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Compressing polyethylene glycols: the effect of compression pressure and speed

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Abstract

The effect of compression speed and pressure on the compaction properties of PEG 1500 (1638), 4000 (4129), 6000 (6343), 10000 (12774), 20000 (23494) and 35000 (34650) were investigated. Heckel analysis, pressure at zero porosity, crushing strength, tablet porosity, gross and net energy and net energy/crushing strength ratio have been investigated using a compaction simulator. Resistance to densification increases with molecular weight and compression speed and was confirmed by the increase in the mean yield pressure and the pressure at which they reach zero porosity and the increase in gross energy. PEGs have a melting range of approximately 48–67°C and increasing compression speed makes asperity melting more likely. Resolidification of melted material increases bonding which limits the disruptive effect of any elasticity. At any compression speed, low molecular weight PEGs undergo greater densification and form compacts of low porosity. Consistent with the time dependency of plastic materials, at any molecular weight the tablets made at 10 mm/s were harder than those made at 300 mm/s. PEG 12774 gave the hardest tablets at all compression speeds. However, compressibility was less than lower molecular weight PEGs. The crushing strengths suggested that plastic deformation is not directly responsible for the harder tablets. PEG 34650 is less plastic, but more resistant to densification and formed tablets with the highest porosity and produced the weakest tablets. A good correlation was found between the plastic energy/crushing strength ratio and compression speed and an equation is proposed to describe the relationship. The compactibility of the material may be estimated from the slope. The lowest slope was found for PEG 12774 and the highest for PEG 34650. © 1997 Elsevier Science B.V.

Keywords: Polyethylene glycol; Molecular weight; Compressibility; Compression pressure; Compression speed; Crushing strength; Porosity; Gross energy; Plastic energy

1. Introduction

The consolidation of powder to form a dense compact requires deformation and an increase in

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interparticulate contact. Under compression, materials undergo complex stresses. This causes successive and simultaneous rearrangement, elastic and plastic deformation, fracture, the forming and breaking of interparticulate bonds, and cold sintering, etc. Which process prevails depends on the physical characteristic and structure of the consolidating material (Nesic, 1987) and polymers behave differently from crystalline materials. Although polymers have played an important role in the development of sustained release delivery systems, the only pharmaceutical polymer to be extensively investigated is microcrystalline cellulose (Sixsmith, 1995; Roberts and Rowe, 1987). More recently investigators have studied the compaction properties of other polymers such as hydroxypropylmethylcellulose (Nokhodchi et al., 1994; Malamataris et al., 1994), ethylcellulose (Nesic, 1987; Upadreshta et al., 1994), and polyethylene glycol (Al-Angari et al., 1985; Lin and Cham, 1995).

The compaction properties of PEGs varies since they range from soft, plastic material at lower molecular weights to hard brittle material at higher values. From the literature, it appears little work has been done on their compaction properties (Al-Angari et al., 1985; Blattner et al., 1986; Lin and Cham, 1995). The incorporation of a large amount of PEGs may cause capping following compression (Ravis and Chen, 1981).

The present work investigates PEGs in the molecular weight range 1638–34 650 and compression pressure and speed to choose a suitable carrier(s) for the formulation of solid dispersions and the tabletting of liquids.

The effect of compression pressure over the range 41–164 MPa and compression speed from 10–300 mm/s on the compression properties of PEG 1500, 4000, 6000, 10 000, 20 000 and 35 000 using a high-speed compaction simulator has been investigated.

2. Materials and methods

Six samples of PEG with labelled average molecular weights of 1500, 4000, 6000, 20 000, were supplied by BDH Laboratory, Poole, UK, whilst PEG 10 000 and 35 000 were supplied by Merck Schuchardt, Germany. All the samples, in the form of flakes were milled and separated by sieving to yield a 250–355 μm fraction. Due to the low melting point of PEGs (48–67°C) a low drying temperature had to be used: 37°C was satisfactory. The true density was determined using a Bechman air pycnometer model 930 ($n = 5$).

