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Evaluation of the deformation behavior of binary systems of methacrylic acid copolymers and hydroxypropyl methylcellulose using a compaction simulator

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Abstract

Methacrylic acid copolymers have been shown to enhance release of weakly basic drugs from rate controlling polymer matrices through the mechanism of microenvironmental pH modulation. Since these matrices are typically formed through a compaction process, an understanding of the deformation behavior of these polymers in there neat form and in combination with rate controlling polymers such as HPMC is critical to their successful formulation. Binary mixes of two methacrylic acid copolymers, Eudragit® L100 and L100-55 in combination with HPMC K4M were subjected to compaction studies on a compaction simulator. The deformation behavior of the powder mixes was analyzed based on pressure–porosity relationships, strain rate sensitivity (SRS), residual die wall force data and work of compaction. Methacrylic acid copolymers, L100-55 and L-100 and the hydrophilic polymer, HPMC K4M exhibited Heckel plots representative of plastic deformation although L-100 exhibited significantly greater resistance to densification as evident from the high yield pressure values (∼120 MPa). The yield pressures for the binary mixes were linearly related to the weight fractions of the components. All powder mixes exhibited significant speed sensitivity with SRS values ranging from 21.7% to 42.4%. The residual die-wall pressures indicated that at slow speeds (1 mm/s) and at lower pressures (<150 MPa), HPMC possesses significant elastic behavior. However, the good compacts formed at this punch speed indicate significant plastic deformation and bond formation which is able to predominate over the elastic recovery component. The apparent mean yield pressure values, the residual die-wall forces and the net work of compaction exhibited a linear relationship with mixture composition, thereby indicating predictability of these parameters based on the behavior of the neat materials.

Keywords: Compaction; Tablets; Eudragit®; pH modulating; Methacrylic acid; HPMC

1. Introduction

Traditionally, methacrylic acid copolymers have been used for enteric coating purposes. The use of these polymers, alone, and in combination with other polymers, in sustained release matrix formulations has been suggested (McGinity et al., 1983; Cameron and McGinity, 1987a,b; Farhadieh et al., 1971; Takka et al., 2001). The applicability of these polymers in sustained release matrix formulations is limited because they are non-gelling and soluble in intestinal fluids, often necessitating the use of a gelling polymer such as hydroxypropyl methylcellulose (HPMC). However, the solubility of these enteric polymers at intestinal pH allows them to form pores in certain matrix systems, wherein interstitial channels are created due to the dissolution of these polymers, which enables enhanced drug release via diffusion through the channels (Oren and Seidler, 1990). Recently, it has been shown that the methacrylic acid polymer, Eudragit® L100-55 can significantly lower matrix microenvironmental pH and enhance the release of a weakly basic drug, papaverine HCl in simulated intestinal fluids from HPMC based hydrophilic matrices (Tatavarti et al., 2004; Tatavarti and Hoag, 2006). Since the formation of these polymer incorporated matrices is through a compaction process, an understanding of the deformation behavior of the neat polymers as well as their mixes with rate controlling polymers such as HPMC is critical to the successful formulation of these matrices.

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Previous studies in the area of compaction analysis of these Eudragit® polymers, have primarily dealt with determination of tensile strength and such tableting indices as brittle fracture and bonding indices in binary mixes with brittle and plastic drugs (Schulze et al., 1990; Schulze and McGinity, 1993). However, information on pressure–porosity relationships for the neat polymers and their mixtures with other brittle or plastic materials has not been reported. Pressure–porosity relationships have been extensively used for understanding powder densification (Muller and Augsburger, 1994; Sun and Grant, 2001; Sonnergaard, 1999). The most widely used relationship, as proposed by Heckel, considers the densification process as being analogous to a first-order chemical reaction with the pores acting as the reactant and the densification of the bulk as the product (Heckel, 1961). Though the Heckel equation has been successfully used for analyzing neat powders (except at very high pressures), analysis of powder mixtures is not well understood, and some mixtures have exhibited positive and negative deviations from predicted yield values of ideal mixtures based on their weight fractions (Ilkka and Paronen, 1993).

Apart from the relationships between the compaction behavior of powder mixtures and neat materials, sensitivity to varying compaction speeds is also critical. Materials exhibiting time-dependent plastic deformation are more sensitive to speed changes (Roberts and Rowe, 1986) and can result in lower tensile strengths whereas materials exhibiting a high degree of reversible elastic deformation are prone to capping and lamination (Garr and Rubinstein, 1991). With the use of compaction simulators, time-dependent compaction behavior of materials can be studied with varying punch speeds (Celik and Marshall, 1989).

The objective of this study is to analyze the deformation of powder mixtures based upon the performance of the neat materials. The deformation of binary mixes of Eudragit® L100-55 and L100 with the rate-controlling polymer, HPMC K4M, were studied under varying punch speeds using double-ended compression on a compaction simulator. Radial die-wall force measurements using an instrumented die enabled determination of residual die-wall forces which help assess the lubricity requirements during ejection. Parameters such as work of compaction and strain rate sensitivity were evaluated from the force–displacement data.

