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Compression speed on polyethylene glycol and dicalcium phosphate tableted mixtures

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Abstract

The effect of compression speeds between 10–500 mm s^{-1} on the compaction of PEG/DCP mixtures has been investigated using relative density (D_0), mean yield pressure, tensile strength, plastic energy (*PE*), work of failure (*WF*) and *PE*/*WF* ratio. At any speed, D_0 was found to increase with PEG concentration due to the smooth surface of PEG particles, and their lubricant activity reducing interparticulate friction. No synergistic interactions between PEG and DCP during compression with mean yield pressure occurred at the slowest compression speed (10 mm s^{-1}). However synergism was observed at higher compression speeds (100–500 mm s^{-1}) indicating DCP dominates compressibility with a reduction in plastic deformation of PEG. The tensile strength and normalized work of failure of the mixtures decreased with increasing compression speed. However they increased, reaching a maxima at 80:20 PEG/DCP (%), at all compression speeds. The plastic energy/work of failure ratio increased with speed. Increasing PEG, decreased the ratio and a minimum was observed at 80:20 PEG/DCP (%) where the least energy was required for making good tablets. © 1998 Elsevier Science B.V.

Keywords: Compression speed; Relative density; Mean yield pressure; Tensile strength; Work of failure; Plastic energy; Polyethylene glycol; Dicalcium phosphate

1. Introduction

In practice, two or more materials are blended to improve compressibility, tablet appearance and reduce capping and lamination of poorly compressible drugs (Wells and Langridge, 1981; Malamataris et al., 1984). Mixtures also yield harder tablets than individual excipients (Newton et al., 1977; Vromans and Lerk, 1988).

Occasionally a little polyethylene glycol (PEG) is introduced to improve rheological properties: as a lubricant or to enhance cohesion within the tablet. To date, PEGs have rarely been used as a major component. Single direct compression aids

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are generally not adequate to produce direct compression formulations of high capacity, tensile strength, low friability and good disintegration properties. Tablets with higher tensile strengths than individual components can be prepared by mixing material with higher compressibility such as microcrystalline cellulose (MCC) with a material which undergoes extensive fragmentation during compression such as dicalcium phosphate (DCP; Wells and Langridge, 1981). PEG consolidates by plastic deformation indicated by very low mean yield pressures, even at high compression speeds, and exhibits no capping tendency (Larhrib et al., 1997a). Optimum tableting characteristics may therefore be expected from blends of PEG with DCP.

The rate at which PEGs cool from the melt has been shown to affect their morphology and structure (Chatham, 1985; Craig and Newton, 1991; Larhrib et al., 1997b). Differences in particle shape and rugosity may also have contributed to the difference in their tensile strengths (Larhrib and Wells, 1997a). Slow cooling showed higher crystallinity and formed stronger tablets than those made from untreated and quench cooled PEG, and therefore was the method of choice and will be used in this study.

The present work, investigates the compaction properties of mixtures of a plastic, soft material, polyethylene glycol (PEG 10000, Merck Schuchardt, Germany) and a fragmenting material, dicalcium phosphate (Emcompress®, E. Mendell, New York) with respect to compression speed.

2. Methods

2.1. Preparation of heat-treated PEG

PEG flakes were held at 100°C in an electric oven (Memmert SE 400: Schwabach, Germany) for 30 min and then allowed to cool to room temperature over a period of about 1 h. The sample was stored over phosphorus pentoxide (BDH, Poole, UK) for 24 h before grinding. PEG was carefully ground in an open mortar and pestle, care being taken to ensure that there was no obvious and visible signs of the PEG melting.

2.2. Particle size fraction

The PEG and DCP were sieved (Pascall, Sussex, UK) and a 250–355 μm size fraction was collected. The powders were dried (PEG at 37°C and DCP at 50°C) until their moisture content was less than 0.3% w/w and then stored in sealed jars.