2.1. *Differential scanning calorimetry*

Model DSC-7 (Perkin Elmer, Beaconsfield, UK) was controlled by a Perkin Elmer TAC7. The equipment was calibrated using indium and zinc. Samples of 4–6 mg were weighed into aluminium pans (40 μl Perkin Elmer, Norfolk, UK) using an AV/WE Analytical balance (Oertling, Smethwick, UK), the pans were sealed hermetically. The samples were heated at 10°C/min under nitrogen. An empty pan was used as a reference. Melting points were calculated by the instrument ($n = 4$).

2.2. *Compression*

Compression was carried out using a high speed compaction simulator (ESH Testing, West Midlands, UK), fitted with 12.5-mm flat faced punches. A sawtooth time displacement profile

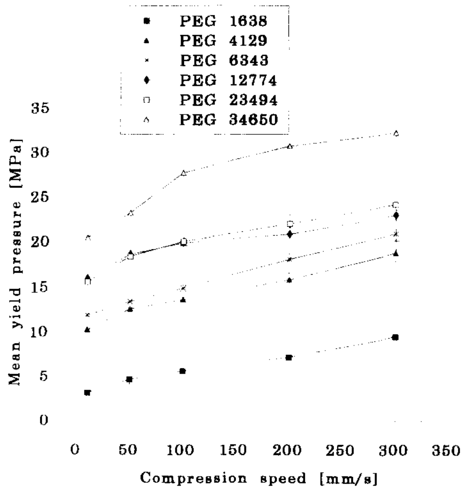

Fig. 1. The effect of the compression speed and molecular weight on the mean yield pressure of PEG (250–355 μm) compacts, made at a compression pressure of 82 MPa.

Table 1
The effect of compression speed on the pressure at zero porosity of PEG compacts of different molecular weights made at a compression pressure of 82 MPa

Compression speed (mm/s)	PEG 1638	PEG 4129	PEG 6343	PEG 12 774	PEG 23 494	PEG 34 650
Pressure at zero porosity (MPa)						
10	7.96 ± 0.27	31.25 ± 0.23	32.42 ± 0.45	37.77 ± 1.21	36.80 ± 0.10	51.50 ± 0.65
50	11.79 ± 0.10	35.23 ± 0.19	36.93 ± 0.52	41.60 ± 0.83	40.42 ± 0.55	57.00 ± 1.07
100	15.18 ± 0.81	39.86 ± 0.59	41.56 ± 0.41	43.43 ± 0.52	45.54 ± 0.61	60.81 ± 1.34
200	22.21 ± 1.20	42.30 ± 1.41	44.93 ± 1.40	48.97 ± 0.83	49.82 ± 0.79	63.09 ± 1.23
300	29.74 ± 1.32	46.51 ± 0.11	48.27 ± 1.17	52.46 ± 0.91	53.96 ± 0.56	67.48 ± 0.68

Results are the means ± S.D. of four determinations.

was used to control both upper and lower punches. Powder (0.4 g) was used for each molecular weight. To examine the effect of compression speed, the compression pressure was held constant at 82 MPa varying compression speeds at 10, 50, 100, 200 and 300 mm/s. At a compression speed of 10 mm/s, compression pressures of 41, 82, 123 and 164 MPa were used. Before each compression, the punches and die were cleaned with acetone and brushed with 2% w/v of stearic acid in chloroform providing external lubrication. During compression, upper punch load and punch separation were monitored to an accuracy of ± 0.05 kN and 0 ± 12 μm, respectively (Bateman et al., 1989).

2.3. Tablet crushing strength

Tablet crushing strength was determined by diametral compression on a motorised tablet hardness tester (Model 2E, Schleuniger, Switzerland). Tests were carried out 24 h after ejection ($n = 4$).

2.4. 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:

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

where V is the tablet volume and V_0 the volume of the material at zero porosity ($n = 4$).

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) is used to perform Heckel gross and net work of compaction analysis (Nokhodchi et al., 1995). All data were statistically analysed using a two way analysis of variance and Tukey's multiple comparison test. Results are significant at $p < 0.05$.

3. Results and discussion

The average molecular weight (MW) for six grades of PEG were determined using matrix assisted laser desorption/ionisation (MALDI) in Reflectron mode (Larhrib et al., 1997). The molecular weights determined were: 1500 (1638); 4000 (4129); 6000 (6343); 10 000 (12 774); 20 000 (23 494); 35 000 (34 650).

