ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 46 (1998) 31–38

European Journal of Pharmaceutics and Biopharmaceutics

Research paper

The effect of an increase in chain length on the mechanical properties of polyethylene glycols

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Received 21 May 1997; accepted 29 September 1997

Abstract

The mechanical properties of different molecular weights of polyethylene glycol (PEG) have been determined by formation of compacted tablets and beams, which were subjected to diametral compression and 3-point bending, respectively. From diametral compression, the tensile strength for the different grades of PEG was determined. Flat beams made from powder by compaction were used to determine Young's modulus of elasticity. Beams into which a notch had been introduced after formation allowed the fracture mechanical parameters of critical stress intensity factor, K_{IC}, and fracture toughness, R, to be determined. Evaluation of these parameters as a function of compact porosity allowed extrapolation to values at zero porosity, providing an estimate of the material properties. The increase in chain length of the PEG was found to have a non-linear effect on tensile strength and Young's modulus. The ductility of the polymer increased proportionally to the increase in chain length, reflected by the linear relationship between K_{IC} and the molecular weight. Young's modulus and critical stress intensity factor allowed the estimation of the strain energy release rate, G_{IC}, which is the driving force in crack propagation. Consequently, the tensile strength at zero porosity was found to be predictable from the values of G_{IC} and the molecular weight of the different grades of PEG.

Keywords: Critical stress intensity factor; Fracture mechanics; Fracture toughness; Mechanical strength of compacts; Polyethylene glycol; Strain energy release rate; Young's modulus

1. Introduction

In the field of powder compaction, the process of formulation optimisation is still, at times, a matter of trial and error. However, during the past few years improvements in the understanding of the physical nature of the compaction process have gradually shifted formulation habits towards scientific argumentation rather than trial and error. For example, the use of expert systems in tablet formulation could save a lot of time when choosing a robust formula. However, the facility to predict material properties, processing and compaction behaviour of pharmaceutical powders, based on physical, structural and molecular data, is not clearly established.

York [1] demonstrated how Young's modulus at true particle density could be predicted from the single crystal elastic potential for single acetylsalicylic acid crystals. Newton et al. [2] investigated the relationship between the mechanical properties and the chain length of a homologous series of benzoic acid esters. It was noted that changes in the chemical constitution produced changes in the mechanical properties of the esters under investigation. The effect of the molecular weight of PEG on the mechanical strength of compacts was studied by Al-angari et al. [3]. They found an increase in the mechanical strength of tablets with a decrease in molecular weight except for 'PEG-10000' which exhibited a higher mechanical strength than the other tested materials.

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0939-6411/98/$19.00
PII S0939-6411(97)00151-3

In this study the mechanical properties of PEG powders of different molecular weights were determined and the effect of an increase in the polymer chain length on the mechanical parameters was investigated. The interaction between the different mechanical parameters was assessed using statistical analysis, in an attempt to understand the relation between structural changes and its reflection on the mechanical behaviour of the polymeric materials.

2. Materials and methods

2.1. Materials

Five molecular weight grades of polyethylene glycol (PEG) with an increase in molecular weight from PEG-4000 to PEG-35 000 were selected for this study and supplied by Hoechst (Frankfurt, Germany). The batch characteristics are listed in Table 1.

2.2. Methods

2.2.1. Pre-treatment of the coarse powder

Polyethylene glycol powders were received in a coarse flaky form. These coarse materials were reduced in size using the end-runner mill (Pascal Engineering, London, UK). After milling the powders were sieved using a mechanical sieve shaker (Endecotts, London, UK) and the size fraction between 150–355 μm was collected for each grade of PEG. The aim was to use a similar particle size for the different grades of PEG, because the particle size of a powder affects its mechanical properties with respect to brittleness and compaction behaviour [4].

2.2.2. Apparent particle density measurements

An air comparison pycnometer (model 930, Beckman Instruments, CA, USA) was used for apparent particle density measurements. The equipment was calibrated with the two steel test balls supplied by the manufacturer. Three determinations for each grade of PEG have been performed on accurately weighed samples of each material. Table 1 contains the average apparent particle density values and their variability. The apparent particle density values were used for the calculation of the beam and tablet porosity.