2. Materials and methods

2.1. Materials

Methacrylic acid copolymers, Eudragit® L100-55 (Lot no. 1220504036) and Eudragit® L100 (Lot no. 1221203048) were kindly donated by Rohm Pharma polymers, Piscataway, NJ. Hydroxypropyl methylcellulose (HPMC K4M) was kindly donated by Dow chemical company; Midland, MI.

2.2. Preparation of powder mixes

Binary mixes of HPMC K4M with Eudragit® L100-55 and Eudragit® L100 were prepared in increments of 20% (w/w) (0:100, 20:80, 40:60, 60:40, 80:20, and 100:0). The powders were charged in a twin shell blender (Patterson-Kelley Co., East Stroudsburg, PA) and mixed for 15 min. Since the die-wall and the punch faces were externally lubricated using a magnesium stearate suspension, the powder mixes did not contain any lubricant. The mixes were discharged and double-bagged until further use.

2.3. Compaction studies

All compaction studies were conducted on a Mand compaction simulator (Mand Testing Machines Ltd., Stourbridge, UK) located at GlaxoSmithkline (King of Prussia, PA), Round flat-faced tooling with a 10 mm diameter was used. A symmetric double-ended saw-tooth waveform was used due to the ability of this waveform to provide constant punch speed. The upper and lower punch force calibration was performed using a piezoelectric load cell (Model 9021, Kistler Instrument Corporation, Amherst, NY). The output of the force transducers was linear in the 0–45 kN range with a resolution of 15 N. The linear voltage displacement transducers (LVDTs) provided a linear response with a resolution of 7.3 μm. Radial die-wall forces were measured using an instrumented slotted web die, previously designed in our laboratory (Hoag et al., 2000). The web die employed four strain gauges configured in a full Wheatstone bridge for maximum sensitivity. Neoprene rubber plugs were used to calibrate the die. Due to the hydraulic nature of these rubber plugs, the pressure transmitted through the upper punch can be assumed to be equal to the pressure exerted on the die-wall.

Compacts of the neat polymers and the binary mixes were prepared at a peak compression force of 18 kN. The fill weights for the neat polymers and the mixes were calculated based on the true densities measured using a multivolume helium pycnometer (Micromeretics Model 1330, Norcross, GA) The compacts were prepared at linear punch speeds of 1 mm/s and 100 mm/s. A 5% (w/v) magnesium stearate suspension in acetone was swabbed onto the die-wall and punch faces before each compression cycle. The force and displacement data were collected using a digital oscilloscope with four channels (Nicolet Instrument technologies Inc., Madison, WI). The radial die-wall force and the upper punch displacement data were collected on a second oscilloscope and all data were synchronized based on the upper punch displacement data collected on both oscilloscopes.

2.4. Data analysis

Compression behavior of the neat polymers and the binary mixes was analyzed based on the classical Heckel equation which describes change in porosity as a function of compression pressure (Heckel, 1961):

$$\ln\left(\frac{1}{1-D}\right) = kP + A \qquad (1)$$

where D is the relative density of the compact at a given pressure, P, and is defined as the ratio of the apparent density to the true density. Since porosity is the fraction of the compact occupied by the voids, the term $(1-D)$ represents the total porosity of the compact at any given pressure:

$$1-D=1-\left(\frac{V_t}{V_b}\right)=\left(\frac{V_b-V_t}{V_b}\right)=\text{Total porosity} \qquad (2)$$

where V_t and V_b denote true and bulk volume, respectively. Typically, a plot of $\ln(1/1-D)$ versus compression pressure (P) results in a curvilinear plot with an initial curved region followed by a linear region. The initial curved region results from particle slippage and rearrangement, and the densification due to this phenomenon is characterized by the term A. The apparent mean yield pressures (P_y) of the materials were calculated from the slopes of the linear region (k). The regression on the linear region was performed based on the method of least squares ($R^2>0.99$).

The effect of punch speed on the deformation of the powder mixes was analyzed based on their strain rate sensitivities (SRS). SRS values for the neat materials and the powder mixes were calculated using the following equation:

$$\text{SRS}=\left(\frac{P_{y2}-P_{y1}}{P_{y2}}\right)\times 100 \qquad (3)$$

where P_{y1} and P_{y2} are the yield pressures at the slow and high punch speeds, respectively.

