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Polyethylene glycol and dicalcium phosphate mixtures: effect of tableting pressure

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Abstract

The effect of compression pressure on Polyethylene glycol 10 000 (PEG): Dicalcium phosphate (DCP) mixtures has been evaluated. The tensile strength increased with PEG content exhibiting a maxima between 40 and 80% w/w PEG depending on the compression pressure. Similar strengths could be obtained using lower pressures however higher amounts of PEG was required. PEG densified rapidly and increasing the pressure above 82 MPa has no effect on plastic energy whilst only a small increase in tensile strength was observed. Above 82 MPa, asperity melting probably occurred. DCP expended less energy in tablet expansion than PEG or their mixtures, whilst at higher pressures the plastic energy for DCP was the greatest. However the tensile strength of DCP was smaller than that of PEG and their mixtures at any compression pressure. At higher pressure, extensive fragmentation of DCP occurred and a large number of contact points were created. Although the area of contact was greater, the amount of energy involved for bonding on each contact point was smaller and consequently the bonds formed between particles were weak and the compact has low strength. The tablets containing 80% PEG:20% DCP produced the best tablets, consuming the smallest energy while producing tablets that were mechanically tough. This study showed that mixtures of a brittle material (DCP) and a plastic material (PEG) produced tablets with higher tensile strengths than those made from the pure materials alone. © 1997 Elsevier Science B.V.

Keywords: Polyethylene glycol 10 000; Dicalcium phosphate; Binary mixture; Compression pressure; Tensile strength; Gross energy; Plastic energy; Elastic energy; Asperity melting; Tablet deformation; Work of failure

1. Introduction

The polyethylene glycols (PEGs) are a series of water soluble synthetic polymers used in phar-

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macy as excipients for suppositories, ointments, suspensions and capsules. In tableting, PEG is used as a flow agent, lubricant, dry binder (Wehrle et al., 1988), wet granulating agent (Ford, 1980) and as a plasticizer (Wells et al., 1982; Aulton et al., 1985). Their mechanical properties vary according to molecular weight. In practice, two or more compression aids are blended together because tablet appearance and their hardness is often better than the individual excipients (Wells and Langridge, 1981).

The choice of PEG 10 000 rather than other molecular weight PEG was dictated by its superior mechanical properties (Larhrib et al., 1997). Furthermore, Larhrib and Wells (1997) studied thermal history and found that slow cooled PEG 10 000 exhibited even better compressibility and produced tablets with higher tensile strength than untreated and quench cooled material. Slow cooled PEG 10 000 is an excellent choice of carrier.

Sometimes a small amount of PEG is introduced into a formula to improve rheological properties, as a lubricant or to improve cohesion within the tablet. To date, PEGs are rarely used as a major component. This work investigates the compaction properties of mixtures of a plastic and soft material, PEG (Lin and Cham, 1995; Larhrib et al., 1997) and a fragmenting material, dicalcium phosphate (Emcompress®; David and Augsburger, 1977; De Boer et al., 1978) using tensile strength, energy analysis and work of failure. The longer term strategy is to investigate the tableting of liquids using PEG 10 000 as the principal carrier.

2. Materials and methods

2.1. Materials

Polyethylene glycol (PEG 10 000) Merck Schuchardt, Germany.

Dicalcium phosphate dihydrate (Emcompress®) E. Mendell, New York.

2.2. Methods

2.2.1. Preparation of heat-treated, slow cooled PEG 10 000

PEG 10 000 was held at 100°C for 30 min using a calibrated, electronically controlled oven (Memmert SE 400: Schwabach, Germany) and then cooled naturally to room temperature. The sample was stored over phosphorus pentoxide (B.D.H., Poole, UK) for 24 h before grinding.

2.2.2. Particle size fraction

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

2.2.3. Blending

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

2.2.4. Compression

Compression was carried out using a high speed compaction simulator (ESH Testing, Brierley Hill, West Midlands, UK), fitted with 12.5 mm diameter, flat faced punches. A sawtooth time displacement profile was used to control both upper and lower punches. Details of the simulator have been published elsewhere (Nokhodchi et al., 1995a,b). 500 mg of powder was used for each sample. Tablets were compressed at 10 mm/s and pressures of 41, 82, 123 and 164 MPa. Before each compression, the punches and die were cleaned with acetone and brushed with 2% w/v stearic

acid in chloroform providing external lubrication. During compression, upper punch load and punch separation were monitored to a precision of ± 0.012 kN and ± 4.9 μm respectively.