2.2.3. Preparation of rectangular beams

Rectangular beams from different grades of PEG were prepared in a 9×45 mm punch and die system previously described by Mashadi and Newton [5]. Rectangular beam specimens of varying thickness were prepared by filling the rectangular die with a known weight of powder, evenly distributed in the die. A range of forces, up to 50 kN, was applied using a physical testing machine (Model TT-CM, Instron, High Wycombe, UK) at a crosshead speed of approximately 2 mm/min. The load cell, which was positioned below the punch and die system, was calibrated by dead weight loading. The compaction force was recorded via a flat bed $X-Y$ recorder (Gould, Model 60000, Bryan Southern Instruments, Surrey, UK). The die wall and the punch tips were cleaned, polished and lubricated with a suspension of 4% magnesium stearate in acetone before each beam preparation. Five beams were prepared at each compaction force. The beams were stored at room temperature in plastic bags for a minimum of 2 weeks prior to testing, protected from the influence of air humidity.

2.2.4. Flexure testing of the beams

Modulus of elasticity. Each beam was carefully weighed to ±0.0001 g accuracy on a Sartorius balance (Type 1702, Göttingen, Germany) and its thickness measured to ±0.01 mm accuracy by a micrometer dial gauge (Type Mercer 130/3, UK). The Young's modulus of the beams was determined by 3-point bending (CT 40, Engineering Systems, Nottingham, UK). The displacement transducer (Type DG-5, Sangamo Schlumberger, Bogno Regis, UK) was attached to a $X-Y$ plotter (Gould, Model 60000, Bryan Southern Instruments, Surrey, UK) to measure tensile stress, maximum fracture load and displacement. Beams were tested at a constant bending rate of 1 mm/min. Young's modulus (E) of a specimen can be calculated according to the equation [6,7]:

$$E = \frac{2l^3}{BW^3}\,\frac{P}{\delta} \tag{1}$$

where l is the distance between the lower supports, B is the beam width, W is the beam thickness, P is the load obtained from the linear part of the load-deflection curve and δ is the beam deflection at the mid point.

Fracture mechanics. A crack was introduced in the middle of one face of each specimen using a scalpel attached to

Table 1

Source, batch number and selected properties of different grades of PEG used in this study

Grade	Batch number	n	Average molecular weight	Melting range (°C)	Median particle size (μm)	Apparent particle density (g/cm^3)
PEG-4000	618535	69–84	3000–4800	50–56	259	1.235 ± 0.003
PEG-6000	619962	115–160	5400–6600	55–63	263	1.210 ± 0.009
PEG-10000	620770	198–256	8750–11250	60–63	252	1.223 ± 0.008
PEG-20000	618051	341–454	15000–20000	60–63	270	1.190 ± 0.007
PEG-35000	618920	696–895	30625–39375	63–67	270	1.214 ± 0.008

a stainless steel holder to guarantee that the depth of the crack always was the same. The depth of the crack was measured using an image analyser (Seescan solitaire 512, Cambridge, UK) attached to a CCD-4 black and white camera (Rengo Co., Toyohashi, Japan) and a microscope (Olympus BH-2, Tokyo, Japan). The cracked beam specimens were loaded (one day after crack introduction) in 3-point bending the crack facing downwards in the same manner as described for Young's modulus test. The value of the critical stress intensity factor K_{IC} can be calculated from the equation derived by Brown and Srawley [8], previously used by Podczeck and Newton [9]:

$$K_{IC} = \frac{3Pa^{1/2}l}{2BW^2}c \quad (2)$$

The constant c is a function of the specimen geometry to allow the influence of the ratio between crack length a and beam thickness W to be calibrated:

$$c = A_0 + A_1\left(\frac{a}{W}\right) + A_2\left(\frac{a}{W}\right)^2 + A_3\left(\frac{a}{W}\right)^3 + A_4\left(\frac{a}{W}\right)^4 \quad (3)$$

The constants for A_0, A_1, A_2, A_3 and A_4 vary for different ratios of a to W [8].

The value for fracture toughness R is independent of the bending technique (i.e. 3- or 4-point bending) and can be obtained by applying the equation used by Roberts et al. [10] and Mashadi and Newton [5]:

$$R = \frac{P\frac{\delta}{2}}{BW - aB} \quad (4)$$

2.2.5. Preparation of the flat faced tablets

Tablets of 10 mm diameter were prepared using a single stroke tablet press (Manesty F3, Liverpool, UK) instrumented with piezoelectric force transducers attached to the upper and lower punch holders. The speed was adjusted to give 1 tablet/s. Powder was fed directly into the machine feeder and the weight of the tablet was adjusted to give a constant tablet weight. A range of compaction pressures was used to produce tablets of different porosity. The tablets with the least weight variation were collected. Five of these tablets at each compaction pressure were stored at room temperature for at least 2 weeks before testing. Before each pressure setting, the die wall and the punch tips were lubricated with a suspension of magnesium stearate in acetone 4% w/w.

