the sequence of retarded elasticity is different from the previous ones: Pregeflo CH 20 > Pregeflo P 100 > Pregeflo C100 > Pregeflo M > Cosmogel 10 > Cosmogel 40. G_0 and G_R are not directly proportional.

Fig. 6 shows the viscosity values (η) obtained from the creep test at the different porosities for the six starches.

Viscosity also undergoes an exponential increase as the porosity of the tablets decreases. In this case as well, at elevated porosities there is no difference in the η value among the six starches. Differences become visible at low porosity values (20%). The order of viscosity among the six starches is different from the elastic ones: Pregeflo P 100 > Pregeflo CH 20 > Pregeflo M > Pregeflo C 100 > Cosmogel 10 > Cosmogel 40. Elasticity and viscosity cannot be considered proportional, since they are associated, respectively, with the spring and the dashpot of the Maxwell element.

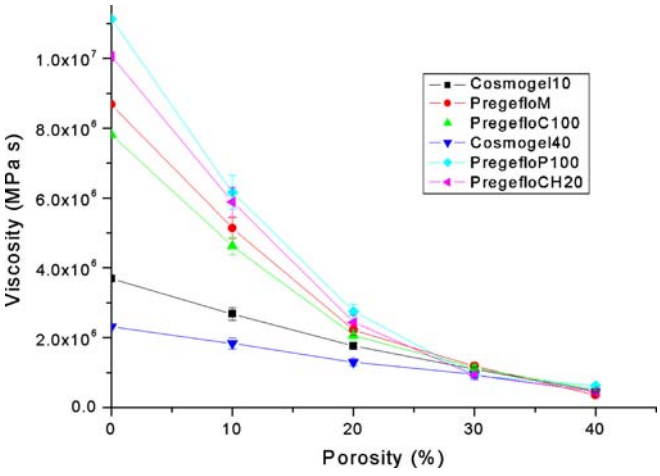

Fig. 6. Evolution of the viscosity (η) with tablet porosity.

On the other hand, the trend of the retardation times differs. Fig. 7 shows the retardation times (τ) obtained from the creep test at the different porosities for the six starches. Retardation times do not substantially change with porosity. This result, in agreement with previously reported data[10], should not come as a surprise, since retardation time is an intrinsic property of a material.

As previously stated, τ_n depend on the viscosity of the dashpots of the Voigt elements and the elastic modulus of the corresponding springs in the generalized model ($\tau = \eta_{Voigt}/G_{Voigt}$). Therefore, since the retarded elasticity of a material increases exponentially with the porosity reduction, then the internal viscosity also behaves in the same way and increases exponentially and proportionally.

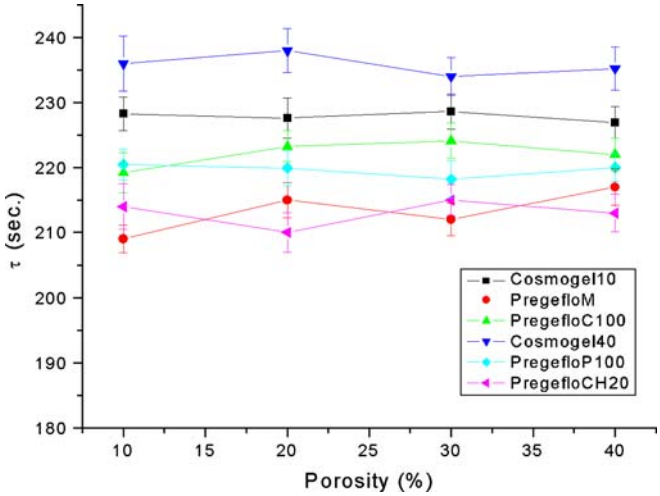

Fig. 7. Evolution of the retardation time (τ) with tablet porosity.

At this point, since retarded elasticity is also known ($G_R = G_{Voigt}$) the internal viscosities (η_{Voigt}) of the six starches at the different porosities could be easily calculated but, they do not offer additional information to the previously described considerations because they are more than one order of magnitude lower than the viscosities relative to the Maxwell dashpot (Fig. 6). Therefore, their influence on the whole flow behaviour of the materials is minimal, and for this reason they are not presented. Concerning the τ values, a small difference can be noticed between Pregeflo and Cosmogel, which present somewhat longer retardation times.

Concerning the six materials used, Cosmogels (wheat derivatives), particularly Cosmogel 40, proved to be less elastic and more plastic than Pregeflo (maize derivatives). These differences may depend on the different moisture level [10], but also on other parameters such as the particle size, the type of derivative, and the pregelatinization process. This process is not known and, in any case, the study of the specific solid structure of the six starches is not the subject of the present work.

3.3. Heckel analysis

Table 3 reports the parameters calculated from the Heckel plots. Some of these plots are reported as an example in Fig. 8. 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 more notable in ductile materials [18].

As expected, the D'_b values are low, confirming the poor fragmentation ability of starches. Also, P_Y values are rather low and this confirms their ductility, already described in the literature [10,19]. The six starches can be classified according to their P_Y value: Pregeflo P 100 > Pregeflo CH 20 > Pregeflo C 100 > Pregeflo M > Cosmogel 10 > Cosmogel 40.