2.2.5. 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 calculate gross and elastic energies (Nokhodchi et al., 1995b).

2.2.6. Tablet porosity

The thickness and diameters of tablets were measured 24 h after ejection using a micrometer and the weight measured to ± 0.1 mg. The percentage porosity ϵ was calculated using:

$$\epsilon = (1 - V_0/V) \times 100$$

where V is the tablet volume and V_0 the volume of the material at zero porosity. The porosity was the average of four determinations.

2.2.7. Tablet testing

24 h after ejection, the tablet weight and dimensions were recorded and the crushing strength, diametral deformation and work of failure (Rees and Rue, 1978) were measured using a compression tester (Type LR 30K, Lloyd, Fareham, UK). The rate of platten movement was 3 mm/min. The tensile strength was calculated according to Fell and Newton (1970).

2.2.8. Scanning electron microscopy (SEM)

The tablet made at a compression pressure of 164 MPa and containing 60% PEG: 40% DCP was totally immersed in 95% ethanol and left for 24 h to ensure all the PEG particles dissolved. The resulting suspension was mixed and a sample examined by Scanning Electron Microscopy (Jeol Model JSM T200, Tokyo, Japan). The size of the particles in this suspension was compared to that of the original DCP powder (i.e., 250–355 μm sieve size).

2.2.9. Particle size distribution after the compaction

In order to have an idea on the extent of fragmentation of DCP particles within the tablet containing 60% PEG:40% DCP, the suspension already prepared (Section 2.2.8) was wet sieved through an 63 μm sieve. The fraction passing through the sieve was collected in an evaporating basin and dried in an oven at 105°C. Material with particle size less than 63 μm was calculated by subtracting the weight of the evaporating basin from the weight of evaporating basin plus dried particles. The fraction retained on the sieve was dried at 105°C then cooled and sieved through 250, 125 and 63 μm sieves using a sieve stack shaker for 10 min with an amplitude of 1 mm on a sieve shaker (Fritsch-Analysette 3, Idor-Oberstein, Germany). The fraction retained on each sieve were weighed.

3. Results and discussion

The effect of compression pressure on the tablet porosities of PEG–DCP mixtures is shown in Fig.

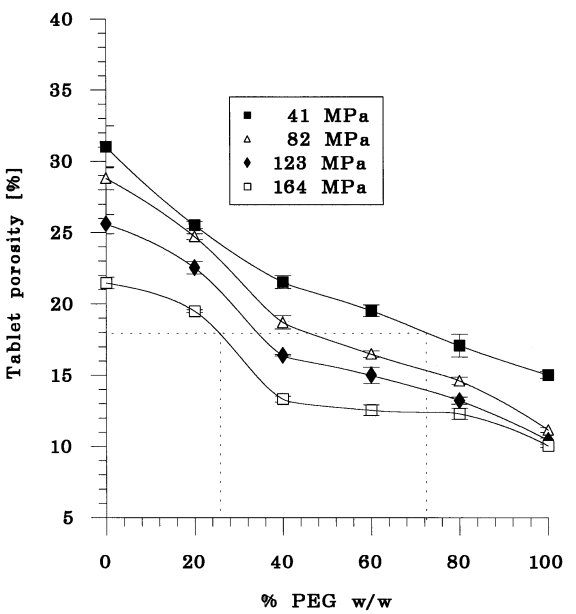

Fig. 1. The effect of compression pressure on tablet porosity of PEG, DCP and their mixtures.

