Compression of thermally treated Polyethylene glycol 10 000

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Abstract

The effect of cooling rate on compression properties of melted Polyethylene glycol (PEG) 10 000 has been evaluated. The mean yield pressures, gross and plastic energies have been investigated using a compaction simulator. Tensile strengths, tablet deformation and work of failure of the tablets were determined using a JJ Lloyd compression testing machine. The increase in compression speed increases the mean yield pressure and decreases the tensile strength. Slow cooled sample is the most crystalline and exhibit higher compressibility and produce stronger tablets than untreated and quench cooled samples at all compression speeds. The untreated sample has intermediate crystallinity and shows more resistance to densification and produces tablets of low strength. Quench cooled is the least crystalline but shows better compressibility and give harder tablets in comparison with untreated sample. The study highlights the difficulty in obtaining relationships between crystallinity and compressibility, because particle shape and surface rugosity differ from one sample to another. However a good correlation is observed between the plasticity of PEG and the work of failure. Slow cooled PEG is therefore the most compressible and produces tough tablets which undergo greater deformation before failure. Untreated PEG however, shows less plasticity and produces tablets of low toughness. © 1997 Elsevier Science B.V.

Keywords: PEG 10 000; Cooling rate; Crystallinity; Particle shape; Particle surface; Compression speed; Compression pressure; Tensile strength; Work of failure; Tablet deformation; Plasticity

1. Introduction

The usual method of making solid dispersions is to melt a mixture of the drug and carrier and then cool. Sekiguchi and Obi (1961) melted sulphathiazole-urea, solidified on an ice bath and pulverised. The many modifications since involve changes in the rate of cooling:

1. Pouring the melt onto a stainless steel plate and allowing natural cooling (Chiou and Riegelman, 1971; Sheu et al., 1994).

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2. Spreading the melt in a thin layer on a glass slab, and allowing to cool and solidify gradually at room temperature (Geneidi et al., 1976; Singla and Vijan, 1990).
3. Continuously stir during cooling at room temperature until solidified (El-Banna and Abdallah, 1980).
4. Pouring into a petri-dish maintained at 0°C to solidify (Ford and Rubinstein, 1977).
5. Immediate quenching by spreading in a thin layer over a stainless steel plate, pre-cooled over an ice-bath (Ali and Sharma, 1991).
6. or by immersion in liquid nitrogen (Collett et al., 1976).

The rate of cooling has been shown to determine the structure of Polyethylene glycols (PEGs) and different crystallinities result which may influence tablet characteristics. The present study examines different cooling rates on PEG 10 000 compression.

2. Materials and methods

PEG 10 000 [12774, vide Larhrib et al., 1997a] was supplied by Merck Schuchardt (Germany), in flakes.

2.1. Preparation of heat-treated PEG

2.1.1. Preparation of the melt
The temperature of the oven was adjusted to 100°C using a calibrated electronically controlled oven (Memmert SE 400: Schwabach, Germany). The molten PEG was poured and held at 100°C for 30 min.

2.1.2. Cooling conditions
Samples were either cooled naturally to room temperature or quench cooled by immersing the container in liquid nitrogen for 20 min. Both slow and quench cooled samples were stored over phosphorus pentoxide (B.D.H. Chemicals, Poole) for 24 h. They were ground using a pestle and mortar. A sieve fraction of 250–355 μm was taken.

2.2. Moisture content

Untreated, slow and quench cooled sieve cuts (250–355 μm) were accurately weighed. Due to the low melting point of PEG 10 000 (67°C) a low drying temperature of 37°C was used. When constant weights were obtained, the weight loss was calculated. The equilibrium moisture content was less than 0.3% w/w for all the samples.

2.3. Differential scanning calorimetry

A 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). The pans were sealed hermetically. The samples were heated at 10°C min^{-1} under nitrogen. An empty pan was used as reference. Melting points and enthalpies of fusion were calculated by the instrument ($n = 4$).