The residual die-wall force is given by the radial die-wall force at the point where the axial stress drops to zero during decompression. The work of compaction was calculated from the area under the force–displacement curve. The upper and lower punch force traces were almost identical. Hence, only the upper punch force profile was used for calculating work done. The net energy expended in compact formation was deduced from the difference of the area under the compression profile and the area under the decompression profile:

$$W=\int F\,\mathrm{d}D \qquad (4)$$

3. Results and discussion

3.1. Heckel analysis

The relationship between applied axial pressure and compact porosity for neat materials is well defined by the Heckel equation. The initial curved region of the Heckel plots can be explained on the basis of particle rearrangement, which results from a decrease in void volume. There can be some fragmentation during this initial stage depending upon the material properties. Beyond the particle rearrangement phase, powder densification occurs linearly as a function of applied pressure. The particle deformation is completely reversible if the applied pressure is below the elastic limit of the material. However, at higher pressures, permanent deformation occurs either through plastic flow or fragmentation. Since both phenomena may occur, some investigators have suggested that P_y should be termed a deformation stress rather than a yield stress (Roberts et al., 1989). In the case of many materials, at high axial pressures where the apparent density approaches true density, the Heckel number approaches infinity and the Heckel plots show significant curvature (Roberts and Rowe, 1985).

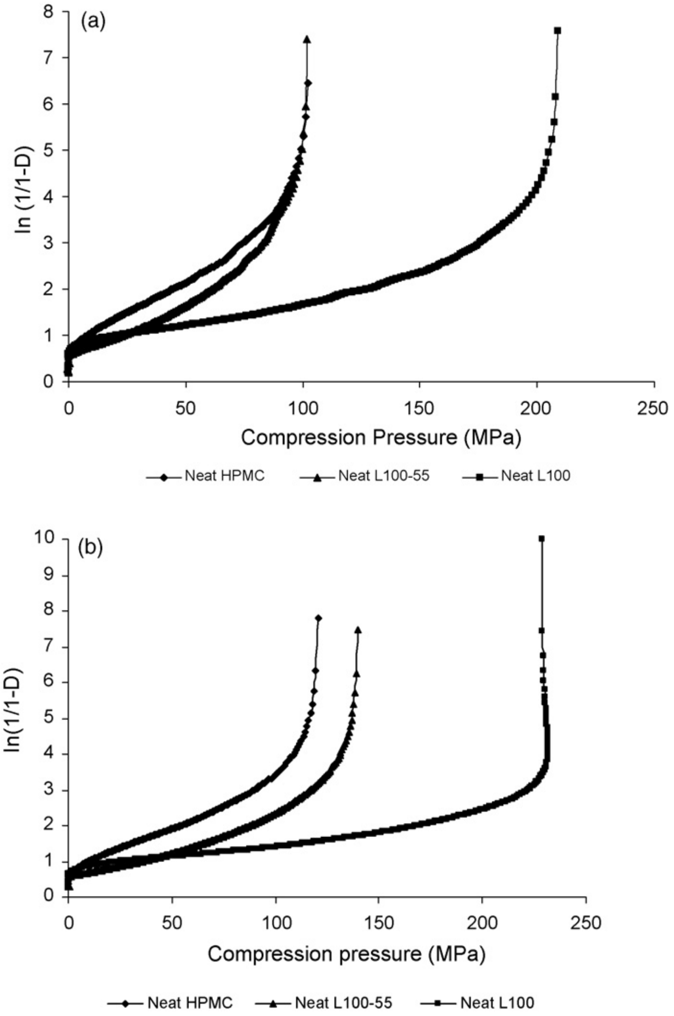

Fig. 1. Representative Heckel plots for the neat polymers at a punch speed of (a) 1 mm/s and (b) 100 mm/s.

Representative Heckel plots for the three neat polymers, Eudragit® L100-55, Eudragit® L100 and HPMC K4M are given in Fig. 1. The highest compression pressure that is plotted is the maximum pressure above which apparent negative porosity results ($D<1$). Pedersen and Kristensen (1994) have reported a measured increase in the true density of acetyl salicylic acid crystals which was responsible for the apparent negative porosity seen. The true density rapidly recovered to the original density upon decompression (Pedersen and Kristensen, 1994). Though all three polymers exhibit behavior that is typical of plastic materials, it can be clearly seen that HPMC and L100-55 behave similarly and unlike L100 which exhibits a greater resistance to densification. This difference in the densification behavior can be more clearly seen from Table 1, wherein the Heckel numbers at an arbitrary pressure of 100 MPa are given at the two different speeds (1 and 100 mm/s). Time dependent deformation behavior can be analyzed based on the strain rate sensitivity values as described in Section 2.4. However, since the Heckel numbers represent the extent of pressure based porosity reduction, these

Table 1
Heckel numbers ($\ln(1/1-D)$) for the neat polymers at a compression pressure of 100 MPa for punch speeds of 1 and 100 mm/s

Polymer	1 mm/s		100 mm/s	
	$\ln(1/1-D)$	Pressure at apparent negative porosity (MPa)	$\ln(1/1-D)$	Pressure at apparent negative porosity (MPa)
HPMC K4M	5.309	103.54	3.429	121.54
L100-55	5.384	102.30	2.331	140.57
L100	1.664	199.97	1.405	228.36