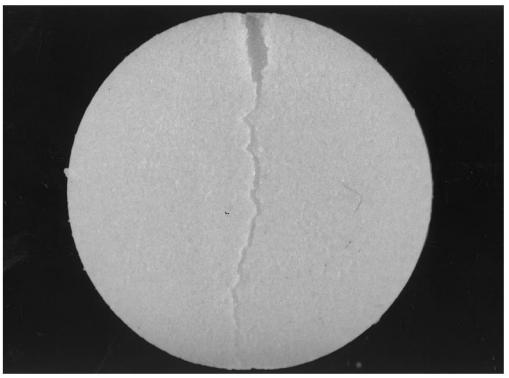

Fig. 2. Tensile failure of PEG 10 000 tablet induced by the diametrical compression test (note characteristic flattening at the pattern surfaces).

1. Pure PEG showed the lowest porosity values at any compression pressure in comparison with the pure DCP and their mixtures. PEG is a very plastic material (Larhrib et al., 1997) and its incorporation in the mixtures brings about an increase in the compressibility of the blend (Larhrib and Wells, 1997) leading to a decrease in tablet porosity. The greatest decrease in tablet porosity of pure PEG was observed between 41 and 82 MPa, while increasing the compression pressure above 82 MPa had no further significant effect. The compacts containing a low amount of PEG were less compressible, suggested by the highest porosity values and higher pressure required to bring about their densification. For example to obtain a tablet porosity of 18%, a pressure of 164 MPa was required at 26% PEG, whilst a pressure of 41 MPa was required when the PEG content was 72% (Fig. 1).

PEG is a soft material shown by the flattening of the tablet at the platten surface, but also failed in tension, suggesting that PEG is strong enough to resist fracture when subjected to tensile testing (Fig. 2). The relationship between tensile strength and PEG content at different compression pressures is shown in Fig. 3. The tensile strength increased with PEG content and maximum tensile strength was observed between 40 and 80% of PEG depending on the maximum pressure used. Tablets made at compression pressures between 41 and 123 MPa showed a maximum tensile strength at 80% w/w PEG and those made at 164 MPa reach a plateau from 40 to 80% w/w PEG followed by a decrease with further increases in PEG content. This shift was also observed for dicalcium phosphate–phenacetin (Newton et al., 1977) and for dicalcium phosphate–microcrystalline cellulose mixtures (Wells and Langridge, 1981).

PEG shows a rapid increase in tensile strength with increasing compression pressure in the range 41 to 82 MPa, increasing the pressure above this range brought about a smaller increase in the tensile strength as the tablet approached minimum porosity. The mixtures containing low amounts of PEG are less compressible and need a higher pressure to achieve the same tensile strength. As Fig. 3 shows, a compact containing 60% w/w PEG and compressed at 41 MPa has a similar tensile strength to that of a tablet containing 0 and 20% w/w PEG using a compression pressure of 164 and 123 MPa respectively. Using higher amounts of PEG leads to the requirement of maximum lower compression pressures and thereby reducing tablet machine wear.

Gross energy comprises the friction with the die wall, the amount of work required for elastic and plastic deformation of the particles and for the

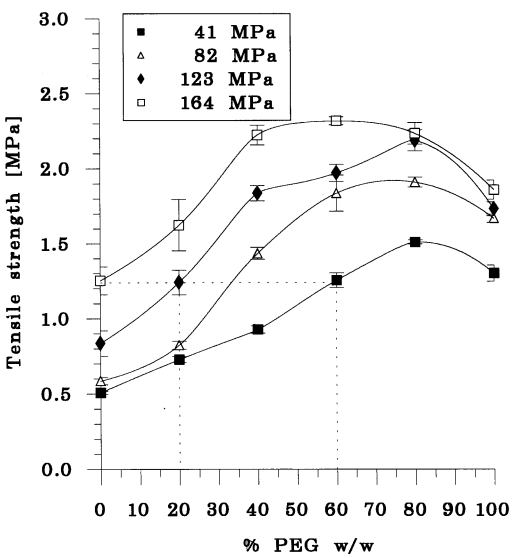

Fig. 3. Effect of compression pressure on the tensile strength of PEG, DCP and their mixtures.