2.4. X-ray powder diffraction

X-ray diffraction spectra were obtained using a PW1729 fixed $\theta/2$ Goniometer with a PW 1710 Diffractometer (Phillips, Almelo, Netherland). The cavity of the metal sample holder was filled with the ground powder of sample and then smoothed with a spatula. A scanning rate of 0.04°.2θ/s over the range of 10–50°.2θ was used to produce the spectra.

2.5. Compression

Compression was carried out using a high speed compaction simulator (ESH Testing Ltd, Brierley Hill, West Midlands, UK), fitted with 12.5 mm flat faced punches. A sawtooth displacement profile was used to control both upper and lower punches. 0.4 g of powder was used for each sample. To examine the effect of compression speed, the pressure was held at 82 MPa varying speed at 25, 75, 100 and 200 mm s^{-1}. Additionally at a compression speed of 10 mm s^{-1}, pressures of 25, 41, 62 and 82 MPa were used. 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 ± 0.05 kN and ± 12 μm respectively (Bateman et al., 1989).

2.6. Manipulation of the data

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 (1961), gross and net work of compaction analysis (Nokhodchi et al., 1995).

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) of tablets were measured using a compression tester (Type LR 30K: Lloyd Instruments, Fareham, UK). The rate of platten movement was 3 mm min^{-1}. The tensile strength was calculated according to Fell and Newton (1970).

3. Results and discussion

3.1. Characterization of PEG 10 000

Differential Scanning Calorimetry (DSC) has been shown to be an appropriate method for characterising solid state changes for Polyethylene glycols (Chatham, 1985; Craig and Newton, 1991; Larhrib et al., 1997a). The lowest values of the melting temperature and the enthalpy of fusion were exhibited by quench cooling, suggesting that the molecules of the crystal are less tightly packed. Studies using X-Ray powder diffraction supported the DSC studies (Table 1).

3.2. Effect of compression speed

In all cases, the mean yield pressure increases with increasing compression speed (Fig. 1) which

Table 1
Melting point (TM°C), enthalpy of fusion (ΔH_f J g^{-1}) and degree of crystallinity for PEG 10 000

PEG sample	TM $\pm$ S.D	$\Delta H_f \pm$ S.D	% Crystallinity
Untreated	65.1 $\pm$ 0.3	177.9 $\pm$ 2.7	78.1
Slow cooled	67.5 $\pm$ 0.1	184.3 $\pm$ 0.3	81.5
Quench cooled	64.3 $\pm$ 0.2	169.4 $\pm$ 0.4	71.5

would tend to confirm that the degree of plastic flow was reduced. With increasing compression speed the material becomes more resistant to densification and a higher pressure is needed to bring about its densification and this accounts for an increase in the gross energy (Fig. 2).

Fig. 3 shows typical Heckel plots for untreated, slow and quench cooled PEG 10 000 [12774]. Compressibility is affected by thermal history. The rank order of mean yield pressure was: slow cooled < quench cooled < untreated (Fig. 1) and the slow cooled sample was the most compressible. The order of crystallinity was: slow cooled > untreated > quench cooled (Table 1). Quench cooling produces the least crystalline and activated inherent structure with greatest tendency to deform (Morita et al., 1984; Vromans et al., 1985). Our results contradict this and show slow cooling is the most crystalline and compressible. This is not surprising in the case of PEG, since lower molecular weights are more crystalline,
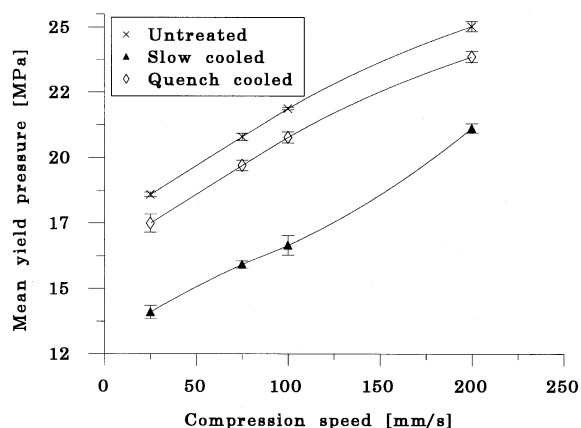