2.3. Mixing

Binary mixtures of DCP containing 0, 20, 40, 60, 80 and 100% w/w PEG were prepared by mixing in a sealed jar attached to an electric motor rotating at 40 rev./min for 15 min. The true density of PEG (1.235 g cm^{-3}) and DCP (2.325 g cm^{-3}) was measured using an air comparison pycnometer (Beckman, Model 930, UK) from the mean of five determinations. The densities of the binary mixtures were calculated from the values of the pure materials according to their proportions in the mixture.

2.4. Compression

Compression was carried out using a high speed compaction simulator (ESH Testing, Brierley Hill, UK), fitted with 12.5-mm flat faced punches. A sawtooth displacement profile was used to control both upper and lower punches. Details of the simulator have been published elsewhere (Nokhodchi et al., 1995a,b). The effect of compression speed (10, 100, 300 and 500 mm s^{-1}) was examined upon 500-mg powder samples whilst the maximum compression pressure was held constant at 82 MPa. This speed range is of particular importance, as it encompasses the compression speeds of single punch machines (50–100 mm s^{-1}) through to high speed rotary machines (100–400 mm s^{-1}). Before each compression, the punches and die were cleaned with acetone and brushed with 2% w/v stearic acid in chloroform to provide external lubrication. During compression, upper punch load and punch separation were monitored to a precision of ± 0.012 kN and ± 4.9 μm, respectively.

Storage of the compressed tablets at high relative humidity may destroy bonds formed during

compression and consequently, the tablet structure and strength would crumble, resulting in rapid breakdown of the tablet on exposure to water and fast disintegration (Ford, 1980). To avoid any moisture effects, even though PEG 10000 and DCP are essentially non hygroscopic (Handbook of Pharmaceutical Excipients, 1994), the compressed tablets were stored over phosphorus pentoxide at room temperature for 24 h before mechanical testing.

2.5. Manipulation of the data

During the compression event, the force and displacement data from the upper and lower load cells and the linear variable differential transducers (LVDTs) were captured using a transient recorder. The data was transferred to a mainframe computer, where a statistical package (MINITAB) was used to perform Heckel (1961a,b) and net work of compaction analysis.

Fig. 1 shows pressure–punch separation, where A is punch separation at the first measurable pressure. B is the pressure at minimum punch separation, D represents the minimum punch separation and C is the decompression pressure. The area under the curve $[AUC]ABD$ corresponds to the gross energy (GE), the area under the curve $[AUC]CBD$ corresponds to the elastic energy (EE). The plastic energy (PE) or net work of compaction was determined as: $PE = ([AUC]ABD) - ([AUC]CBD)$ (Nokhodchi et al., 1995b).

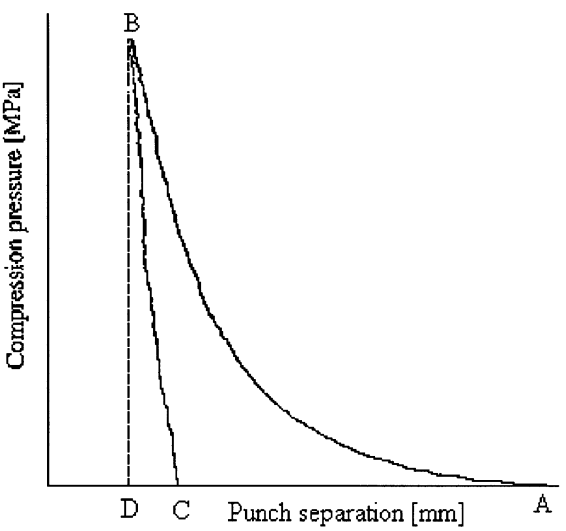


Fig. 1. Plot of compression pressure against punch separation of PEG 10000.

2.6. Tablet porosity

Twenty-four hours after ejection, the tablet weight ± 0.1 mg and dimensions ± 10 μm were recorded. The percentage porosity, ϵ, was calculated from the following equation:

$$\epsilon = [(V - V_0)/V] \times 100$$

where V is the tablet volume and V_0 the volume of material at zero porosity.