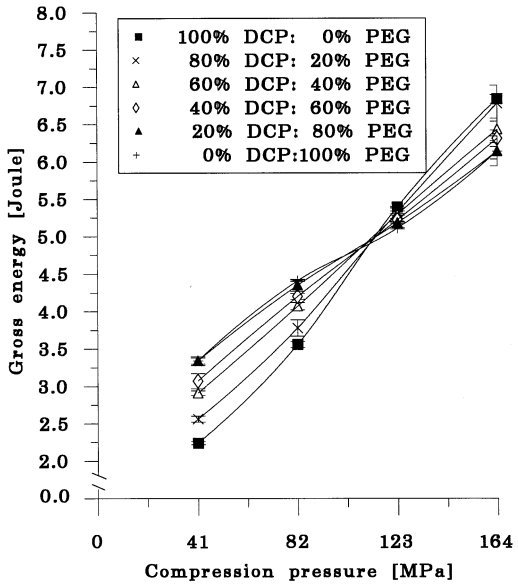

Fig. 4. The effect of compression pressure on the gross energies of PEG, DCP and their mixtures.

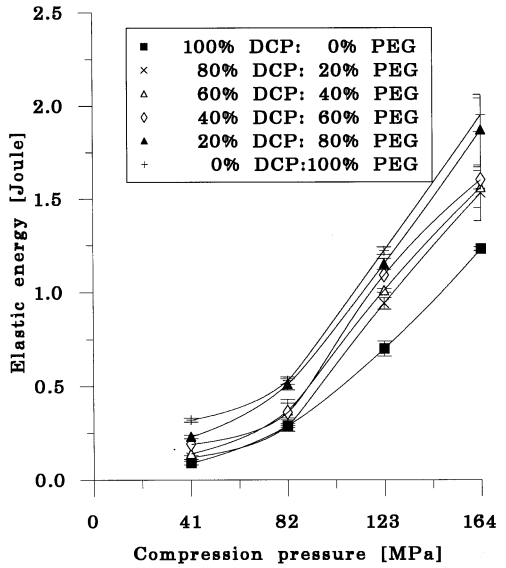

Fig. 5. The effect of compression pressure on the elastic energies of PEG, DCP and their mixtures.

formation of bonds between the particles (De Blaey et al., 1971). The relationship between gross energy, compression pressure and PEG content is shown in Fig. 4. As expected, increasing the compression pressure resulted in an increase in the gross energy, while increasing the PEG level results in an increase or decrease in the gross energy depending on pressure.

At low pressures (41–82 MPa) the gross energy increased with PEG content. Most of the energy was used for particle deformation and the formation of bonds and this is reflected by the low elastic energy (Fig. 5) and greater plastic energy (Fig. 6). Gillard et al. (1977) reported that the energy taken up by the tablet (plastic energy) increases when a plastic material is added to a fragmenting material because more energy is needed to maintain plastic deformation and bond formation. The results obtained by the present authors support these findings only at low pressures (41–82 MPa). Above 82 MPa the increase in gross and plastic energies with compression pressure was greater as the concentration of PEG was reduced. The graphs intersect at 105 MPa at which pressure the properties of DCP begin to predominate. Since DCP is more resistant to densification than PEG higher pressure and energy was required. The additional gross energy supplied to pure PEG above 82 MPa was seen as an

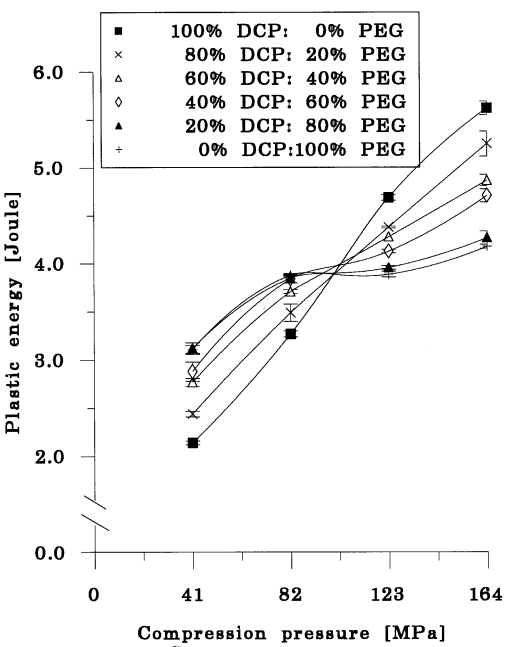

Fig. 6. The effect of compression pressure on the plastic energies of PEG, DCP and their mixtures.