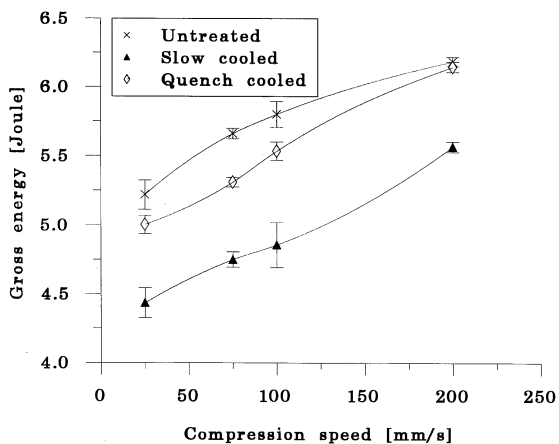Fig. 1. The effect of compression speed on the mean yield pressure of PEG 10 000.

Fig. 2. The effect of compression speed on the gross energy of PEG 10 000.

Beaumont et al. (1966) gave crystallinities for untreated polymers as 81, 91, 92 and 77% for PEG 1500, PEG 4000, PEG 6000 and PEG 20 000 and exhibited better compressibility than higher molecular weights (Al-Angari et al., 1985; Lin and Cham, 1995; Larhrib et al., 1997b). It therefore should follow that untreated PEG should exhibit better compressibility than quench cooled. This, however, as can be seen from Fig. 1 is not the case. The compressibility of untreated sample is less than quench cooled.
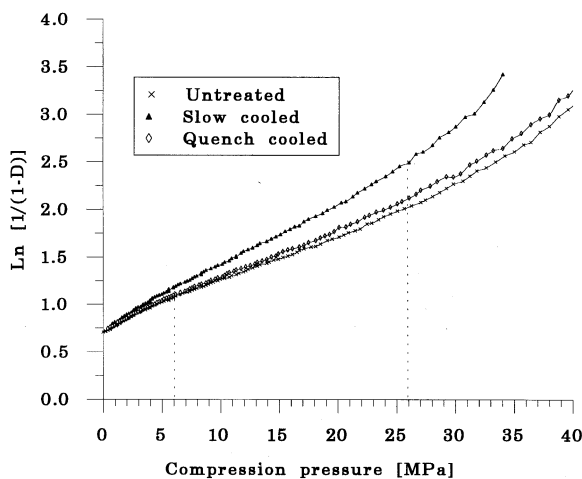

Fig. 3. The effect of cooling rate of PEG 10 000 on the Heckel plots obtained at a compression speed of 100 mm s^{-1}.

PEG is sensitive to changes in solid state properties induced by compaction. Adolfsson and Nystrom (1996) reported an increase in crystallinity for PEG 8000 when compressed at a compression pressure of 1200 MPa. The quench cooled sample is the least crystalline and may increase its crystallinity during compression. However this hypothesis is not probable because the maximum pressure used was about 82 MPa which is too low to produce such changes and the difference between samples is discernible even at low compression speed. The opposite between untreated and quench cooled samples can be attributed to differences in particle shape and surface rugosity (Fig. 4a–c). Quench cooled material is irregular and rough compared to slow cooling which is rougher than untreated material with defined particle faces and a smooth surfaces. Increased surface irregularity provides numerous angular contact points, increase the total bonding surface area, enhancing interparticulate friction and plastic flow (Alderborn et al., 1988).

Karehill et al. (1990) also reported the importance of particle rugosity. The binding capability of plastically deforming materials (Sodium chloride, Avicel PH101 and Starch 1500) were dependent upon surface roughness. Similarly, Vromans et al. (1987) reported that irregular particles give better binding than smooth particles. Wong and Pilpel (1990) investigated the effect of particle shape on the compression of Starch 1500, which consolidates principally by plastic deformation. Large increases in compressibility, a decrease in yield pressure values and elastic recovery was observed from regular through to irregular particles. For Lactose and Emcompress, which consolidate primarily by fragmentation, particle shape had no effect (Wong and Pilpel, 1990).

