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Comparative evaluation of the powder properties and compression behaviour of a new cellulose-based direct compression excipient and Avicel PH-102

M. Reus-Medina, M. Lanz, V. Kumar and H. Leuenberger

Abstract

This study compares the compression behaviour of a new cellulose-based tableting excipient, hereinafter referred to as UICEL-A/102, and Avicel PH-102, a commercial direct compression excipient commonly referred to as microcrystalline cellulose (MCC). UICEL-A/102 shows the cellulose II lattice, while Avicel PH-102 belongs to the cellulose I polymorphic form. The median particle diameters of UICEL-A/102 and Avicel PH-102 fractions used in the study were 107 and 97 μm, respectively. Compared with Avicel PH-102, UICEL-A/102 was more dense; the relative poured and tapped densities were: 0.277 and 0.327 (vs 0.195 and 0.248 for Avicel PH-102), respectively. The true density, ρ_{true}, of the two materials was comparable ($\sim$1.56 g cm^{-3}). The slopes of the in-die and out-of-die Heckel curves for Avicel PH-102 were steeper than for UICEL-A/102. The relative density versus applied pressure plot was in good agreement with the modified Heckel equation. The out-of-die and in-die minimal pressure susceptibility (χ_{pmin}) values calculated were 3.36×10^{-3} and 8.09×10^{-3} MPa^{-1} for UICEL-A/102 and 8.00×10^{-3} and 16.12×10^{-3} MPa^{-1} for Avicel PH-102, respectively. The elastic recovery profiles showed UICEL-A/102 to be more elastic than Avicel PH-102. In conclusion, UICEL-A/102 and Avicel PH-102 differ in their compression behaviour under pressure. The different polymorphic forms could provide a possible explanation.

Introduction

Cellulose, the most abundant natural polymer, is a linear homopolymer consisting of 1, 4-linked β-D-glucose repeat units. It exists as a semicrystalline material. The crystalline component can exist in a number of polymorphs. Cellulosic materials from nearly all natural sources contain the cellulose I polymorph, while cellulose II is produced by a mutant strain of *Glucanoacetobacter xylinum* and occurs in the alga *Halicystis* (Klemm et al 2002). Cellulose II is also present in mercerized fabrics (Klemm et al 2002).

Tablet production by direct compression has steadily increased over the years because of its ease of manufacture. Currently, microcrystalline cellulose (MCC) (e.g. AvicelPH grade (FMC Corporation, Philadelphia, PA)) and powdered cellulose (PC) (e.g. Solka Floc 40 NF grade (International Fiber Corporation, North Tonawanda, NY)), both of which contain the cellulose I lattice, are the most commonly used direct compression excipients. MCC and PC are produced by chemical hydrolysis (Battista & Smith 1961) and mechanical disintegration (Morse 1981, 1984) of cellulose, respectively. We have recently prepared a new cellulose II-based pharmaceutical aid, referred to as UICEL, by soaking the cellulose I powder, prepared from cotton linter by treatment with 1.0 M HCl at boiling temperature for 1.5–2.0 h, in an aqueous sodium hydroxide solution, followed by regeneration in an alcohol–water mixture (Kumar et al 2002). This material serves as a binder as well as a disintegrant. Tablets prepared using this material, irrespective of the compression pressure employed to prepare them, disintegrate rapidly (less than 30 s) in water.

The Heckel analysis has been widely applied to pharmaceutical solids to study the consolidation mechanism (Heckel 1961a, b). The Heckel equation can be deduced from the definition of the pressure susceptibility (equation 1) assuming that the pressure susceptibility (χ_p) is constant over the whole pressure range.