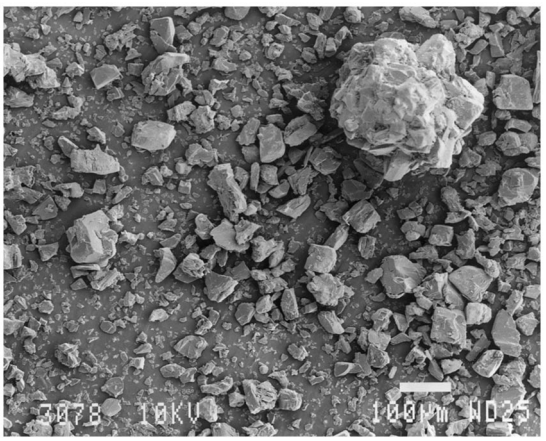

Fig. 7. DCP particles after compression with PEG and an original Emcompress particle for comparison.

increase in elastic energy (Fig. 5). This elastic energy caused tablet expansion such that after 24 h the tablet increased to at least 10% porosity. With the DCP:PEG mixtures the additional gross energy above 82 MPa must have been used by DCP in undergoing fragmentation and bonding (as suggested by the increase in tensile strength, Fig. 3) and as a result less elastic energy was observed with increased DCP content (Fig. 5).

Tablet strength depends on the applied load which determines the degree of fragmentation of particles and the number of new contact points created. This is confirmed by the linear relationship between tablet hardness and compression pressure (Rees and Rue, 1978) for DCP. This may explain the increase in tensile strength with compression pressure for the DCP:PEG mixes. The fragmentation of DCP in the mixtures was confirmed by comparing DCP particles, after compression (Fig. 7) which were much smaller than the original particles, confirming that DCP was not embedded and protected in a plastic tablet matrix but fragmented during compression. This fragmentation of DCP gave rise to a change in the percent frequency distribution by weight. The sieve size of the original DCP particles was in the range 250–355 μm, however after compression, it was found that 8%w/w of DCP particles were ≥ 250 μm, 27% were in the range 125–250 μm, 18% were in the range 63–125 μm, whilst the major proportion (47%) were less than 63 μm.

Melting of asperities has been reported to contribute to the densification process by a combination of frictional heat and the lowering of melting point of the material caused by high pressure (Rankell and Higuchi, 1968; York and Pilpel, 1972). When the pressure is released, welded bonds form, contributing to the strength of the tablets (Esezobo and Pilpel, 1986). As the temperature within the tablet increased, plasticity and stress relaxation increased, while elasticity decreased. PEG has a low melting point of approximately 67°C and the tablet regions experiencing greatest localised temperature rises were those in contact with the punch and die wall and this was seen by the formation of a flaky film at the edge of the tablet at compression pressures above 80 MPa (Larhrib et al., 1997). Melting of PEG 10 000 during compression was supported by the same transparent film around the die holder, the punch tip and the punch shanks and was noted for high molecular weight PEG 35 000 when compressed to 164 MPa and at a compression speed of 300 mm/s (Larhrib et al., 1997). Fassihi (1986, 1988) found complete melting of PEG 6000 at compression pressures above 120 MPa, while in this investigation complete rupture of the compact occurred only if higher pressures (287 MPa) and speeds (600 mm/s) were used in combination (Fig. 8).

Adolfsson and Nystrom (1996) reported an increase in elastic recovery of PEG 8000 even at an extremely high applied load of 1200 MPa. No

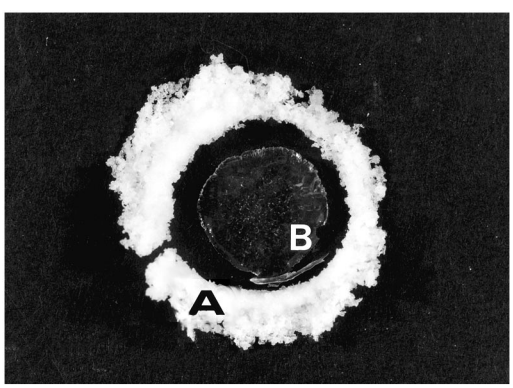

Fig. 8. Extruded halo of PEG (A) with transparent film (B) from punch surface.