The compressibility of pharmaceutical powders can be estimated from the mean yield pressures evaluated from Heckel (1961) analysis. The mean yield pressure was obtained as a reciprocal slope over the best-fit pressure range of 3–23 MPa for all PEGs. Fig. 1 shows the relationship between compression speed, molecular weight and mean yield pressure. The increase in the mean yield pressure with compression speed is due to a reduction in the amount of plastic deformation

Table 2
The effect of compression speed on the gross energies of PEG compacts of different molecular weights made at a compression pressure of 82 MPa

Compression speed (mm/s)	PEG 1638	PEG 4129	PEG 6343	PEG 12 774	PEG 23 494	PEG 34 650
Gross energy (J ± S.D.)						
10	1.79 ± 0.08	3.47 ± 0.04	4.05 ± 0.05	4.94 ± 0.11	4.78 ± 0.09	4.71 ± 0.09
50	2.37 ± 0.09	3.71 ± 0.10	4.22 ± 0.09	5.44 ± 0.09	5.35 ± 0.08	5.45 ± 0.08
100	2.75 ± 0.07	4.08 ± 0.05	4.52 ± 0.06	5.84 ± 0.06	5.70 ± 0.05	6.16 ± 0.09
200	3.56 ± 0.08	4.47 ± 0.18	5.13 ± 0.10	6.61 ± 0.05	6.51 ± 0.08	6.98 ± 0.01
300	3.80 ± 0.05	4.89 ± 0.17	5.65 ± 0.15	6.92 ± 0.12	7.08 ± 0.09	7.54 ± 0.28

Results are the means ± S.D. of four determinations.

(Roberts and Rowe, 1985). Two way analysis of variance showed that compression speed and molecular weight interact together leading to an increase in the mean yield pressure ($p < 0.05$) and contribute to the reduction in plastic deformation and increase in brittleness. Even PEG 34 650 when compressed at the highest compression speed (300 mm/s) exhibited a mean yield pressure which is low (32.22 MPa) indicating that PEGs deform mainly by plastic deformation. Tukey's test showed that there was no significant difference in the mean yield pressures of PEG 12 774 and PEG 23 494.

The rank order of compressibility was PEG 1638 > 4129 > 6343 > 12 774 ≃ 23 494 > 34 650. The results suggest that lower molecular weights are more compressible than the higher molecular weights which agree with the findings of Al-Angari et al. (1985).

All grades of PEG showed increasing resistance to densification with increasing compression speed and molecular weight as shown in Table 1. Two way analysis of variance showed that the effect of molecular and compression speed on the pressure necessary to reach zero porosity were significantly different ($p < 0.05$). Rees and Rue (1980) suggested that particle strength increases by several orders of magnitude at higher speeds resulting in an increased particulate resistance to deformation. The higher molecular weights are less plastic and need more pressure to deform.

The resistance to densification caused by increasing the compression speed, and molecular weight may account for the increase in the gross energy (Table 2). As compression speed and molecular weight increase, more energy is needed to overcome elastic deformation, reducing plastic

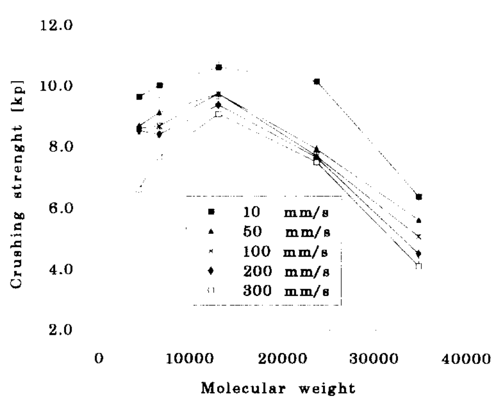

Fig. 2. The effect of the molecular weight and compression speed on the crushing strength of PEG (250–355 μm) tablets made at a compression pressure of 82 MPa.