Division of Pharmaceutics, College of Pharmacy, The University of Iowa, Iowa City, Iowa 52242, USA

M. Reus-Medina, V. Kumar

Institute of Pharmaceutical Technology, Pharmacenter, University of Basel, Klingelbergstrasse 50, CH-4056 Basel, Switzerland

M. Lanz, H. Leuenberger

Correspondence: V. Kumar, Division of Pharmaceutics, College of Pharmacy, The University of Iowa, Iowa City, Iowa 52242, USA. E-mail: vijay-kumar@uiowa.edu

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$$\chi_p \equiv -\frac{1}{\varepsilon}\cdot\frac{d\varepsilon}{d\sigma} = \frac{1}{(1-\rho_r)}\cdot\frac{d\rho_r}{d\sigma} \quad (1)$$

In equation 1, ε is the porosity and ρ_r is the corresponding relative density of the compact at a pressure σ. The integration of equation 1, considering that $\chi_p = K$ and $\rho_r = 1-\varepsilon$, leads to the well-known Heckel equation (2), which describes the change in relative density of a powder as a function of the applied pressure.

$$\ln\frac{1}{1-\rho_r} = K\sigma + A \quad (2)$$

K and A in equation 2 are constants determined from the slope and the intercept, respectively, of the extrapolated linear region of a plot of $\ln(1/(1-\rho_r))$ vs σ. The Heckel plot is linear only at high pressures; for plastically deforming materials (e.g. Avicel PH grade and sorbitol) the linearity is noted at a pressure higher than 20 MPa, whereas for fragmenting materials (e.g. Emcompress (JRS Pharma, Patterson, NY) and lactose) the linear relationship occurs at a pressure higher than 80 MPa (Krumme et al 2000). The non-linear region observed at lower pressures has been suggested to be due to particle movement and rearrangement before inter-particle bonding takes place (Celik 1992). The constant K is inversely related to the ability of a material to deform plastically under pressure (i.e., K α $1/\sigma_y$, where σ_y is called mean yield pressure) (Hersey & Rees 1970). Ductile powders, such as microcrystalline cellulose, have higher K values than brittle powders such as lactose (Kuny & Leuenberger 2003).

Because the Heckel equation shows a lack of fit in the low pressure range and because the practical evaluation of the linear region is arbitrary, Kuentz & Leuenberger (1999) recently proposed a simple function for the pressure susceptibility, χ_p (i.e., the decrease of porosity under pressure). This function assumes that there is a critical porosity, ε_c, where the pressure susceptibility approaches infinity. According to this equation, the pressure susceptibility is not defined above a critical porosity, ε_c, or below the corresponding relative critical density, ρ_{rc}. The relative critical density, ρ_{rc}, is the relative density where the powder bed shows for the first time a mechanical rigidity and can therefore be considered as a compact. The χ_p term, according to Kuentz & Leuenberger (1999), is defined as:

$$\chi_p = \frac{C}{\rho_r - \rho_{rc}} \quad (3)$$

Where ρ_{rc} is the compact relative density and C is a constant. The relative density, ρ_r, versus pressure, σ, relationship can be described in the modified Heckel equation by the following relationship:

$$\sigma = \frac{1}{C}\left[\rho_{rc} - \rho_r - (1-\rho_{rc})\ln\left(\frac{1-\rho_r}{1-\rho_{rc}}\right)\right] \quad (4)$$

The constant C is indicative of the ability of a powder to deform by a plastic mechanism. Thus, the larger the value of C, the greater the ductility of a material is, that is, with increasing value of C, the material becomes less and less brittle in character.

In this paper, we compare the powder and mechanical properties of UICEL-A/102, a new cellulose II product, and Avicel PH-102 using the Heckel and modified Heckel equations.