2.2.6. Diametral compression of the tablets

Each tablet was carefully weighed to ±0.0001 g accuracy on a Sartorius balance (Type 1702, Göttingen, Germany) and the thickness measured to ±0.01 mm accuracy by a micrometer dial gauge (Type Mercer 130/3, UK). The diametral compression test was carried out by placing a tablet centrally on the base of a CT 40 (Engineering Systems, Nottingham, UK) across the diameter in the vertical plane. The platen was then moved down at a crosshead speed of 1 mm/min to apply an increasing load across the diameter of the tablet. The output in kg force was recorded as the fracture load of the tablet and transformed into N by multiplication with the gravity constant (9.81 m/s^2). The tensile strength σ of the tablets was calculated using the equation reported by Fell and Newton [11]:

$$\sigma = \frac{2P}{\pi Dt} \quad (5)$$

where P is the fracture load, D is the diameter of the tablet and t is the tablet thickness. Five tablets were tested for each compaction pressure, and all tablets were failed in tension unless otherwise stated.

3. Results and discussion

3.1. Mechanical strength

The results obtained from the diametral compression test indicate the effect of compaction pressure on the tensile strength of tablets. The higher molecular weights PEG-20000 and PEG-35000 formed coherent tablets at low compaction pressures. Fig. 1 illustrates the relationship between the tensile strength of compacts of different grades of PEG and the compaction pressure. From the graph it can be seen that the grades of PEG with the higher molecular weight exhibit lower tablet strength over the whole range of compaction pressures. Obviously, the rise in compact tensile strength with increase in compaction pressure is rapid at lower pressures and moderate or even not existent at high pressures. Similar findings have been reported by Larhrib et al. [12]. Therefore, it is not necessary to apply compaction pressures above ~150 MPa to any PEG powder, because similar values of tensile strength will result. At lower compaction pressures the rate of increase in tensile strength with pressure is rapid due to plastic deformation of the particles

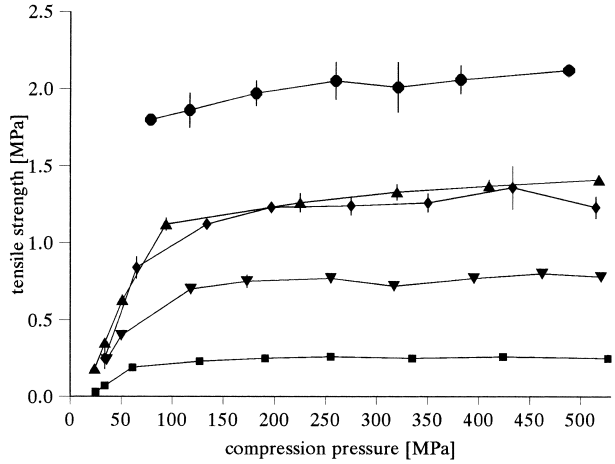

Fig. 1. Tablet tensile strength σ as a function of compaction pressure P for different molecular weights of PEG: ●, PEG-4000; ♦, PEG-6000; ▲, PEG-10000; ▼, PEG-20000; ■, PEG-35000.

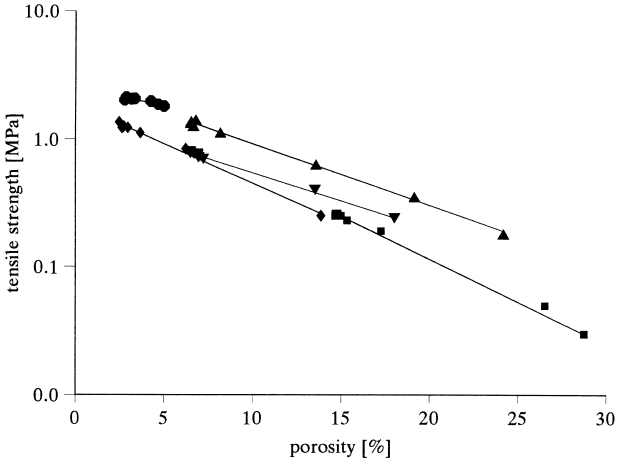

Fig. 2. Tensile strength σ as a function of porosity for different molecular weights of PEG: ●, PEG-4000; ♦, PEG-6000; ▲, PEG-10000; ▼, PEG-20000; ■, PEG-35000.