Both Cosmogel have similar and lower P_Y values than Pregeflo. This result is in agreement with the viscosity values obtained from the creep test. Among the six starches, the viscosity sequence is almost identical to the P_Y sequence. This is to be expected, since a more ductile material will inevitably possess a lower viscosity and vice versa.

The two sequences are not completely identical, but one should not forget that the P_Y also includes the elastic component of the deformation.

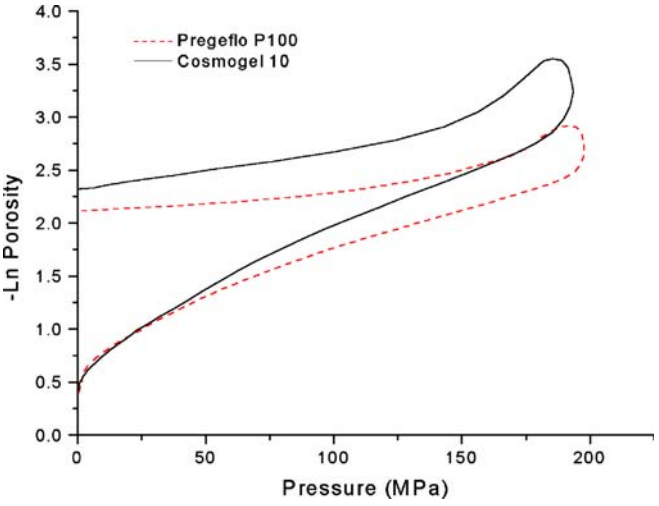

Fig. 8. Examples of the Heckel plots obtained.

A similar correspondence can also be found between the elastic parameters revealed by the creep test and the immediate elastic recovery (E_R) occurring during the decompression phase.

The immediate elastic recovery (7) of the six starches can be calculated from the corresponding D_{max} and D_{fin} values (which are proportional to the respective strain) according to the following equation:

$$E_R = \frac{D_{max} - D_{fin}}{D_{max}} 100 \quad (7)$$

According to the E_R values (Table 3) the six starches can be classified as follows:

Pregeflo CH 20 > Pregeflo P 100 > Pregeflo C 100 > Pregeflo M > Cosmogel 10 > Cosmogel 40.

Once again, both Cosmogel (particularly Cosmogel 40), which are wheat derivatives, show a lower elasticity.

The sequence for elastic decompression is not exactly identical to that obtained for the Young modulus but it should be taken into account that also during decompression, particularly at the beginning of this stage, plastic (viscous) flow of the material occurs in the opposite direction of the decompression [20]. This phenomenon can be pointed out if the decompression portion of the Heckel plot is deconvoluted and converted in a stress/strain curve with negative slope. The curve is not perfectly linear and an

Table 3
Heckel parameters

	Cosmogel 10	Cosmogel 40	Pregeflo M	Pregeflo C 100	Pregeflo CH 20	Pregeflo P 100
D'_0	0.419 ± 0.004	0.365 ± 0.026	0.450 ± 0.006	0.472 ± 0.003	0.452 ± 0.008	0.441 ± 0.004
D_A	0.557 ± 0.022	0.637 ± 0.030	0.593 ± 0.008	0.600 ± 0.009	0.578 ± 0.001	0.594 ± 0.011
D'_B	0.137 ± 0.020	0.271 ± 0.035	0.143 ± 0.014	0.128 ± 0.010	0.125 ± 0.008	0.153 ± 0.008
P_Y	89.60 ± 1.93	92.99 ± 1.81	102.4 ± 0.87	119.2 ± 2.11	121.4 ± 0.22	126.3 ± 1.82
D_{max}	0.972 ± 0.002	0.975 ± 0.002	0.971 ± 0.004	0.963 ± 0.003	0.962 ± 0.004	0.951 ± 0.008
D_{fin}	0.919 ± 0.001	0.928 ± 0.002	0.909 ± 0.004	0.900 ± 0.006	0.891 ± 0.005	0.886 ± 0.006
E_R (%)	5.42	4.84	6.39	6.56	7.28	6.85

elastic decompression modulus cannot be easily calculated (results not shown).

4. Conclusion

Rheological tests, particularly those for creep, proved very useful for a better understanding of solid material characteristics beyond the characterization possible with the Heckel analysis. In fact, despite the fact that the Heckel test provides a good level of information about fragmentation and deformation (plastic and elastic) of materials, it is not able to quantify parameters such as elastic moduli and viscosity and their evolution under porosity variation, parameters that would be very useful in preventing problems during the tablet production.

In addition, the retardation time could be used as a parameter for evaluating the time that should elapse to permit completion of the retarded elastic response of the ejected tablet.

However, the Heckel test gives valid information about the compression cycle on the whole, and thus there is no good reason to completely replace it with alternative rheological tests.

On the contrary, integration of the two types of tests could provide optimal information about the material. This statement is also based on the consistency between creep and Heckel parameters, even when there are not important differences among the analysed materials.

Concerning the six starches, the parameters calculated from the tests matched rather well with their moisture content. Higher moisture content corresponded to lower viscosity, elasticity and P_Y values.

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