Materials and Methods

Materials

Avicel PH-102 was received from FMC Corporation (Philadelphia, PA). Sodium hydroxide and ethanol were purchased from Fisher Scientific (Fair Lawn, NJ). UICEL-A/102 was prepared according to the procedure recently reported by Kumar et al (2002). Briefly, an appropriate amount of Avicel PH-102 was added in portions to an aqueous solution of sodium hydroxide (conc. 5 M) with constant stirring. The resulting cellulose–sodium hydroxide mixture (gel) was allowed to stand at room temperature for about 24 h. Ethyl alcohol (95%, v/v) was then added to the gel. An immediate precipitation of the white powder occurred. The powder was filtered and then washed with water until the filtrate showed a near neutral pH. The wet white solid was air-dried until it could pass through the mesh of one grid (0.025" $\approx$ 635 μm) in an oscillated granulator (Erweka AR 400; Apparatebau GmbH, Germany). The sieved material was then dried in an oven at 50–60°C until the moisture content was $\leq$6%.

Characterization methods

Particle size

UICEL-A/102, as produced, and Avicel PH-102, as received, were fractionated on a Ro-Tap sieve shaker (W. S. Tyler, Mentor, OH) and the fraction that contained particles in the size range 75–105 μm was used in this study. Since both materials contained microfibrous particles, in addition to the aggregated powder, the sieved fraction was analysed for particle size distribution using a Malvern–Master sizer X (Malvern Instruments Ltd, Worcestershire, UK) particle size analyser.

Densities and porosity

The true density, ρ_{true}, was determined by either helium pycnometry (Quantachrome micropycnometer-2; Quantachrome Corporation, Boyton Beach, FL) or using an air compression pycnometer (Model 930; Beckman Instruments Inc., Fullerton, USA). The poured and tapped densities, ρ_{pour} and ρ_{tap}, respectively (Type STAV 2003; Engelsmann AG, Ludvigshafen, Germany), were determined according to European Pharmacopoeia, with the exception that smaller quantities of the substances were used. Porosity, ε, was determined using the relationship: $\varepsilon = [1 - (\rho_{tap}/\rho_{true})]$. The relative tapped density, ρ_{rtap}, equals ρ_{tap}/ρ_{true} and the relative poured density, ρ_{rpour}, equals ρ_{pour}/ρ_{true}. The critical relative density, ρ_{rc}, was calculated according to equation 4, with a non-linear

regression analysis (SYSTAT for Windows Version 10.0, SPSS Inc.)

Flow properties

The flow properties of the materials were assessed by the angle of repose, flow-through-an-orifice, Carr's index and Hausner ratio methods. The angle of repose, ϕ, which is the maximum angle that can be obtained between the self-supporting cone surface of the powder mound and the horizontal plane, was determined according to the relationship: $\tan \phi = 2h/D$, where h is the height of the cone and D is the diameter of the cone. The Carr's index (CI) (Carr 1965) and the Hausner ratio (H) (Hausner 1967) were determined from poured and tapped densities according to the relationships: $CI = [(\rho_{tap} - \rho_{pour})/\rho_{tap}] \times 100$ and $H = (\rho_{tap}/\rho_{pour})$, where ρ_{tap} and ρ_{pour} are the tapped and poured densities, respectively.

The flow of powders through an orifice was measured (Luner et al 2001) using a flow meter consisting of a 2.5 cm × 20.0 cm stainless-steel cylinder, mounted on a metal block, and a replaceable steel plate with a hole and another plate without a hole at the base of the cylinder. The cylinder was filled with the powder and the plate without a hole was removed so that the powder could freely flow through the hole of the other plate. This process was repeated using plates having a decreasing diameter hole. The flow rate was determined by recording time and weight of the powder that passed freely through the smallest size orifice.

Scanning electron microscopy (SEM)

The scanning electron micrographs of the UICEL-A/102 and Avicel PH-102 powders were obtained using a Hitachi S-4000 microscope (Hitachi High Technologies America, Inc., Pleasanton, CA) following the procedure reported earlier (Kumar et al 2002).