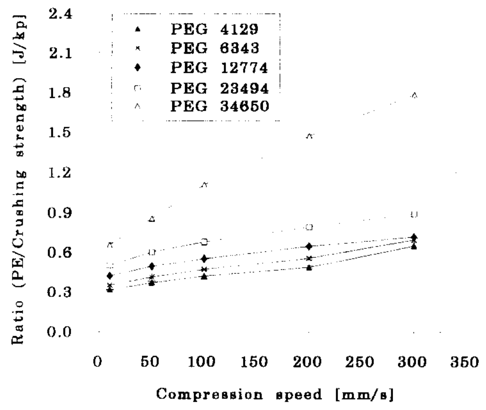

Fig. 3. The relationship between compression speed and the ratio (PE/CS) for different grade of PEGs, made at a compression pressure of 82 MPa.

Table 3
Plastic energy: crushing strength quotient (PE/CS) and punch velocity (v) for different PEGs

PEG	A (J/Kp)	B (J/s per Kp mm)	r	P
4129	0.30886	0.00107	0.988	<0.01
6343	0.34982	0.00112	0.996	<0.001
12 774	0.43801	0.00097	0.988	<0.01
23 494	0.52481	0.00127	0.987	<0.01
34 650	0.66611	0.00384	0.995	<0.001

deformation and bonding and a reduction in tablet strength. The effect of molecular weight and compression speed on the crushing strength of PEG tablets are shown in Fig. 2. At any molecular weight, compact strength was found to decrease with increasing compression speed. This indicates that time dependent bonding (= plastic) contribute to the consolidation of PEGs.

As speed increases, the friction between the particles increases which generates heat and asperity melting. Ejected compacts show a transparent skirt around the tablet edge. The same phenomenon was observed by Lin and Cham (1995) when they compressed heat treated PEG at pressures > 80 MPa. The pressure used here was 82 MPa. The resolidification of melted material after asperity melting contributes to consolidation and increases bonding. This limits disruptive elasticity. However, since crushing strength decreases as compression speed increases, this suggests that elasticity is more important than asperity melting.

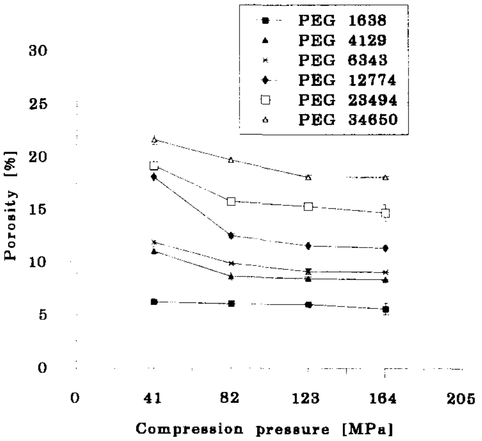

Fig. 4. The effect of the compression pressure and molecular weight on tablet porosity of PEG (250–355 μm) tablets, made at a compression speed of 10 mm/s.

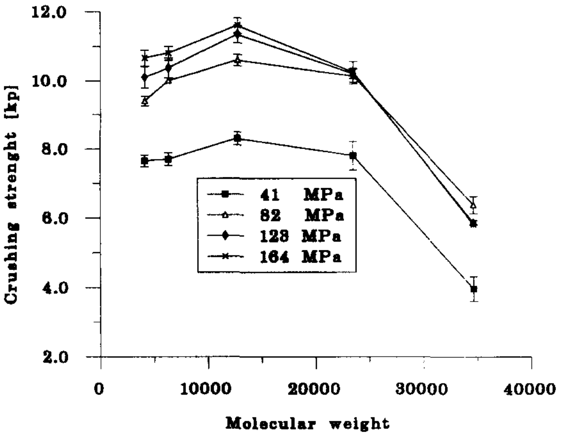

Fig. 5. The effect of the molecular weight and compression pressure on the crushing strength of PEG (250–355 μm) tablets, made at a compression speed of 10 mm/s.

At any compression speed, PEG 12 774 showed higher compactibility compared to the other PEGs. Al-Angari et al. (1985) suggested that PEG 10 000 is soft enough to flow during compaction, but strong enough to resist fracture. Higher molecular weights, such as PEG 34 650, do not deform to form tablets of higher hardness at lower molecular weights.

The compactibility of different grades of PEG could be estimated from the ratio of the plastic energy over crushing strength (PE/CS). It is suggested that a lower ratio indicates a better compactibility. The material consumes less energy to produce stronger tablets. From Fig. 3, it appears that a good correlation between PE/CS and compression speed (v) exists (Table 3):

$$PE/PS = A + Bv \qquad (2)$$

where A and B are constants.