2.7. Tablet testing

The force required to cause tablet failure, tablet deformation at failure and work of failure (Rees and Rue, 1978) of tablets were measured using a tensile tester (type LR30K, Lloyd Instruments, Fareham, UK).

The tester could be operated in either tension or compression modes, although in this work the tester was used in the compression mode at a crosshead speed of 3 mm min^{-1}. The tablet was placed between the movable crosshead and lower platen, and the force as a function of displacement was recorded during tablet testing using 'Dapmat' software. This also reported the tablet deformation at failure, the peak force and the work done to cause tablet failure.

Rees and Rue (1978) stated that the measured displacement is not a tensile strain, but a deformation of the compact in the direction of compressive loading. The area under the force–displacement curve is related to the toughness of the tablet as defined by Carswell and Nason (1944) and described by Dieter (1961) as the ability of a material to absorb energy in the plastic range. Rees and Rue (1978) termed the calculated area 'work of failure' (WF):

$$WF = \int_0^{x_{max}} F \, dx$$

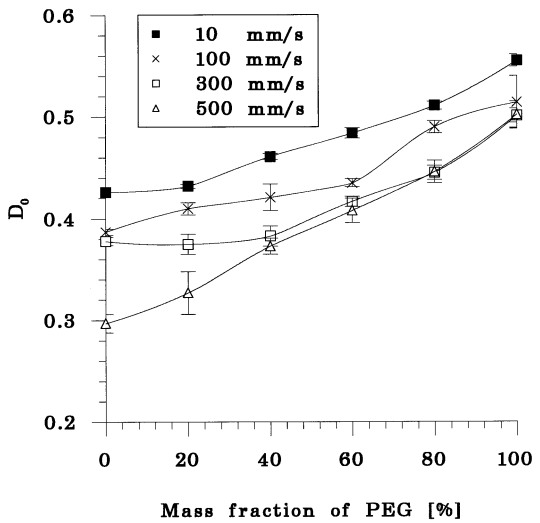


Fig. 2. The effect of compression speed on the relative density (D_0) of PEG/DCP mixtures.

where F is the force applied, F_{max} = force required to cause tablet failure, x = tablet deformation, x_{max} is tablet deformation at failure.

The work of failure was normalized (*NWF*; Patel and Staniforth, 1987) to account for the dimensional differences in tablets prepared from different blend concentrations:

$$NWF = \frac{2}{\pi D t} WF$$

where D is the tablet diameter, t is the tablet thickness and WF is the work of failure.

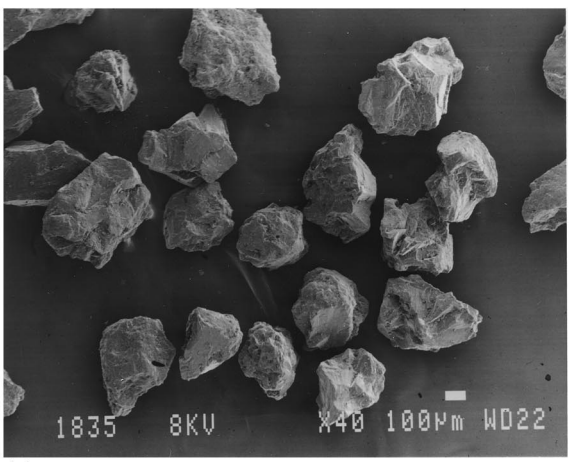
2.8. Statistical analysis

The data were analysed using two-way analysis of variance and Tukey's multiple comparison test. Results are quoted as significant at $p < 0.05$.