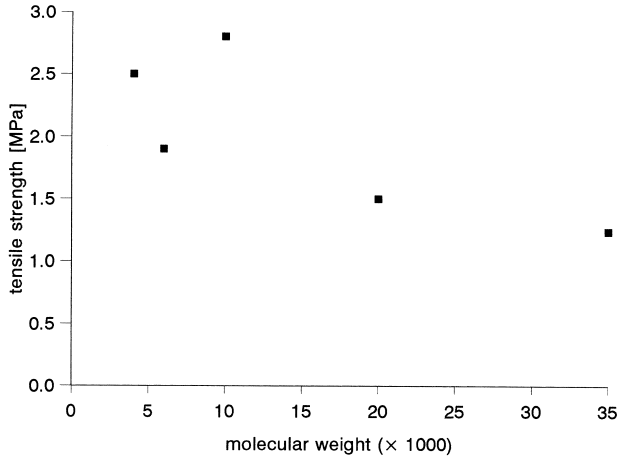

Fig. 3. Tensile strength at zero porosity σ_o as a function of the molecular weight of PEG.

dominating the process of volume reduction. At higher compaction pressures, however, asperity melting of the particles and subsequent formation of sinter bridges between the particles become the probable predominating mechanisms for the volume reduction process. Melting requires comparative large amounts of energy, and voids, which can be filled, become fewer. Thus, the rate of volume reduction with pressure decreases [13].

A linear relationship was found between the natural logarithm of tensile strength and tablet porosity as can be seen from Fig. 2. From this relationship the tensile strength at zero porosity for the different grades of PEG was obtained by extrapolation of the linear graphs to zero porosity. The extrapolated results are shown in Table 2. The effect of increase in chain length and hence the molecular weight of PEG on the tensile strength at zero porosity was investigated by plotting the extrapolated tensile strength values at zero porosity for each grade of PEG against the molecular weight. The scatter-plot is illustrated in Fig. 3. No polynomial or polygonal line function was fitted to the data points, because the underlying physical relationship between tensile strength at zero porosity and molecular weight is unknown. There is a drop in tensile strength from PEG-4000 to PEG-6000, followed by a sharp increase for PEG-10000. For higher molecular weights the tensile strength at zero porosity is lower than for PEG-6000. Thus, PEG-10000 appears to be an exception by breaking the order of decreasing tensile strength at zero porosity. A similar trend in the change of tensile strength with molecular weight was reported by Al-angari et al. [3] and Larhrib et al. [12] using different particle sizes, different tablet sizes and different grades of PEG. Craig et al. [14] investigated the low-frequency dielectric response of PEG of different molecular weights in the molten and in the solid state. They found that PEG-10000 had exceptional behaviour in the molten state, while PEG-6000 became the chain-breaker when the dielectric response was measured in the solid state at high frequencies. Using low frequencies, indirect proportionality was found between molecular weight and conductance of the materials. First, this suggests that severe melting has taken place during tabletting of the PEG samples. Secondly, following the discussion of Craig et al. [14], PEG-10000 might have undergone a restructuring of the polymer chains during the spot melting process whilst tabletted leading to a different tablet structure and thus a different flaw and crack distribution if compared with the other types of PEG. The flaw and crack distribution in a solid determines the tensile strength of a specimen and hence could explain the increased strength of compacts made from PEG-10000.

Table 2

Extrapolated tensile strength at zero porosity for different grades of PEG

Grade	σ_o (MPa)	Slope	RMS (%)
PEG-4000	2.50 ± 0.11	–0.0588	8.52
PEG-6000	1.90 ± 0.05	–0.1151	59.35
PEG-10000	2.80 ± 0.10	–0.1112	35.85
PEG-20000	1.50 ± 0.04	–0.1006	20.75
PEG-35000	1.24 ± 0.37	–0.1080	14.18

3.2. Young's modulus of elasticity

The results obtained from the flexure test of the rectangular beams were treated according to Spriggs' equation [15]. The natural logarithms of the Young's modulus values are presented as a function of the beam porosity in Fig. 4. A linear relationship was obtained for the different molecular weights of PEG indicating that as the beam porosity decreases the stiffness of the specimens increased. The extrapolated Young's modulus at zero porosity is listed for the different grades of PEG in Table 3. The different grades of PEG show only slightly different rates in change in stiffness with porosity, which can be observed from the slopes of the regression lines. Nevertheless, following Spriggs' suggestion [15] about the value of the slopes of these functions, PEG-10000 displays the highest rate of change in Young's modulus with porosity, while PEG-

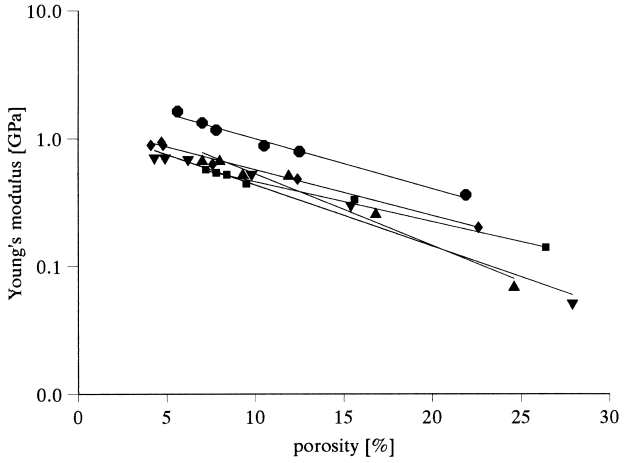

Fig. 4. Young's modulus E as a function of the beam porosity of PEG: ●, PEG-4000; ♦, PEG-6000; ▲, PEG-10000; ▼, PEG-20000; ■, PEG-35000.