Table 2a
Yield values (MPa) and strain rate sensitivity (SRS) values for HPMC: L100-55 binary mixes at punch speeds of 1 and 100 mm/s

Sample composition (HPMC:L100-55)	Yield pressure (MPa) (average (S.D.))		SRS (%)
	1 mm/s	100 mm/s	
100:0	37.04 (0.70)	47.31 (2.13)	21.70
80:20	34.44 (0.07)	55.30 (2.18)	37.73
60:40	37.04 (0.36)	60.49 (0.77)	38.77
40:60	40.03 (1.41)	65.36 (0.43)	38.76
20:80	43.80 (2.78)	71.31 (2.44)	38.58
0:100	50.43 (0.89)	77.50 (4.55)	34.93

values at varying speeds can also provide further insight into time-dependent deformation behavior. Of the three neat polymers, L100 exhibited the least time-dependency as seen from similar Heckel numbers at both speeds.

The yield values for the neat materials and the binary mixes are provided in Tables 2a and 2b, and illustrated in Fig. 2. As can be seen from these tables, for both L100-55 and L100, the yield value increases with an increase in the weight fraction of the methacrylic acid polymer. The yield values for the neat L100-55 and L100 are 50.43 and 122.42 MPa, respectively; thereby suggesting that the latter exhibits greater resistance to densification even at slow speeds, which is evident from the slopes of the neat polymer in Fig. 1a. It is interesting to note that even though both polymers have structural similarities, with only slightly different alkyl groups as part of their ester functionalities and both polymers are manufactured using a spray drying process, the deformation behavior of the two polymers is very different. In addition, optical microscopy showed no significant differences in their morphological features (Fig. 3).

The yield values of the binary mixes as a function of the weight fractions of L100-55 and L100 are plotted in Fig. 2. It can be seen that all plots are very linear, binary mixes of L100-55 at a punch speed of 1 mm/s had an $r^2 = 0.81$, the other three plots exhibit high linear correlation between mixture yield pressures and their respective weight fractions ($r^2 = 0.99, 0.97, 0.99$). Though previous studies have shown both linear and non-linear relationships between the mixture weight fractions and resultant compaction properties, such as tensile strength and yield values, it has been seen that mixtures of plastically deforming and brittle fragmenting materials always show positive or negative deviations due to the predominating behavior of one of the materials.

Ilkka and Paronen (1993) indicated in their study that a linear relationship in the case of mixtures of plastically deforming

Table 2b
Yield values (MPa) and strain rate sensitivity (SRS) values for HPMC: L100 binary mixes at punch speeds of 1 and 100 mm/s

Sample composition (HPMC:L100)	Yield pressure (MPa) (average (S.D.))		SRS (%)
	1 mm/s	100 mm/s	
100:0	37.04 (0.70)	47.31 (2.13)	21.70
80:20	45.37 (2.94)	70.76 (0.76)	35.88
60:40	67.00 (1.84)	98.71 (2.05)	32.13
40:60	75.40 (1.72)	130.98 (2.04)	42.43
20:80	105.28 (1.94)	163.05 (1.52)	35.43
0:100	122.43 (12.90)	191.19 (5.53)	35.97

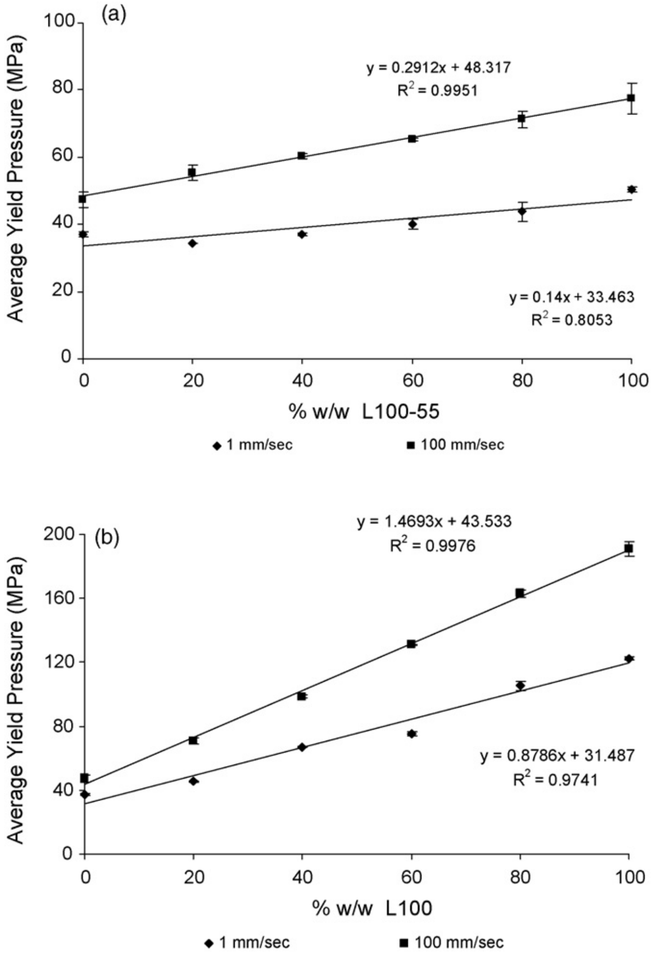

Fig. 2. Linear relationship between the yield pressures of the binary mixes and their weight fractions at punch speeds of 1 mm/s and 100 mm/s for (a) L100-55 and (b) L100.