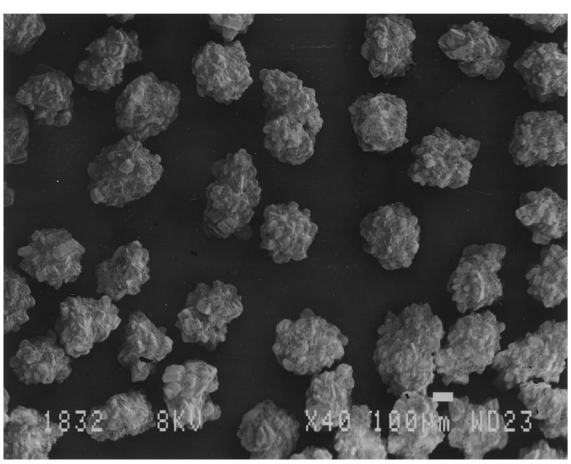
3. Results and discussion

The relative density of the powder bed at the point when a measurable pressure was applied (D_0), decreased with increasing compression speed and increased with PEG content (Fig. 2). The decrease of D_0 with speed was due to a decrease in particle rearrangement and slippage (Roberts and Rowe, 1985) as frictional forces of the rough textured DCP aggregates oppose the rearrangement process. Tukey's test revealed that the values of D_0 obtained at the slowest (10 mm s^{-1}) and the fastest speed (500 mm s^{-1}) were significantly different for PEG, DCP and their mixtures.

Scanning electron micrographs (Fig. 3) show that PEG particles are smooth compared with the rough DCP particles. Dense packing may be reduced by microirregularities at the surface of the DCP particles and therefore particle interlocking is expected to be greater resulting in a highly porous structure (Table 1).



(a)



(b)

Fig. 3. Scanning electron micrographs of (a) PEG and (b) DCP particles (magnification: × 40).

Table 1
Relative density (D_0), porosity and strain rate sensitivity (*SRS*) of PEG, DCP and their mixtures

% PEG	$D_0 \pm$ S.D. at 10 mm s^{-1}	Porosity (%) at 1st measurable pressure $\pm$ S.D. at 10 mm s^{-1}	*SRS* (%) $\pm$ S.D. at 10 and 500 mm s^{-1}
0	0.426 ± 0.000	57.525 ± 0.267	16.012 ± 0.009
20	0.432 ± 0.002	56.524 ± 0.411	17.217 ± 1.002
40	0.461 ± 0.003	54.313 ± 0.874	30.409 ± 1.037
60	0.484 ± 0.005	51.548 ± 0.597	41.141 ± 2.266
80	0.511 ± 0.004	48.845 ± 0.499	47.660 ± 1.226
100	0.555 ± 0.006	44.489 ± 0.697	60.436 ± 1.349

Increasing PEG content increased the D_0 values. PEG is a lubricant (Gold and Palermo, 1965; Etienne, 1971) and its presence probably enhances particle movement by reducing interparticulate friction and helps particles pack closer.

The effect of compression speed on the mean yield pressure of PEG, DCP and their mixtures is shown in Fig. 4. Two-way analysis of variance showed that both compression speed and PEG content had an effect on the mean yield pressure. The increase in mean yield pressure with increasing compression speed could be due to a reduction in the amount of plastic deformation and/or an increase in fragmentation (Roberts and Rowe, 1987). At the slowest compression speed (10 mm s^{-1}), the mean yield pressure decreased linearly

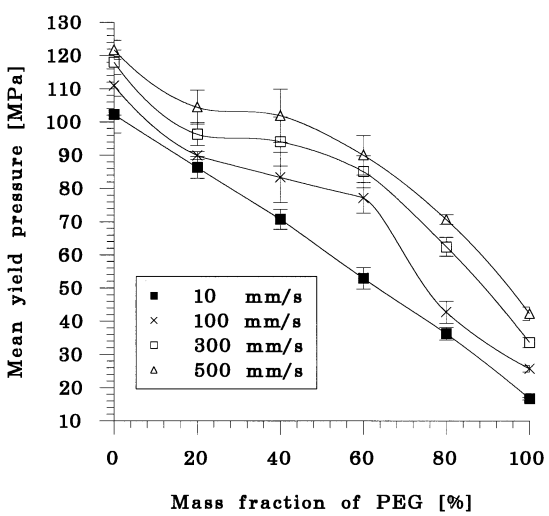


Fig. 4. The effect of compression speed on the mean yield pressure of PEG/DCP mixtures.