The strain rate sensitivity (SRS) was calculated from the slopes of the Heckel plots for the compacts made at 25 and 200 mm s^{-1}. The SRS for untreated, slow cooled and quench cooled PEG 10 000 were calculated as 25.81 ± 0.53, 33.99 ± 1.07 and $28.49 \pm 1.68\%$ respectively. The materials which are more strain sensitive are those materials which plastically deform (Roberts and Rowe, 1985). Slow cooled is the most sensitive to increases in compression rate, while untreated
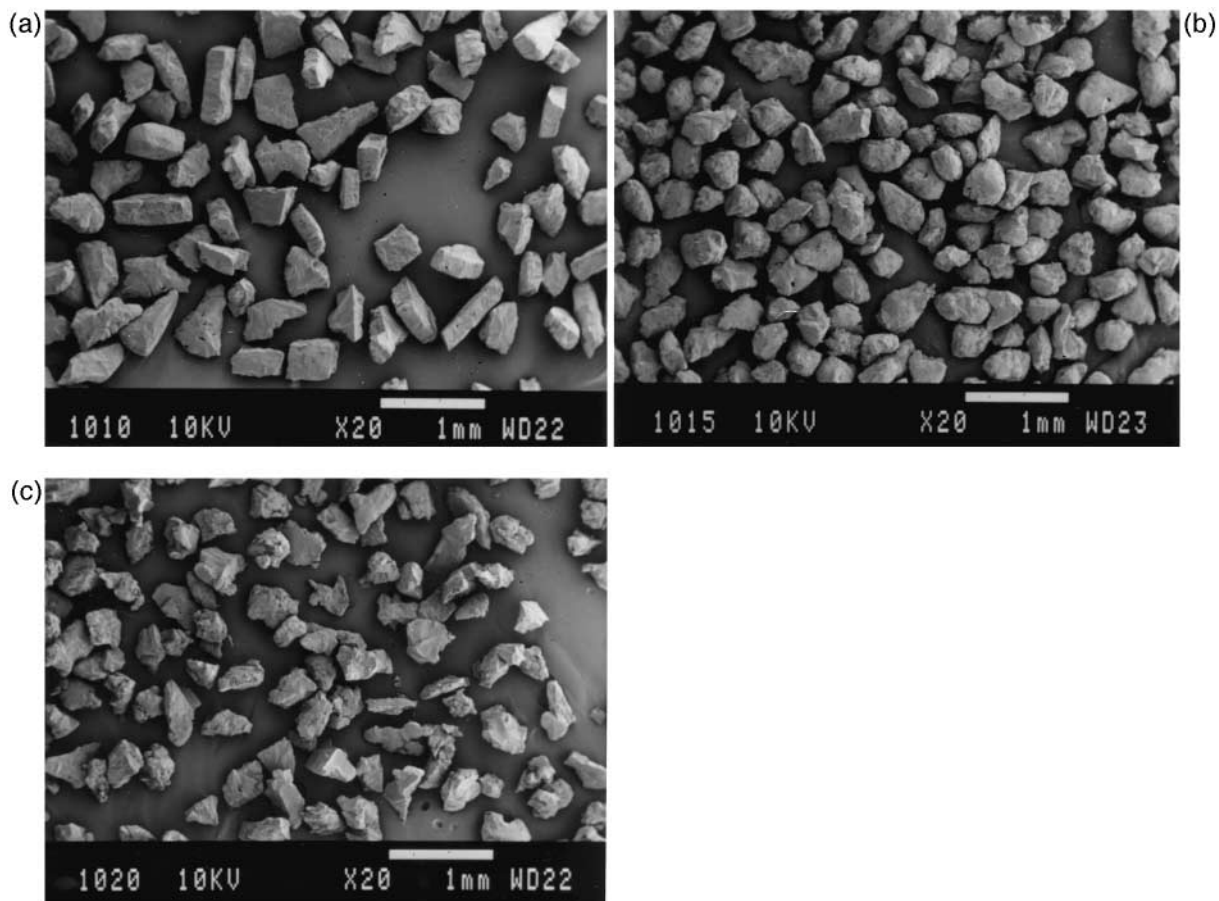
Fig. 4. Photomicrographs of (a) untreated (b) slow cooled and (c) quench cooled PEG 10 000.