Compression study

Both materials were stored for seven days at 20 ± 2°C and at 45 ± 5% relative humidity before use. The same temperature and the humidity conditions were employed during the compression study. Round, flat tablets, each weighing about 400 mg and measuring 11 mm in diameter, were made using a Zwick-Universal Testing Instrument (Type 1478; Zwick Gmbh, Ulm, Germany) at a velocity of 10 mm min^{-1} and a compression pressure in the range 1.06–111.60 MPa. Before each compression cycle, the punches and the die were lubricated with magnesium stearate. Excess lubricant was removed with compressed air. The height of the tablets was measured during compression at different pressures (in die) and 48 h after manufacture (out of die). The porosity, ε, of the tablet was calculated according to the equation: $\varepsilon = [1 - (m/(V_{tablet})/\rho_{true})]$, where m and V_{tablet} are weight and volume of the tablet, respectively, and ρ_{true} is the true density of the powder. The in-die and the out-of-die compression data were evaluated for each powder system using the Heckel equation (Heckel 1961a, b) (equation 2) and the modified Heckel equation (Kuentz & Leuenberger 1999) (equation 4). The program used for fitting was SYSTAT for Windows Version 10.0 (SPSS Inc.). For the Heckel equation the fitting was performed using a linear regression, whereas for the modified Heckel equation a non-linear regression was used. Gauss–Newton was applied as algorithm for estimating the models. The principle of least squares was specified as loss function.

The elastic recovery (ER) of the tablet was determined using the equation: $ER = [(H_t - H_o)/H_o]$, where H_t is the height of the tablet 48 h after compression and H_o is the height of the tablet in the die at different compression pressures applied (Armstrong & Haines-Nutt 1973). The effect of Avicel PH-102 and UICEL-A/102 on the ER was statistically examined at each compression pressure using a Mann–Whitney U test.

Results and Discussion

The SEM photographs of UICEL-A/102 and Avicel PH-102 are shown in Figure 1. Both materials consisted of an aggregated structure composed of small fibres with coalesced boundaries. The UICEL-A/102 particles, however, had rough surfaces compared with the Avicel PH-102 particles. The selected powder properties of UICEL-A/102 and Avicel PH-102 are compared in Table 1. UICEL-A/102 is denser than Avicel PH-102, attributable to its low porosity and higher poured and tapped densities. The true density of the two materials is comparable (~1.56 g cm^{-3}).

The flow behaviour of powders can be assessed using angle of repose, Hausner ratio and Carr index values. An angle of repose value of up to 40° indicates reasonable flow potential and above 50° suggests that the material flows only with great difficulty (Lachman et al 1986). Wells (1988) reported that a Hausner ratio of less than 1.2 is indicative of good flowability, while a value of 1.5 or higher suggests a poor flow display by the material. The Carr index values of 5–10, 12–16, 18–21 and 23–28 have been used to represent excellent, good, fair and poor flow properties, respectively (Carr 1965). The angle of repose, Hausner ratio and Carr index values obtained for UICEL-A/102 and Avicel PH-102 are compared in Table 1. The results show that UICEL-A/102 possesses improved flow compared with Avicel PH-102. The flow rate of UICEL-A/102 determined by the flow through an orifice with a diameter of 17.5 mm (0.688") was 13 g s^{-1}. Avicel PH-102 could only pass freely through an orifice with a diameter of 19.0 mm (0.750"). However, the flow was too fast and the rate could not be determined.

Microcrystalline cellulose is well known for its ductile behaviour under pressure. Unlike brittle substances, ductile materials are characterized in the Heckel plot with a dominant linear region and a curvature at the beginning of the Heckel plot. The steeper the slope of the linear region, characterized by the parameter K of the Heckel equation, the more ductile the material is. The in-die and out-of-die Heckel plots for UICEL-A/102 and Avicel PH-102 are shown in Figure 2. Figure 3 shows the plots constructed according to the modified Heckel equation. The Heckel and modified Heckel parameters calculated from the in-die and out-of-die data over the whole compression pressure range employed and from the linear portion of the curves are listed