with increasing PEG concentration suggesting no interaction between the materials during compression. Duberg and Nystrom (1985) found that, using binary mixtures of Avicel 105 (sic) with other materials (i.e. Emcompress, Lactose and Paracetamol), the mean yield pressure decreased linearly with Avicel concentration. Furthermore, the addition of a second component did not alter the deformation of the tested materials. For the compacts made at higher compression speed (100–500 mm s^{-1}), positive deviation from linearity indicated that the deformation mechanism of poorly compressible DCP, with a higher mean yield pressure than PEG dominated the compressibility. This was probably due to a reduction in the amount of plastic deformation by PEG. Bateman (1988) found that the interaction between lactose and ibuprofen was compression speed dependent: at the slowest compression speed (25 mm s^{-1}) a simple relationship was obtained whilst a positive interaction was noted at 380 mm s^{-1}. However, at a very high compression speed (1100 mm s^{-1}), both materials exhibited similar mean yield pressures suggesting similar deformation mechanisms, and no interaction between the materials was observed (Bateman, 1988).

The strain rate sensitivity (*SRS*) of PEG, DCP and their mixtures was calculated from the slope of the Heckel plots for the compacts made at 10 and 500 mm s^{-1} (Table 1). Although DCP is a fragmenting material, it showed some rate dependency on yield pressure but to a much smaller extent than PEG. The *SRS* of PEG was four times higher. There was no difference in the SRS between pure DCP and the mixture containing

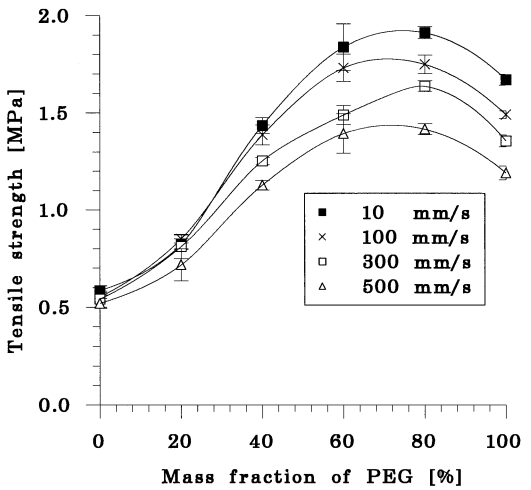


Fig. 5. The effect of compression speed on the tensile strength of PEG/DCP mixtures.

20% PEG (Tukey's test), whereas above this PEG level the SRS always showed an increase with PEG concentration suggesting that the material became more plastic and therefore more sensitive to compression speed.

Fig. 5 illustrates the relationship between the fraction of PEG and tensile strength at different compression speeds. DCP did not show any significant change in tensile strength because of its brittle nature. PEG and the mixtures generally showed a decrease in tensile strength with increasing compression speed (Tukey's test) and the curves are well distinguished from each other especially at higher PEG concentrations. Tensile strength of the mixtures was dominated by PEG above 20% and changes in compression speed will affect tensile strength. Compression speeds from 10 to 100 mm s^{-1} had no significant effect on the tensile strength of the compacts containing 40% and 60% PEG. The tablets made from this latter mixture also showed similar tensile strength with increasing compression speed from 300 to 500 mm s^{-1}. The tensile strengths of mixtures containing 60 or 80% PEG were similar at 10, 100 and 500 mm s^{-1} (Tukey's test).

At any compression speed, PEG exhibits a higher tensile strength than DCP. For example, the tensile strength of PEG compacts made at 10 mm s^{-1} was three times higher than DCP. The higher tensile strength of PEG will be due to greater densification during compression allowing particles to establish large areas of intimate contact. The greater densification of PEG is reflected in tablet porosity and a reduction in tablet thickness (Table 2); 100% PEG showed the most reduced thickness, formed tablets with the lowest porosity, exhibited the lowest mean yield pressure value and should therefore produce tablets with the highest tensile strength. In fact mixtures containing from 60 to 80% PEG (Fig. 5) produced the strongest tablets at any compression speed. Larhrib and Wells (1997b) showed that fragmentation of DCP within the 60:40 PEG/DCP (%) blend occurred, which probably enhances bonding of PEG on compaction and so leads to increased tensile strength. Garr and Rubinstein (1991) studied the effect of compression speed on the compaction characteristics of various combinations of a microcrystalline cellulose (MCC) and DCP, and found that 75:25 MCC/DCP (%) produced tablets with higher tensile strength than the individual materials even though the compressibility of pure MCC is higher. These workers attributed their finding to the extensive fragmentation of DCP which enhanced the filling of voids spaces during compression leading to optimum force utilization, improved consolidation and better bonding of MCC.