sample is the least plastic and showed less sensitivity to increases in compression speed and this can be seen from Fig. 5.

The effects of the compression speed and thermal history on the tensile strengths of PEG 12774 tablets is shown in Fig. 5. The tensile strength shows a reduction as compression speed is increased and may be explained by a decrease in the time available for plastic flow, which is the major mechanism of deformation for PEGs (Larhrib et al., 1997b). Consequently the area available for interparticulate bonding is reduced.

The tablets made from slow and quench cooled PEG exhibit high tensile strength compared with untreated material. Heat treated samples yield better tablets than non-thermally treated sample. Slow cooling has greater plastic deformation and produces stronger tablets, while untreated samples show less plastic deformation during compression and produce tablets of low strength. Quenched material is the least crystalline and gives tablets with higher strength than untreated samples, but less than slow cooling which is the most crystalline. The superior bonding of quench cooling could be due to irregular particle shape and surface roughness.

The plastic energies used to form the compacts are shown in Fig. 6. More energy is required to form the compacts at higher compression speeds, this may be due to the utilization of more energy to overcome the increased cohesiveness of particles that occur at higher compression speeds. The energies required to form the PEG compacts were dependent on the cooling rate. The slow cooled
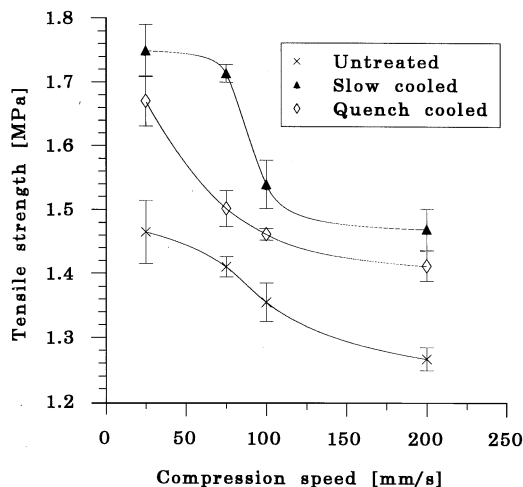
Fig. 5. The effect of compression speed on the tensile strength of PEG 10 000.

Fig. 7. The effect of compression pressure on the tensile strength of PEG 10 000.

compacts consume less plastic energy and produce tablets with higher strength at any compression speed, suggesting better energy utilization.

3.3. Effect of compression pressure

The effect of compression pressure on the tensile strength of PEG samples is shown in Fig. 7. The tablets made from untreated material exhibited the lowest tensile strength. Higher plastic deformation takes place during compression of
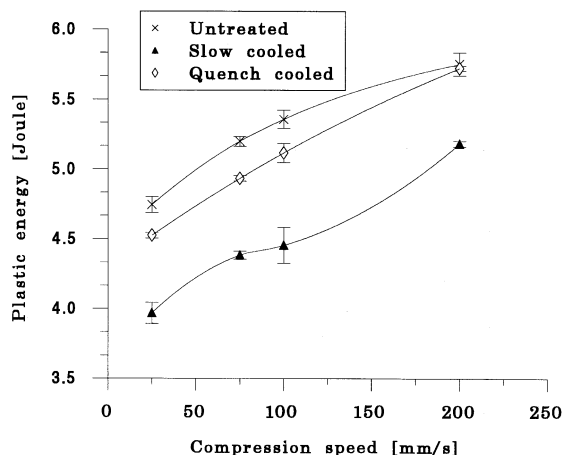