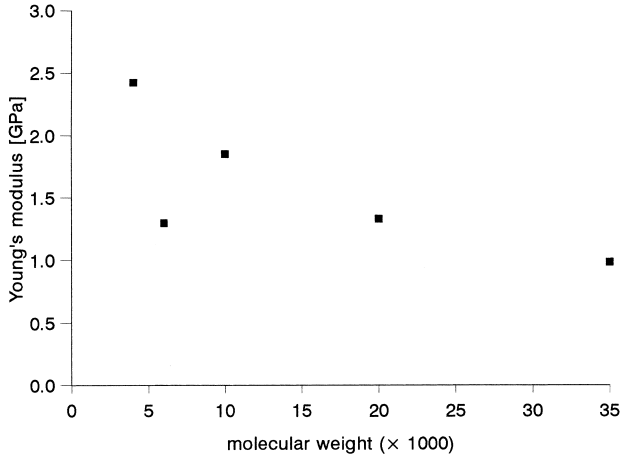

Fig. 5. Young's modulus at zero porosity E_o as a function of the molecular weight of PEG.

35000 provides the smallest change. PEG-10000, therefore, could have the highest proportion of open to closed pores, which determines the volume reduction and consolidation of this grade of PEG. On the contrary, PEG-35000 possesses the lowest proportion of open to closed pores leading to porous, soft beams under similar compaction conditions.

The relationship between Young's modulus of elasticity and the molecular weight of PEG is illustrated in Fig. 5 as a scatter-plot. No fit to a polynomial or polygonal line function was attempted for the same reason given for Fig. 3. Apparently, as the molecular weight of PEG increases, Young's modulus decreases. However, PEG-6000 shows an exceptional large decrease in Young's modulus when compared to the other materials. This coincides with the dielectric response in the solid state as reported by Craig et al. [14] and the fact that PEG-6000 has the highest degree of crystallinity of the series tested [16,17]. Hence, the influence of molecular weight and related room structure on tensile strength and Young's modulus of different grades of PEG is different. While the first is obviously driven by the reduction and distribution of flaws and cracks inside the specimens due to plastic deformation of the powder particles, the latter is a pure expression of the material properties. Kinloch and Young [18] proposed that tensile strength is theoretically related to Young's modulus via $\sigma \approx E/10$. However, in practice polymers show ratios between tensile strength and Young's modulus of $E/50$–$E/100$. The present finding also suggests that the proposed relationship by Kinloch and Young is not valid for polymers, or not at least with respect to PEG.

Table 3

Extrapolated Young's modulus at zero porosity for the different grades of PEG

Grade	E_o (GPa)	Slope	RMS (%)
PEG-4000	2.42 ± 0.12	–9.00	67.6
PEG-6000	1.30 ± 0.04	–8.35	58.6
PEG-10000	1.85 ± 0.15	–12.62	105.5
PEG-20000	1.33 ± 0.10	–11.25	144.3
PEG-35000	0.98 ± 0.03	–7.50	40.2

3.3. Fracture mechanics

The natural logarithm of the K_{IC} values has been plotted as a function of the beam porosity in Fig. 6 for the different grades of PEG. The relationships found indicate that as the beams become more porous, the critical stress intensity factor decreases. Extrapolations to zero porosity enabled the K_{IC} values at zero porosity to be calculated for each grade of PEG. The extrapolated results are listed in Table 4.

The natural logarithm of the fracture toughness values, R, was also drawn as a function of the beam porosity for each grade of PEG. A linear relationship was obtained for the different grades of PEG indicating an increase in the energy necessary to propagate a crack when the beams become less porous. The fracture toughness at zero porosity was determined by extrapolation and is listed in Table 4 for the different grades of PEG.