Rees and Rue (1978) suggested that the work required to cause tablet failure is a better parameter than tensile strength and related better to tablet toughness. Patel and Staniforth (1987) used normalized work of failure (*NWF*) to distinguish brittle and plastic materials. Fig. 6 shows the relationship between *NWF* and PEG fraction at different compression speeds. DCP did not show any changes in *NWF* with increasing compression speed. Fragmentation was rapidly achieved and prolonged exposure to the pressure has no further effect (Armstrong and Palfrey, 1989). Conversely the plastic PEG showed a decrease in *NWF* as the compression speed increased. This was due to both a decrease in the tensile strength and tablet deformation, leading to a reduced tablet toughness (Fig. 7). PEG becomes brittle with increasing compression speed.

Table 2
Effect of PEG content on the reduction in tablet thickness (i.e. thickness at 1st measurable pressure − thickness at minimum punch separation) and tablet porosity (%) of the compacts made at a compression pressure of 82 MPa and a compression speed of 10 mm s^{-1}

PEG (% w/w)	Thickness at 1st measurable pressure (mm)	Thickness at minimum punch separation (mm)	Reduction in tablet thickness (mm)	Porosity (%)
0	4.107 ± 0.023	2.080 ± 0.010	2.026 ± 0.023	26.234 ± 0.071
20	4.457 ± 0.042	2.272 ± 0.027	2.185 ± 0.016	25.167 ± 0.705
40	4.727 ± 0.088	2.378 ± 0.035	2.349 ± 0.060	18.441 ± 1.144
60	5.047 ± 0.058	2.609 ± 0.020	2.438 ± 0.044	16.841 ± 0.693
80	5.490 ± 0.059	2.886 ± 0.005	2.604 ± 0.060	14.589 ± 0.382
100	5.948 ± 0.042	3.184 ± 0.013	2.764 ± 0.055	10.425 ± 0.439

Results are the means and standard deviations of four determinations.

Although tensile strength of PEG could be three times higher than DCP at 10 mm s^{-1}, the *NWF* is 16 times higher and decreased by 50% at the highest compression speed (500 mm s^{-1}). That increasing plasticity increased the work of failure was confirmed by stress relaxation measurements (Rue et al., 1980) and mean yield pressure (Larhrib and Wells, 1997a).

The toughest tablets were obtained from a mixture containing 80:20 PEG/DCP (%) at any compression speed even though the plasticity is less than 100% PEG (Fig. 4). The *NWF* combines tensile strength and the deformation during diametral testing. Tablet deformation is not affected by increasing the amount of PEG between 80 and 100% (Tukey's test) and the decrease in the *NWF* is due solely to a decrease in tensile strength (Fig. 8).

The relationship between *NWF* and Plastic Energy (*PE*) at different compression speeds is shown in Fig. 9. The *PE* energy required to form the tablets increased with speed (Tukey's test). More energy is required to overcome the increased cohesiveness of particles occurring at higher speeds. The PE required to form PEG compacts is higher than that required to form DCP compacts and this is apparent at the highest compression speed (500 mm s^{-1}). It is probable