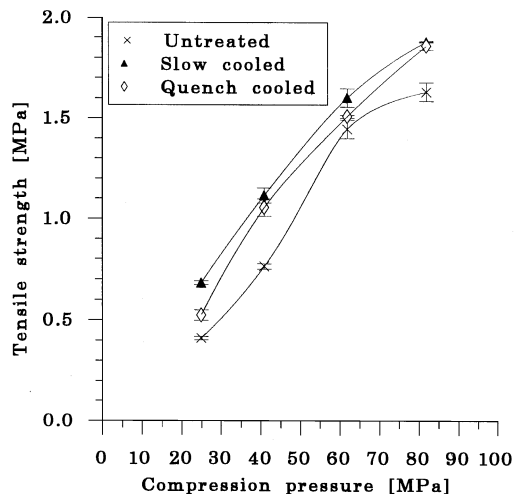Fig. 6. The effect of compression speed on the plastic energy of PEG 10 000.

quench and naturally cooled PEGs allowing particles to establish areas of intimate contact. Greater differences in tensile strength between slow and quench cooled sample was observed with varying compression speed (Fig. 5) rather than varying compression pressure (Fig. 7). Work of failure (WF) or toughness is better than tensile strength to quantify the resistance of tablet to mechanical failure (Rees and Rue, 1978). Slow and quench cooled PEG showed approximately the same tensile strength at any compression pressure (Fig. 7). However the work done to cause tablet failure is much greater for the tablets made from slow cooled material.

The work of failure is a combination of tablet strength and diametral deformation (Rees and Rue, 1978). Results show that slow cooling undergoes greater deformation before failure occurs, whereas untreated material produce tablets which exhibit less deformation before failure and consequently possess lower toughness (Table 2).

Numerous authors have related this parameter to plasticity (Rees, 1982; Patel and Staniforth, 1987) confirmed by stress relaxation measurements. Rue et al. (1980) studied the bonding mechanisms in granules prepared by precompression, wet massing and spray drying. Spray dried granules had the largest and most rapid relaxation

Table 2
Tablet deformation and work of failure (mean ± S.D. of four) from untreated, slow and quench cooled PEG 10 000 at 10 mm^{-1} and at different pressures.

Compression pressure (MPa)	Tablet deformation $\times 10^{-5}$ (m)			Work of failure $\times 10^{-4}$ (J)		
	Untreated	Slow cooled	Quench cooled	Untreated	Slow cooled	Quench cooled
25	17.23 ± 0.80	24.60 ± 0.74	19.29 ± 0.83	30.32 ± 0.29	74.09 ± 5.74	41.76 ± 2.32
41	21.39 ± 0.33	29.64 ± 0.60	22.13 ± 0.19	62.28 ± 1.54	124.84 ± 6.26	83.79 ± 4.62
62	24.44 ± 0.48	32.09 ± 0.46	26.60 ± 0.12	128.79 ± 2.40	185.37 ± 17.9	136.83 ± 3.69
82	26.39 ± 0.13	34.95 ± 0.45	27.27 ± 0.77	153.62 ± 2.71	236.67 ± 5.83	169.70 ± 6.10

and exhibited the largest work of failure. Our results support this. Slow cooled PEG exhibited the lowest values of mean yield pressure and highest values of WF followed by quench cooled and finally untreated. A good correlation was found between plasticity and WF.

4. Conclusion

This study shows that cooling rate significantly affects the compression of PEG 10 000. Heat treated samples deform more readily during compression and produce tablets of higher tensile strength compared to untreated material. Differences in their tensile strength are more discernible with varying compression speed than pressure. Slow cooling gives the most crystalline, exhibits the highest plasticity and requires the least energy for compression to produce tough tablets. Untreated material with intermediate crystallinity showed less plastic deformation and therefore tablets of low toughness.

A good correlation exists between plasticity and work of failure. The results also suggest that crystallinity is not the only important factor controlling tablet characteristics. Compressibility is also affected by particle shape and surface rugosity.

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