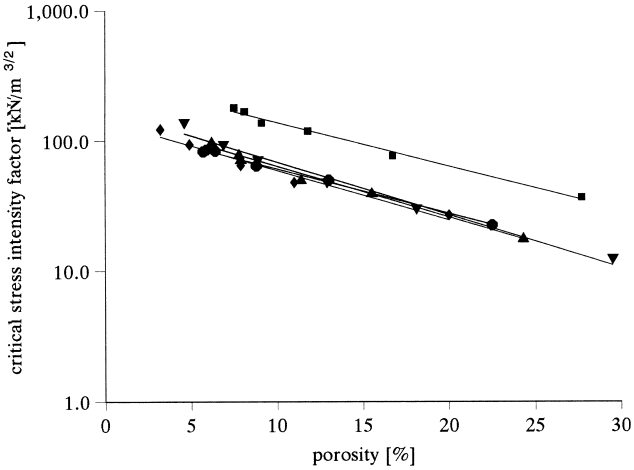

Fig. 6. Critical stress intensity factor K_{IC} as a function of the beam porosity of PEG: ●, PEG-4000; ♦, PEG-6000; ▲, PEG-10000; ▼, PEG-20000; ■, PEG-35000.

Table 4

Critical stress intensity factor K_{IC} and fracture toughness R at zero porosity for different grades of PEG

Grade	K_{IC} (kN/m$^{3/2}$)	Slope	RMS (%)	R (N/m)	Slope	RMS (%)
PEG-4000	134.6 ± 4.2	–0.0437	1.79	9.7 ± 1.1	–0.0792	13.63
PEG-6000	142.5 ± 12.4	–0.0888	5.39	19.9 ± 1.2	–0.0877	20.52
PEG-10000	157.0 ± 11.9	–0.0902	3.90	25.7 ± 1.2	–0.0899	20.11
PEG-20000	175.3 ± 18.2	–0.1065	6.74	43.0 ± 1.2	–0.0935	28.50
PEG-35000	298.5 ± 19.0	–0.1075	3.00	49.9 ± 1.3	–0.0770	28.02

The different grades of PEG have different values for K_{IC} and R at zero porosity. Obviously, as the molecular weight of PEG increases, the powders become more ductile in structure and hence require more energy to propagate a crack. The effect of the increase in molecular weight of the different grades of PEG on the critical stress intensity factor and fracture toughness is illustrated in Figs. 7 and 8. The relationship between the increase in molecular weight and K_{IC} at zero porosity is linear, indicating that as the molecular weight of PEG increases the material becomes less brittle and therefore can resist crack propagation when subjected to an applied stress. Craig et al. [14] had found a linear relationship between the molecular weight of PEG and conductivity at low dielectric frequencies. Low-frequency dielectric spectroscopy characterises the surface properties of a powder, while high-frequency dielectric spectroscopy characterises the bulk properties of a powder. In this respect the linear relationship between K_{IC} and molecular weight found in this work could also be discussed as a measure of the number and strength of bonds formed, because bonding occurs at the surfaces of powder particles during compression. Obviously, an increase in molecular weight increases either the number of bonds formed per surface area, or the strength of the bonds formed increases. The relative proportion of hydroxyl end groups, which are directed towards the outside of the particle surfaces, to carbon chains decreases with an increase in molecular weight. This is probably complemented by a reduction in thickness of the hydrate shell. In consequence, carbon chains can come into close contact and contribute to the number of bonds formed.

The fracture toughness shows a logarithmic increase in value with increase in molecular weight of PEG (Fig. 8). Although both R and K_{IC} are expressions of the resistance of a material to crack propagation, they describe different modes of fracture and thus different relationships are possible.

3.4. The relationship between tensile strength and fracture mechanics parameters

Crack propagation occurs, if the extension of the crack results in more energy being available than is absorbed by the creation of the new surfaces [19]. Irwin [20] introduced the concept of 'strain energy release rate', G_{IC}, as a measure of the energy that is released during the crack extension by one unit length. The breaking of bonds requires an amount of energy $\Delta\gamma dA$, where $\Delta\gamma$ is the thermodynamic work of adhesion, and the excess $(G_{IC} - \Delta\gamma)$ is changed into kinetic energy assuming that there is no energy dissipation [21]. The value of $\Delta\gamma dA$ is therefore the mechanical energy released when the crack extends by dA. Tensile failure of tablets is a phenomenon of crack propagation [20,22] driven by the amount of G_{IC} released, and hence it appears reason-