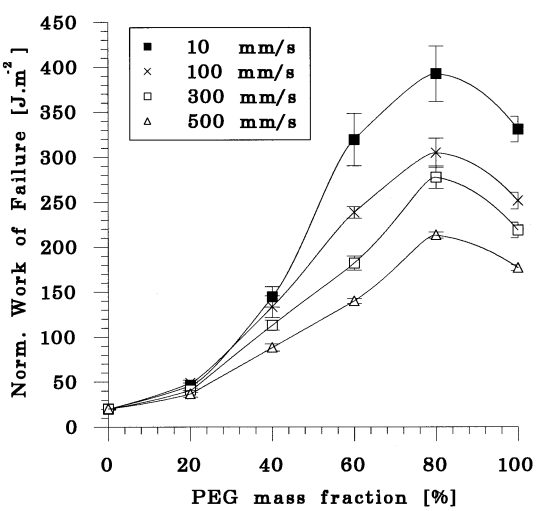


Fig. 6. The effect of compression speed on the normalized work of failure of PEG/DCP mixtures.

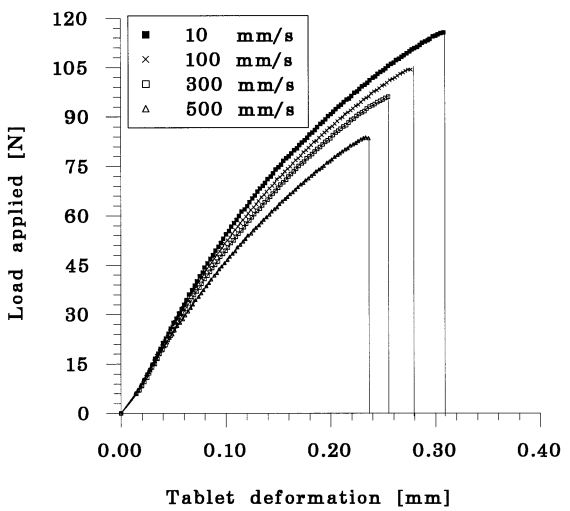


Fig. 7. The effect of compression speed on tablet strength of PEG 10000.

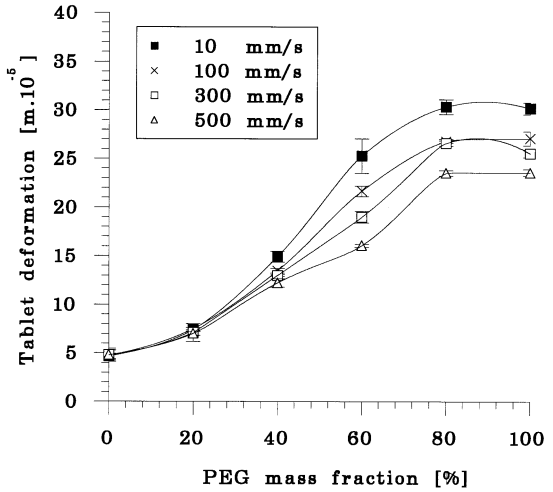


Fig. 8. The effect of compression speed on tablet deformation during diametral testing of PEG/DCP mixtures.

that some of this extra energy has been used to generate more plastic deformation and subsequent bonding, with a much higher *NWF* for PEG. Indeed 100% PEG consumes more energy and produces tablets with a lower toughness compared to the mixture containing 80:20 PEG/DCP (%).

Higher values of plastic energy do not always mean robust tablets. An important parameter to consider is the ratio between plastic energy and

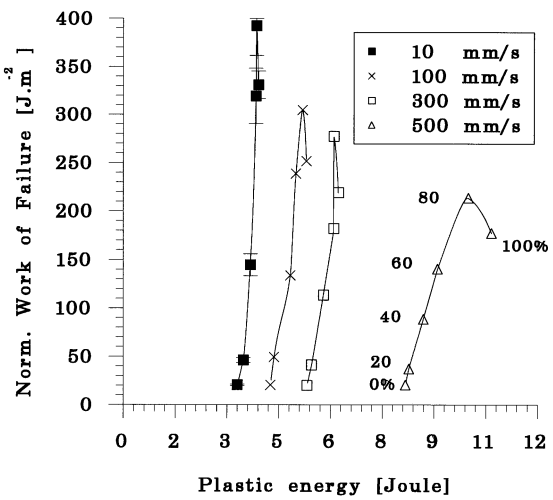


Fig. 9. Relationship between normalized work of failure and plastic energy at different compression speeds and with increasing PEG content.