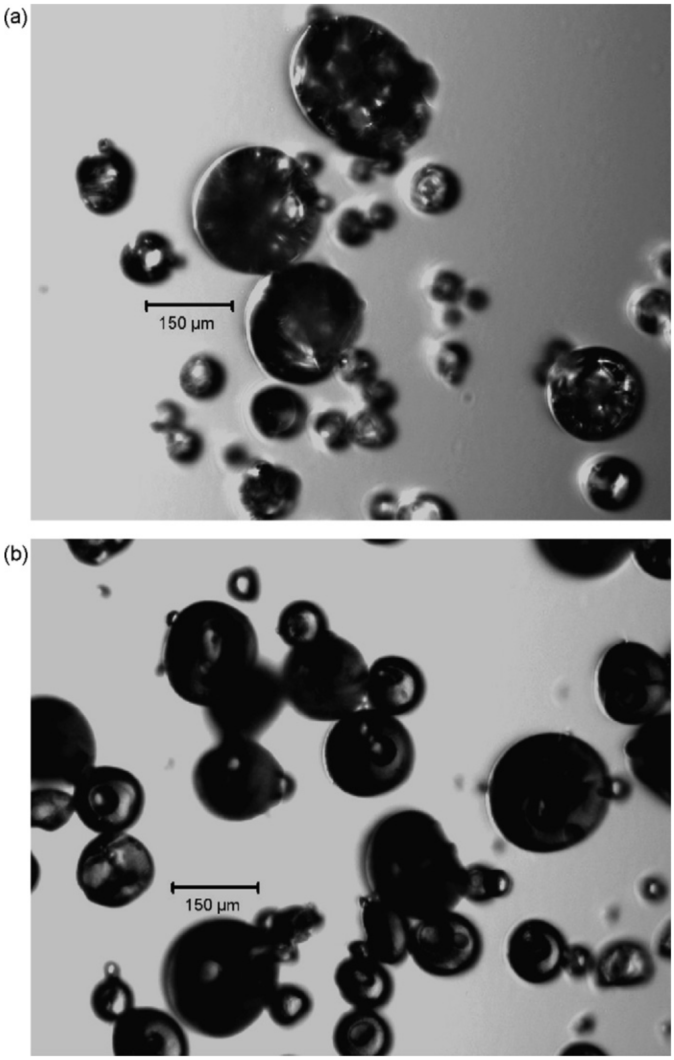

Fig. 3. Optical microscopy picture of (a) L100-55 and (b) L100 under 20× magnification.

materials can be explained based on the nature of deformation; i.e. since plastic flow is dependent on the extent and duration of applied stress at the deformation site, the particles are increasingly deformed after the applied stress exceeds the yield limit. Thus, the total deformation of the powder column increases steadily as the effective stress steadily increases since the effective surface area remains nearly constant due to the non-fragmenting nature of the material. Although their study indicated that the yield values of the mixtures of two plastically deforming substances, microcrystalline cellulose and pregelatinized starch were linearly dependent on their weight fractions, it was recognized that the neat materials had very similar yield values; hence, the observed linear relationship was not statistically significant. However, in the current study the two plastically deforming materials have significantly different yield values; 37.04 MPa for HPMC and 50.43 MPa for L100-55 at 1 mm/s punch speed and 47.31 and 77.50 MPa at 100 mm/s punch speed. In the case of L100, the yield values were even more markedly different; 122.43 MPa at 1 mm/s and 191.19 MPa at 100 mm/s. The high correlation coefficients given in Fig. 2a and b, even for these systems where the neat materials have markedly different yield values, suggests that the yield values obtained from the linear regions of the Heckel plots can be used for predicting the yield behavior of their mixtures.

A study by Sonnergaard (1999) has critically examined and questioned the suitability of yield pressures obtained from the reciprocal of the slopes of the linear regions of the Heckel plots as a universal parameter for characterizing compressibility of materials. It is their contention that these yield values are susceptible to significant change based on such parameters as peak compression pressure, tooling dimensions and compact weight. Also, they indicate that due to the logarithmic transformation involved in the Heckel equation, an error of 1% in the measured true density leads to an error of more than 10% in the apparent mean yield pressure estimate. However, Carstensen et al. (1989) have reported that the Heckel plots of Emcompress$^{®}$ were fairly independent of the die diameter and the fill weight. Also Kiekens et al. (2004) have reported that the yield pressures were influenced to a greater extent by parameters such as punch diameter, filling depth and compression pressure, in the case of concave punches as compared to flat-faced punches, the type of tooling used in the current study. The yield pressures from the current study compare well with those published in literature. For example, in the current study the mean yield pressure for neat HPMC K4M tablets compressed to a peak compression force of 18 kN at a punch speed of 100 mm/s was determined to be 47.31 MPa. This compares well with the study published by Nokhodchi et al. (1995) in which the mean yield pressure for K4M at 15 mm/s and 10 kN was reported to be around 47 MPa.