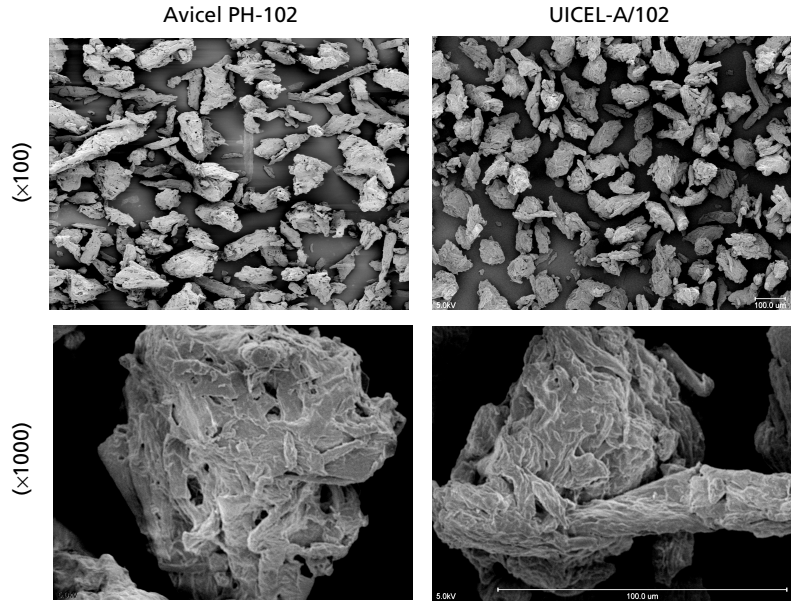

Figure 1 SEM photographs of UICEL-A/102 and Avicel PH-102.

Table 1 Powder properties of UICEL-A/102 and Avicel PH-102

	UICEL-A/102	Avicel PH-102
Particle size (n = 3)		
Mean (μm)	110.90 (0.09)	102.40 (0.22)
Median (μm)	106.80 (0.06)	97.00 (0.14)
Mode (μm)	108.60 (0.10)	100.80 (0.16)
ρ_{true} (n = 8) (g cm^{-3})	1.570 (0.002)	1.550 (0.002)
ρ_{rpour} (n = 3)	0.277 (0.008)	0.195 (0.007)
ρ_{rtap} (n = 3)	0.327 (0.005)	0.248 (0.004)
Porosity (%)	67.30 (0.51)	75.20 (0.45)
Hausner ratio	1.180 (0.037)	1.270 (0.048)
Carr index	15.29 (2.69)	21.37 (2.98)
Angle of repose (°)	36.00 (0.23)	41.00 (0.69)
Flow rate (g s^{-1})	13.76[a]	—[b]

Data are presented as mean (s.e.m.). [a]Orifice diameter was 11/16". [b]The powder did not flow freely through the 11/16" diameter orifice. The smallest size orifice through which the powder had unrestricted flow was ¾". However, no flow rate could be determined because the powder passed through the orifice rapidly.

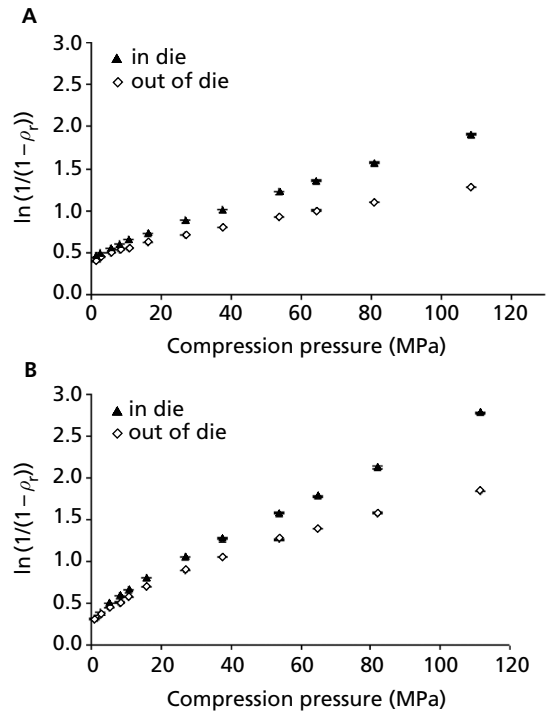

Figure 2 Heckel plots for UICEL-A/102 (A) and Avicel PH-102 (B).