The lowest slope was found for PEG 12 774 suggesting the best compactibility. The highest slope was for PEG 34 650 (Fig. 3). It would be interesting to examine the applicability of Eq. (2) to other materials.

The effect of compression pressure and molecular weight on tablet porosity is shown in Fig. 4.

Fig. 6. Adhesion of PEG 34 650 to tablet tooling.

At any compression pressure, PEG 1638 has the lowest porosity. No decrease in tablet porosity was observed for PEG 4129–23 494 above 82 MPa. PEG 34 650 most resists consolidation and required a higher pressure to achieve maximum densification (123 MPa).

The effect of molecular weight and compression pressure on crushing strength is shown in Fig. 5. At any molecular weight increasing the compression pressure from 41 to 82 MPa resulted in an increase in the crushing strength. Compression above 82 MPa brought about small increases in hardness for PEG 4129–12 774 and no increases for PEG 23 494 and 34 650. These results can be explained by changes in tablet porosity. The greatest decrease in porosity occurred between 41 and 82 MPa. Above 82 MPa there is little change in tablet porosity. Asperity melting can be considered significant for PEGs because of their low melting temperature (47°C for PEG 1638 to 67°C for PEG 34 650). Above 82 MPa, asperity melting becomes probable since a flaky film appeared at the edge of the tablets. The molten material forced through the punch die space, solidifies on contact with the vertical surface of the punch shank forming a white film (Fig. 6). Additionally no hardness value could be obtained for PEG 1638, as they collapsed under the applied load.

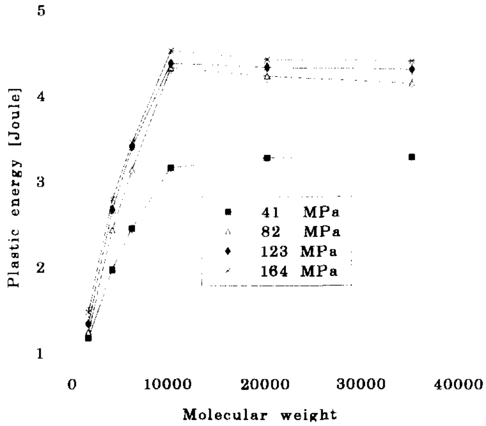

Fig. 7. The effect of the molecular weight and compression pressure on the plastic energy of PEG (250–355 μm) compacts, made at a compression speed of 10 mm/s.

At any compression pressure, PEG 12 774 exhibited the highest hardness. However compressibility was less than PEG 4129 (Fig. 1), although PEG 4129 underwent more plastic deformation than PEG 12 774. PEG 34 650, had the lowest plastic deformation, measured by the mean yield pressure values (Fig. 1). Consequently the tablets had the highest porosity and smallest true area of particle contact and hence the weakest tablets.

The relationship between molecular weight, compression pressure and plastic energy is shown in Fig. 7. Relatively large increases in plastic energy was obtained at lower pressures (41–82 MPa). Above 82 MPa, there is little or no void space and the plastic energy no longer increased once the porosity of the tablet become minimal (De Blaey et al., 1971). With increasing molecular weight, the net energy increased with MW = 1638–12 774. Above 12 774 the energy remained constant although PEG 12 774 had the highest crushing strength.

4. Conclusions

At any compression pressure or speed, lower molecular weight PEGs are easier to deform and form compacts of lower porosities. The very low mean yield pressures confirm that they deform by plastic deformation and due to their low melting points, asperity melting and bonding becomes highly probable. Above 82 MPa gave small increases in hardness and high compression speed led to decreases in the hardness. This suggests elasticity is more important than asperity melting. PEG 12 774 gave the hardest tablets although compressibility was less than PEG 4000.

An equation has been proposed to estimate the compactibility of PEGs from the slope of the ratio (plasic energy/crushing strength) against compression speed and it would be interesting to test its applicability to other materials.

In order to produce PEG tablets of good quality, it is recommended that PEG 12 774 (10 000) is used, at a compression pressure of 80 MPa and lower compression speed.

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