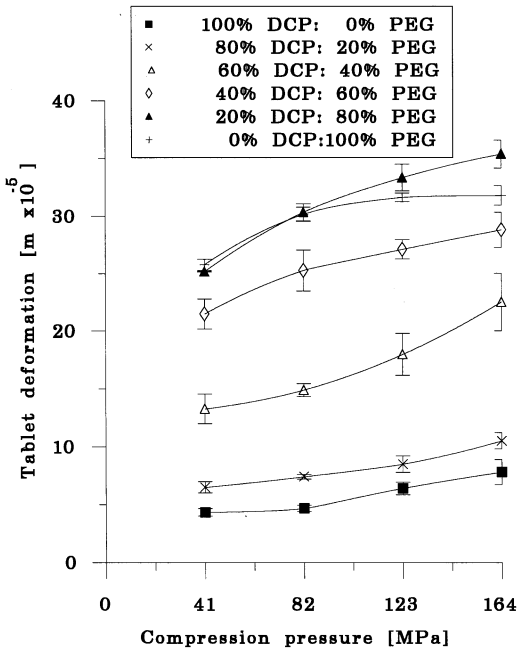

Fig. 9. The relationship between tablet deformation during diametral testing and compression pressure of PEG, DCP and their mixtures.

decrease in tablet strength occurred at a compression pressure above 82 MPa for PEG and mixtures, suggesting that bonds are strong enough to resist elastic recovery.

The relationship between tablet deformation and compression pressure of PEG, DCP and their mixtures is shown in Fig. 9. PEG deforms plastically during compression, forms robust tablets and requires a greater platten displacement before tablet failure. In contrast, DCP, which is brittle material, forms tablets of low strength and a small amount of upper platten displacement causes tablet fracture and failure (Fig. 10).

DCP shows little change in tablet deformation with increasing compression pressure. DCP is a fragmenting material and increasing compression pressure increases the number of brittle interparticulate bonds. All mixtures were intermediate between DCP and PEG with exception of the tablets containing 80% PEG:20% DCP where greater deformation before failure occurred especially at higher compression pressure suggesting better bonding between PEG and DCP as confirmed by tensile strength data.

The relationship between work of failure and plastic energy for PEG, DCP and their mixtures with varying compression pressure is shown in Fig. 11. It was assumed that the work of plastic deformation or a certain fraction of it was used for bond formation, which would explain the good correlation between net work and tablet crushing strength (De Blaey et al., 1971). Plastic energy increases with PEG level especially at 41 and 82 MPa and form tough tablets. DCP showed the highest value of plastic energy when compressed at 164 MPa. However, the work of failure does not show any significant increase over the tablets made at 41 MPa. At higher pressures, extensive fragmentation of DCP occurred (Fig. 7) and a large number of contact point are created (Duberg and Nystrom, 1982). Although this energy is greater, it acts over a larger number of contact points hence the amount of energy involved for bonding on each contact point is smaller and consequently the bonds formed between particles are weak to give a tablet of low strength.

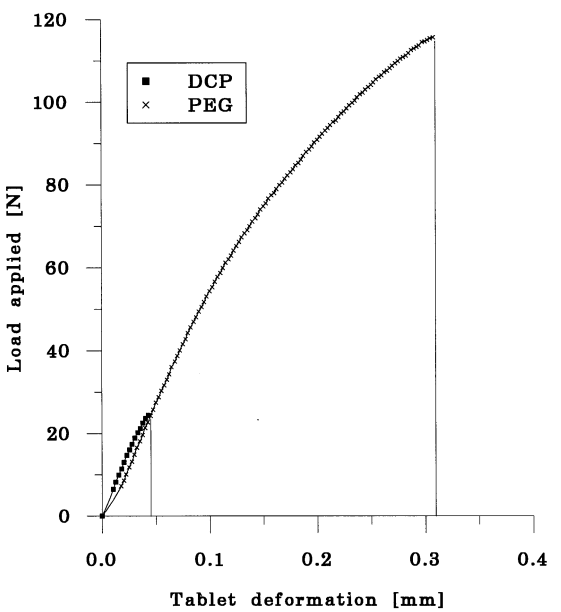

Fig. 10. Tablet deformation vs load applied during diametral testing for plastically deforming PEG and brittle material DCP.