Based on the yield pressure values at 1 and 100 mm/s punch speeds, the time-dependent deformation behavior of the neat material and the binary mixes were evaluated using the strain rate sensitivity equation (see Section 2.4). The SRS values indicate that both L100-55 and L100 show significant time-dependent deformation. Although L100 has much higher yield values compared to L100-55, comparable SRS values for their binary mixes with HPMC indicates similar time-dependency for both polymers. Even though the apparent yield pressure values of L100 are at the high end of what is typically observed for plastically deforming materials, the SRS values indicate that the material exhibits plastic deformation. Usually brittle materials exhibit very low or insignificant time dependency as is the case with acetaminophen and dibasic calcium phosphate dehydrate (Narayan and Hancock, 2003). The SRS value for neat HPMC K4M in this study (21.7%) compares well with a study published by Nokhodchi et al. (1996) in which the SRS value for this polymer was reported at 21.6%.

3.2. *Radial die-wall pressures*

Radial pressures during tableting arise due to compaction of the powder mass in a confined die. As the applied axial pressure increases, some of this stress is transmitted to the die-wall. During decompression, the radial pressure exerted on the die-wall decreases; however, upon complete removal of axial pressure, some die-wall pressure still remains. This is referred to as the residual die-wall pressure (RDWP) and is inversely proportional

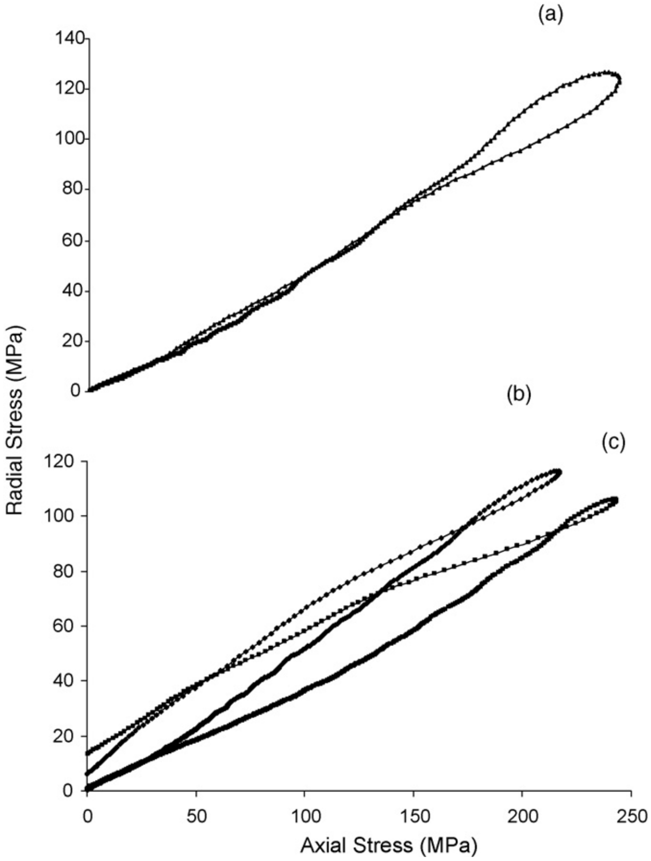

Fig. 4. Axial vs. radial stress profiles for (a) HPMC, (b) L100-55 and (c) L100 at a punch speed of 1 mm/s.