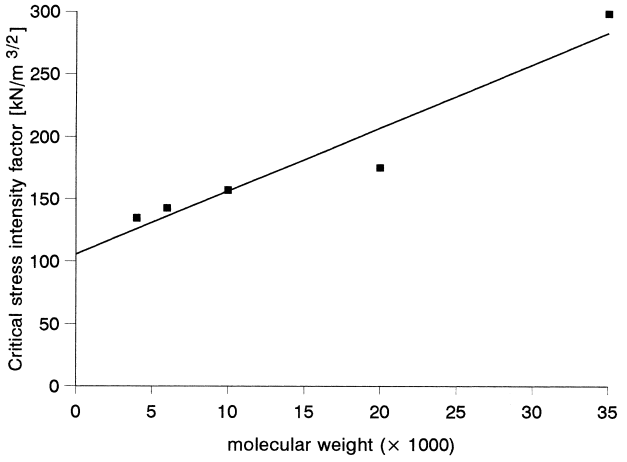

Fig. 7. Critical stress intensity factor K_{IC} at zero porosity as a function of the molecular weight of PEG.

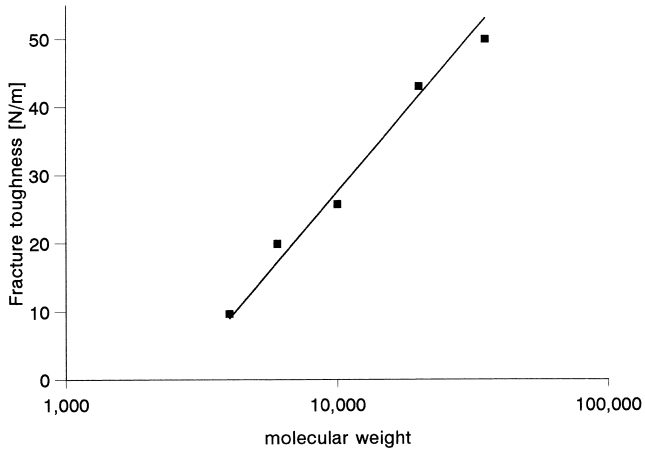

Fig. 8. Fracture toughness R at zero porosity as a function of the molecular weight of PEG.

able to model the values of σ_0 of the PEG powders as a function of G_{IC}.

The value of G_{IC} can be obtained from [23]:

$$G_{IC} = \frac{K_{IC}^2}{E} \quad (6)$$

The values of G_{IC} for the PEG samples are listed in Table 5. To model the proposed relationship, an indication of the flaw size is also required [22]. At zero porosity, the flaw size of the tablets is infinitively small for all PEG powders. However, the consolidation properties of PEG vary with molecular weight. For higher molecular weights it becomes more difficult to decrease the compact porosity (see for example Fig. 2), and the size of cracks and flaws should therefore be different from that of low molecular weight PEG. Hence, the molecular weight (MW) of PEG was used in the model to provide an indication of change in flaw size with chain length, although a direct relationship between fracture mechanical properties and molecular weight is rarely obtained for polymers [18]. The calculations were undertaken using the SPSS software package (Version 4.1, SPSS, London, UK).

The simplest statistical treatment to study the influence of more than one influence variable on one response variable is the use of the multiple regression in combination with analysis of variance (ANOVA). The analysis proposed a quadratic relationship of σ_0 on G_{IC}, which agrees with Irwin's [20] original observations. The relationship between the MW of the PEG samples appears to be linear. The final model has the form:

$$\sigma_0 = 0.001G_{IC}^2 - 0.136G_{IC} + 0.032\frac{MW}{1000} + 3.599 \quad (7)$$

Residual analysis (RMS deviation = 7.5%) verified the model equation to be an acceptable predictor for the tensile strength at zero porosity for different grades of PEG. Table 5 lists the experimental and predicted σ_0 values.

The ease of crack propagation increases the greater the amount of energy released [21]. Thus, an increase in the value of G_{IC} above a critical limit will be related to a decrease in σ_0. For PEG, the critical limit, i.e. the root point of the quadratic function, appears to lie between 13 and 15 N/m (see Table 5).

Table 5

Experimental and predicted values for the tensile strength at zero porosity for differentgrades of PEG

Grade	Strain energy release rate G_{IC} (N/m)	Experimental tensile strength σ_o (MPa)	Predicted tensile strength σ_o (MPa)
PEG-4000	7.5	2.50	2.77
PEG-6000	15.6	1.90	1.94
PEG-10000	13.3	2.80	2.31
PEG-20000	23.0	1.50	1.69
PEG-35000	90.1	1.24	1.24

4. Conclusions

PEG can be considered as material, which is weak from a strength point of view, but behaves in a ductile and a plastic manner, deforming under applied pressure. A linear relationship between the natural logarithm of the K_{IC} value and the molecular weight of PEG exists indicating a decrease in the brittleness of the polymer with the increase in oxyethylene units (chain length). However, the increase in chain length of the PEG has a non-linear effect on tensile strength and Young's modulus. The former appears to be driven by the reduction and distribution of flaws and cracks inside the specimens due to plastic deformation, while the latter appears to be a pure expression of the material properties. The tensile strength at zero porosity can be predicted from the values of the strain energy release rate and the molecular weight of the different grades of PEG.