in Tables 2 and 3. The Heckel curves for both UICEL-A/102 and Avicel PH-102 showed a curvature spanning the compression pressure range between 1.06 MPa and 8 MPa (Figure 2). This, as noted by Celik (1992) and Paronen & lkka (1996), is attributed to the fragmentation and rearrangement of the powder bed. The linear regression analyses of the UICEL-A/102 in-die and out-of-die Heckel curves over the whole compression pressure range gave the correlation coefficient values of 0.996 and 0.984, corresponding to mean yield pressures of 74.96 and 125.63 MPa, respectively. The corresponding correlation coefficient values for Avicel PH-102 were 0.995 and 0.972 and the mean yield pressure values 46.51 MPa and 70.82 MPa. Considering the linear region of the curves only, the respective mean yield pressures values for UICEL-A/102 were 79.95 and 151.13 MPa, and for Avicel PH-102 49.12 and 94.01 MPa. Irrespective of the compression pressure range employed in the regression

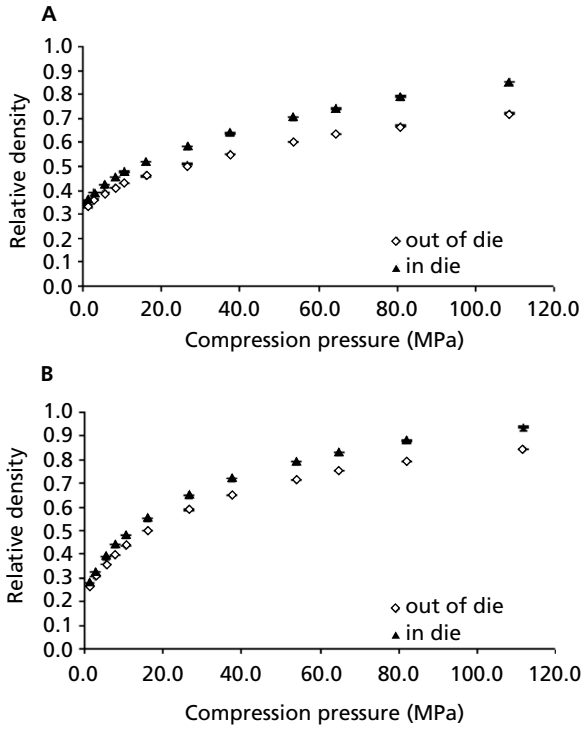

Figure 3 Modified Heckel plots for UICEL-A/102 (A) and Avicel PH-102 (B).

Table 2 Values of in-die and out-of-die Heckel equation parameters

	UICEL-A/102		Avicel PH-102	
Compression pressure range (MPa)[a]	1.06–111.00	37–108	1.06–111.00	37–111
In die				
K (10^{-3} MPa^{-1})	13.34 (0.27)	12.51	21.50 (0.47)	20.36
σ_y (MPa)	74.96 (0.02)	79.95	46.51 (0.02)	49.12
A	0.490 (0.013)	0.551	0.401 (0.023)	0.483
r^2	0.996	1.000	0.995	0.999
Out of die				
K (10^{-3} MPa^{-1})	7.96 (0.32)	6.62	14.12 (0.78)	10.64
σ_y (MPa)	125.63 (0.04)	151.13	70.82 (0.06)	94.01
A	0.463 (0.016)	0.564	0.413 (0.038)	0.681
r^2	0.984	0.999	0.972	0.997

Data are presented as mean (s.e.m.). [a]Used in the regression analysis.

analysis, the slopes of the linear region of the in-die and out-of-die Heckel curves for Avicel PH-102 were steeper than the respective curves for UICEL-A/102, suggesting that the latter is less ductile than the former.