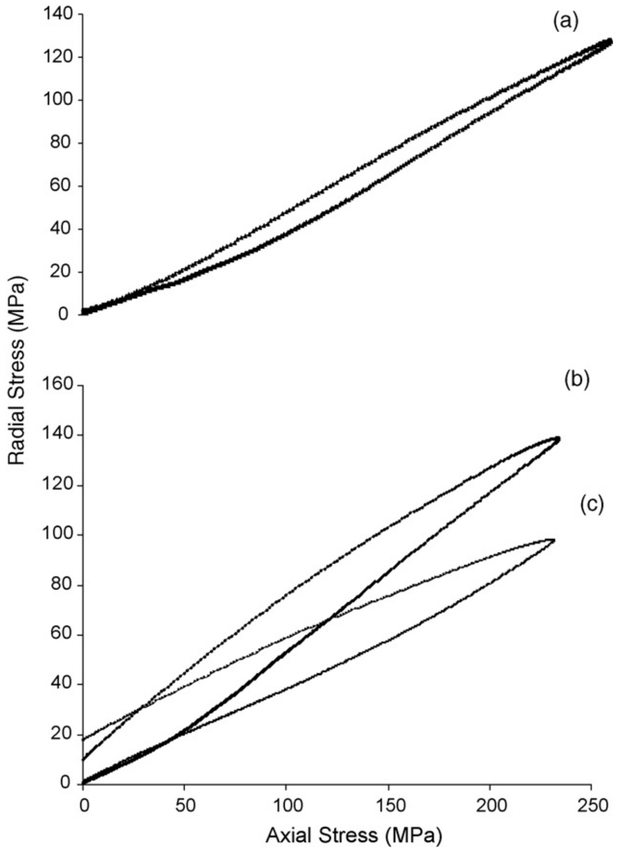

Fig. 5. Axial vs. radial stress profiles for (a) HPMC, (b) L100-55 and (c) L100 at a punch speed of 100 mm/s.

to the ejection pressure. Plots of axial versus radial pressures during tableting can provide valuable data and are referred to as the “compaction profiles” (Kottke and Rudnic, 2002). A typical compaction profile can provide information about elastic deformation, plastic deformation and brittle fracture on compression and elastic recovery and residual die-wall forces during decompression. The compaction profile typically takes the form of a hysteresis loop as seen in Figs. 4 and 5, the enclosed area being representative of the departure of the material from a purely elastic behavior. Hence, purely elastic material would have overlapping compression and decompression profiles.

Fig. 4 gives the axial versus radial stress profiles of the neat polymers at a punch speed of 1 mm/s. We can see that for HPMC, except at very high axial stress values, the compression and decompression profiles overlap, suggesting that its elastic behavior is greater than the methacrylate polymers. This is also supported by the insignificant RDWP seen for this material (Table 3). The RDWP for the binary mixes increased as the weight fraction of both L100-55 and L100 increased; possibly indicating that the elastic recovery of HPMC is higher than those for the neat methacrylic polymers. RDWP values for L100 were consistently higher than those for L100-55. Lower RDWP values can indicate higher elastic recovery. During decompression, the elastic recovery component is responsible for breaking the bonds that are formed during the compression process; an excess of elasticity can result in capping and lamination phenomenon. At punch speeds of 100 mm/s, residual die-wall forces for all compositions were higher than those at a punch speed of 1 mm/s. At higher punch speeds, the in-die elastic recovery is less due to the inability of the compact to release the residual stresses in

Table 3
Residual die-wall force values for the binary mixes at punch speeds of 1 and 100 mm/s

Sample composition (HPMC:L100-55)	RDWP (MPa) (average (S.D.))		Sample composition (HPMC:L100)	RDWP (MPa) (average (S.D.))	
	1 mm/s	100 mm/s		1 mm/s	100 mm/s
100:0	0.91 (0.49)	2.85 (0.86)	100:0	0.91 (0.49)	2.85 (0.86)
80:20	1.70 (0.23)	5.52 (0.81)	80:20	2.19 (0.17)	5.73 (0.93)
60:40	3.76 (0.84)	5.39 (0.21)	60:40	5.08 (0.25)	8.43 (0.53)
40:60	4.41 (0.10)	7.89 (0.66)	40:60	6.98 (1.14)	11.95 (0.45)
20:80	5.80 (0.79)	10.28 (0.69)	20:80	10.50 (1.32)	14.48 (2.41)
0:100	6.48 (0.27)	11.98 (1.76)	0:100	12.47 (1.26)	17.01 (3.43)