Table 3
The effect of compression speed and mass fraction of PEG on the Plastic energy/Work of failure quotient [*PE*/*WF*]

% PEG	Compression speed (mm s^{-1})			
	10	100	300	500
0	3.65 ± 0.20	4.79 ± 0.23	6.04 ± 0.43	9.09 ± 0.15
20	1.56 ± 0.10	1.89 ± 0.11	2.79 ± 0.04	4.77 ± 0.64
40	0.50 ± 0.03	0.71 ± 0.05	0.95 ± 0.04	1.88 ± 0.13
60	0.22 ± 0.01	0.37 ± 0.00	0.59 ± 0.02	1.14 ± 0.02
80	0.15 ± 0.01	0.27 ± 0.01	0.35 ± 0.03	0.72 ± 0.03
100	0.17 ± 0.01	0.30 ± 0.01	0.41 ± 0.02	0.85 ± 0.05

Values are expressed as $[PE/WF] \times 10^3 \pm$ S.D.

the crushing strength, tensile strength or work of failure values providing all the tablets are tested with the same instrument and under the same conditions. The lower this ratio, the better the compactibility (i.e. the material consumes less energy and produces stronger tablets). This *PE*/*WF* quotient is shown in Table 3. Work of failure (*WF*) was used instead of *NWF* in order to obtain a dimensionless ratio. Two-way analysis of variance showed that the *PE*/*WF* ratio is affected by compression speed and PEG content. According to Table 3, the mixture containing 80% PEG is the most compactible. It consumed less energy but still produced the toughest tablets.

4. Conclusion

The effect of compression speed on the compaction properties of PEG, DCP and their mixtures have been investigated.

The relative density (D_0) of a powder bed when the first measurable pressure is applied, increased with PEG content and decreased with compression speed. DCP particles are rough, likely to interlock and consequently offer more resistance to rearrangement and slippage. Increasing the amount of PEG increased D_0, probably due to the smooth surface of PEG particles reducing interparticulate friction.

The interaction between PEG and DCP with respect to mean yield pressures was found to depend on the compression speed. At low speed,

the mean yield pressure was found to decrease linearly with increasing PEG content, suggesting no interaction between PEG and DCP during compression. At higher speeds, positive deviation indicated that fragmentation of DCP dominated the compressibility. The strain rate sensitivity (SRS) increased with PEG content suggesting that the mixtures become more plastic and consequently more sensitive to compression speed.

The tensile strength of PEG was higher than DCP at any compression speed. The incorporation of PEG in the mixtures brings an increase in plasticity, leading to an increased area of true contact between particles and/or a reduction in the number of weak bonds DCP–DCP (Duberg and Nystrom, 1985). Mixtures between 60 and 80% PEG (w/w) produced tablets with the highest tensile strength at any compression speed. Fragmentation of DCP within the PEG does occur (Larhrib and Wells, 1997b), which allows an increased number of physical bonding sites.

Brittle DCP showed no change in normalized work of failure (*NWF*) with increasing compression speed. Conversely plastic PEG showed a decrease in tablet toughness as the compression speed increases, suggesting an increase in brittle behaviour.

Tablet toughness increases with PEG content and the toughest tablets were produced from mixture containing 80:20 PEG/DCP (%) at any compression speed. Tablet deformation is not affected by increasing the amount of PEG between 80 and 100% and the decrease in tablet toughness is due solely to a decrease in the tensile strength.

High plastic energy (*PE*) does not always mean hard tablets. What should be considered is the ratio between plastic energy and tensile strength or plastic energy and work of failure (*PE*/*WF*). This ratio increased with compression speed and decreased with increasing PEG concentration. A lower ratio suggests better energy utilisation. This was found in the case of a mixture containing 80:20 PEG/DCP (%) which produced tablets of high strength at any compression speed.

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