Acknowledgements

We should like to thank Hikma Pharmaceuticals (Amman-Jordan) for the financial support of Muhammad A. Al-Nasassrah.

References

[1] P. York, Crystal engineering and particle design for the powder compaction process, Drug Dev. Ind. Pharm. 18 (1992) 677–721.
[2] J.M. Newton, A.B. Mashadi, F. Podczeck, The mechanical properties of an homologous series of benzoic acid esters, Eur. J. Pharm. Biopharm. 39 (1993) 153–157.
[3] A.A. Al-angari, J.W. Kennerley, J.M. Newton, The compaction properties of polyethylene glycols, J. Pharm. Pharmacol. 37 (1985) 151–153.
[4] K. Kendall, The impossibility of comminuting small particles by compression, Nature (London) 272 (1978) 710–711.
[5] A.B. Mashadi, J.M. Newton, The characterisation of the mechanical properties of microcrystalline cellulose: a fracture mechanics approach, J. Pharm. Pharmacol. 39 (1987) 961–965.
[6] P. Stanley, Mechanical strength testing of compacted powders, in: Postgraduate School, Production Process on Tablet Manufacture, The Pharmaceutical Society of Great Britain, London, 1985, pp. 123–144.
[7] F. Podczeck, J.M. Newton, Determination of Young's modulus of different microcrystalline cellulose products, Pharmazie 47 (1992) 387–388.
[8] W.F. Brown, J.E. Srawley, Plane strain crack toughness testing of high strength metallic materials, ASTM Special Tech. Publ. 410 (1967) 1–65.
[9] F. Podczeck, J.M. Newton, Determination of the critical stress intensity factor and the fracture toughness of different microcrystalline cellulose products, Pharmazie 47 (1992) 462–463.
[10] J.C. Roberts, J.M. Powers, R.G. Craig, Fracture toughness and critical strain energy release rate of dental amalgam, J. Mater. Sci. 13 (1978) 965–971.
[11] J.T. Fell, J.M. Newton, The tensile strength of lactose tablets, J. Pharm. Pharmacol. 20 (1968) 657–658.
[12] H. Larhrib, J.I. Wells, M.H. Rubinstein, Compressing polyethylene glycols: the effect of compression pressure and speed, Int. J. Pharm. 147 (1997) 199–205.

[13] C. Lin, T. Cham, Compaction behaviour and tensile strength of heat-treated polyethylene glycols, Int. J. Pharm. 118 (1995) 169–179.
[14] D.Q.M. Craig, J.M. Newton, R.M. Hill, An investigation into the low-frequency dielectric response of polyethylene glycols, J. Mater. Sci. 28 (1993) 405–410.
[15] R.M. Spriggs, Expression for effect of porosity on elastic modulus of polycrystalline refractory materials, particularly aluminium oxide, J. Am. Ceram. Soc. 44 (1961) 628–629.
[16] H. Larhrib, J.I. Wells, M.H. Rubinstein, G. Ricart, Characterization of PEGs using matrix-assisted laser desorption/ionisation mass spectrometry and other related techniques, Int. J. Pharm. 147 (1997) 187–198.
[17] J.L. Ford, A.F. Stewart, J.-L. Dubois, The properties of solid dispersions of indomethacin or phenylbutazone in polyethylene glycol, Int. J. Pharm. 28 (1986) 11–22.
[18] A.J. Kinloch, R.J. Young, Fracture Behaviour of Polymers, Applied Science, London, 1983, pp. 44, 174–175.
[19] A.A. Griffith, The phenomena of rupture and flow in solids, Trans. R. Soc. A 221 (1921) 163–198.
[20] G.R. Irwin, Analysis of stresses and strains near the end of a crack traversing a plate, J. Appl. Mech. 24 (1957) 361–364.
[21] D. Maugis, M. Barquins, Fracture mechanics and the adherence of viscoelastic bodies, J. Phys. D: Appl. Phys. 11 (1978) 1989–2023.
[22] N. Ouchiyama, J.J. Benbow, J. Bridgewater, On the fracture toughness of extrudates and its relationship to rates of bulk particle attrition, Powder Technol. 51 (1987) 103–114.
[23] M.A. Mullier, J.P.K. Seville, M.J. Adams, A fracture mechanics approach to the breakage of particle agglomerates, Chem. Eng. Sci. 42 (1987) 667–677.