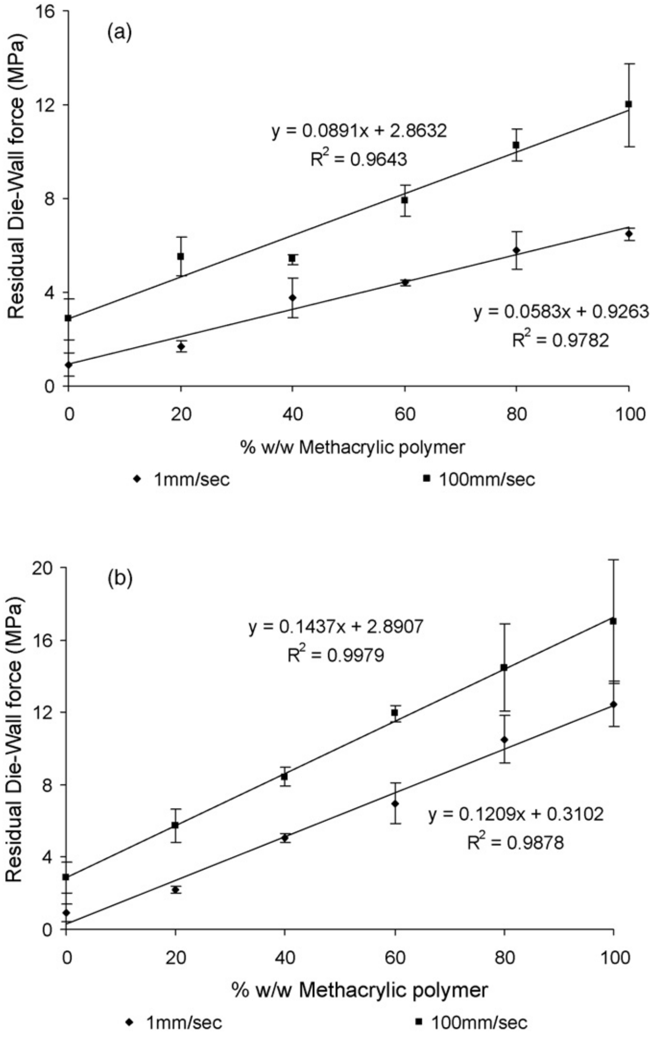

Fig. 6. Effect of increasing methacrylic polymer levels and punch speed on residual die-wall forces for (a) L100-55 and (b) L100.

the axial direction and hence higher RDWP values are recorded. Interestingly, for both polymers and both punch speeds used, a linear relationship between the residual die-wall forces and the weight fractions of the binary mixes was observed (Fig. 6). Thus, in the case of two plastically deforming materials, we can possibly predict the apparent mean yield pressure values and residual die-wall forces.

3.3. Work of compaction

The energy expended during powder compact formation can be estimated from the force–displacement curves. The area under the compression and decompression profiles can provide information regarding the total work input during compression and work recovered during decompression, which is equivalent to the work done by the compact on the tooling; the difference between the two being defined as the work of compaction or the net energy expended during compact formation. Since the area under the decompression profile is related to the elastic recovery of the material, large areas under the decompression profiles may indicate formation of mechanically weaker compacts. Fig. 7 indicates that the net work done during compact formation is lowest for the neat HPMC compacts and increases as the amount of the methacrylic acid polymers (L100-55 and L100) increases. From the yield pressure values (Tables 2a and 2b), it can be seen that the yield values of both L100-55 and L100 are higher than HPMC. Hence, as the methacrylic acid polymers exhibit greater resistance to densification, more energy is expended to form compacts with similar heights. Also, interestingly the total work of compaction for the binary mixes is linearly related to the work done in the case of the neat materials, for both polymers at the slow and high punch speeds, thus again indicating the possibility of predicting this parameter for powder mixtures based on the properties of the neat materials.

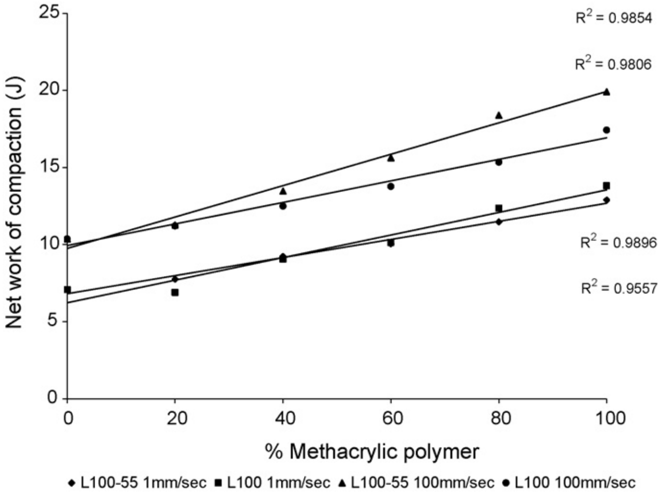

Fig. 7. Effect of increasing methacrylic acid polymer levels and punch speed on net work of compaction.

4. Conclusions

Methacrylic acid copolymers, Eudragit® L100-55 and L100 exhibited Heckel plots characteristic of plastic deformation. Of the two copolymers, L100 exhibited significantly greater resistance to densification, compared to L100-55, as evident from the higher yield pressure values. At both the slow and the high punch speeds, apparent mean yield pressures were linearly related to the weight fractions of the Eudragit® polymers. The yield pressures increased with an increase in the punch speed. Nevertheless, the yield pressures at higher punch speeds were also linearly related to the weight fractions. The residual die-wall pressures indicated that at slow speeds (1 mm/s) and at lower pressures (<150 MPa), HPMC possesses significant elastic recovery. However, the good compacts formed at this punch speed indicate extensive plastic deformation and bond formation which is able to predominate over the elastic recovery component. The capping phenomenon observed in the case of neat L100 at higher punch speed indicates relatively low consolidation, whereas capping seen in the case of low L100-55 levels (High HPMC levels) could possibly be due to high elastic recovery of HPMC and reduced bonds surviving decompression and ejection. Therefore, caution must be exercised when compacting these polymers at higher punch speeds.

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