The modified Heckel equation plots depicted in Figure 3 show that there is an excellent agreement with the experimental data over the whole compression pressure range employed. These fits predict a critical relative density, ρ_{rc}, that is below the relative poured density for both Avicel PH-102 and UICEL-A/102. These findings are reasonable as ρ_{rc} indicates the critical point, where the pressure builds up in the powder bed (i.e., where the force transmitted by the contact points in the powder bed is percolating).

Table 3 Values of in-die and out-of-die modified Heckel equation parameters

	UICEL-A/102	Avicel PH-102
Compression pressure range (MPa)	1.06–111.00	1.06–111.00
In die		
C (10^{-3} MPa^{-1})	6.86 (0.52)	16.78 (1.34)
ρ_c	0.152 (0.028)	−0.041 (0.047)
r^2	0.993	0.994
Out of die		
C (10^{-3} MPa^{-1})	2.57 (0.09)	6.86 (0.20)
ρ_c	0.235 (0.008)	0.142 (0.011)
r^2	0.998	0.999

Data are presented as mean (s.e.m.).

The term C in the modified Heckel equation (Kuentz & Leuenberger 1999) can also be calculated for a powder system with $\varepsilon \to 0$ (i.e., $\rho_r \to 1$). Thus, it is possible to extrapolate the value of χ_p according to equation 3 for $\varepsilon = 0$ (i.e., for a solid continuum), leading to a minimum value χ_{pmin}. It is evident that the calculated values for χ_{pmin} are different for out-of-die and in-die experiments. In both cases, the values of χ_{pmin} for UICEL-A/102 (out of die: 3.36×10^{-3} MPa^{-1}; in die: 8.09×10^{-3} MPa^{-1}) are smaller than for Avicel PH-102 (out of die: 8.00×10^{-3} MPa^{-1}; in die: 16.12×10^{-3} MPa^{-1}).

Compared with the Heckel equation, the modified Heckel equation is clearly superior over the compression pressure range studied for the evaluation of the out-of-die data. The goodness of fit for the evaluation of the in-die data does not differ much for both equations.

Figure 4 depicts the elastic recovery profiles of both materials over the whole compression pressure range used

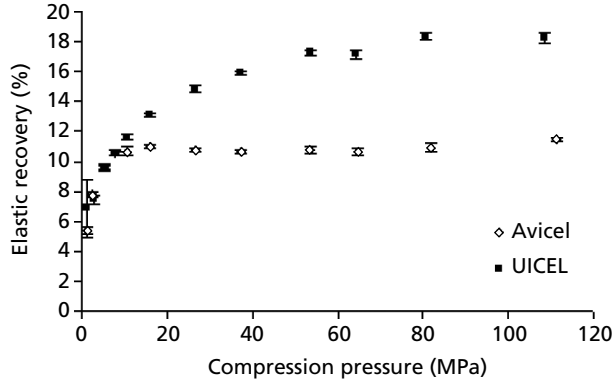

Figure 4 Elastic recovery profiles of UICEL-A/102 (■) and Avicel PH-102 (◆).

in the study. The two materials differed significantly ($P < 0.05$) in their elastic recovery above a compression pressure of 10.6 MPa. The results clearly show that UICEL-A/102 has a greater tendency to recover elastically than Avicel PH-102.

Conclusion

The powder and compression properties of Avicel PH-102 and UICEL-A/102 were compared. UICEL-A/102 is denser than Avicel PH-102 and shows improved flow. The compressibility studies revealed UICEL-A/102 to be less ductile and more elastic than Avicel PH-102. This could be due to the different polymorphic forms of cellulose in the two materials. Further studies are in progress to establish the relationship between various physical–chemical parameters and mechanical properties of UICEL-A/102.

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