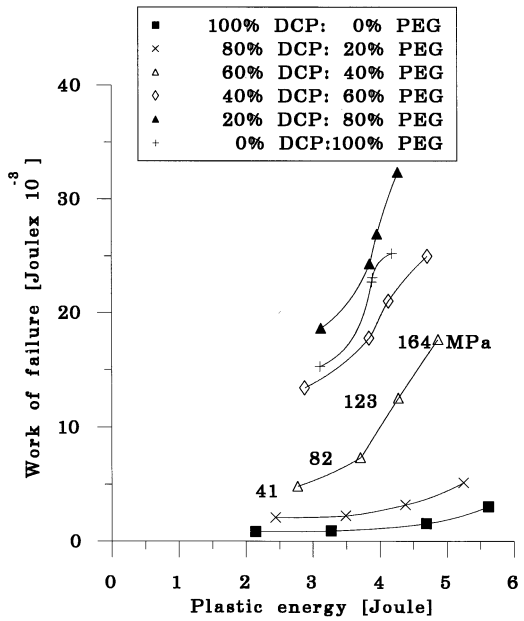

Fig. 11. Relationship between the plastic energy and work of failure of the compacts made from PEG, DCP and their mixtures.

Plastic energy (PE) is not always associated with the formation of hard tablets, for example DCP tablets made at a compression pressures between 123 and 164 MPa, exhibited highest values of plastic energy compared to all other materials (Fig. 6). However, the corresponding tensile strength of its compacts was the lowest of all materials (Fig. 3). Of course, calculation of PE/TS ratio showed DCP to exhibit the highest values at any compression pressure, this suggests that DCP consumed more energy but produced the weakest tablets. The parameter, work of failure (Rees et al., 1977) was used in this work rather than tensile strength because it has been found to be more useful property than breaking strength to quantify the resistance of tablets to mechanical failure (Rees et al., 1977; Larhrib and Wells, 1997). Furthermore, the PE/WF ratio is dimensionless.

The efficiency of the work applied could be estimated by the PE/WF ratio. The mixture containing 80% PEG: 20% DCP showed the lowest values at any compression pressure (Table 1) suggesting that less energy is required for making tablets of sufficient strength.

4. Conclusion

The extent of consolidation and bonding of PEG:DCP depended on the concentration of PEG and the compression pressure. Similar strengths could be obtained using lower pressures however higher amounts of PEG was required.

DCP forms tablets of low strength compared to PEG and a small amount of upper platten displacement causes tablet failure. The tablets containing 80% PEG:20% DCP produced the most efficient tablets, consuming the smallest energy while producing tablets that were mechanically tough. This study showed that mixtures of a brittle material (DCP) and a plastic material (PEG) produced tablets with higher tensile strengths than those made from the pure materials alone.

Table 1
The effect of compression pressure and the PEG content on the plastic energy:work of failure quotient [PE/WF]

Proportion of PEG [%]	$[PE/WF] \times 10^3 \pm$ S.D.			
	Compression pressure [MPa]			
	41	82	123	164
0	2.56 ± 0.14	3.62 ± 0.18	3.03 ± 0.24	1.87 ± 0.22
20	1.18 ± 0.04	1.57 ± 0.12	1.42 ± 0.29	1.04 ± 0.17
40	0.58 ± 0.06	0.51 ± 0.03	0.35 ± 0.04	0.28 ± 0.03
60	0.22 ± 0.02	0.22 ± 0.02	0.20 ± 0.01	0.19 ± 0.00
80	0.17 ± 0.01	0.16 ± 0.01	0.15 ± 0.01	0.13 ± 0.01
100	0.20 ± 0.01	0.17 ± 0.01	0.17 ± 0.01	0.17 ± 0.00

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