JOURNAL OF MATERIALS SCIENCE: MATERIALS IN MEDICINE 7 (1996) 591–595

A comparison of the effects of γ-irradiation and ethylene oxide sterilization on the properties of compression moulded poly-d,l-lactide

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Compression moulded specimens from two batches of poly-d,l-lactide, of different molecular weights, have been subjected to γ-radiation and to ethylene oxide (ETO) exposure to establish the effects of sterilizing procedures on potential orthopaedic implants. Materials were exposed to between zero and 10 Mrad, and up to three standard ETO cycles. Tensile properties, dynamic mechanical behaviour, fracture toughness and hydrolytic degradation rates were measured. Molecular weight change was determined by size exclusion chromatography and solution viscosity. Calculated radiochemical yields suggest that the primary effects of irradiation are random chain scission. A clear relationship between properties and molecular weight was established and is used to interpret the relative effects of the two sterilization procedures. With γ-irradiation scission processes cause a fall in molecular weight in both batches whereas ETO only significantly affected the lower molecular weight batch. It is thought that the ETO effects are determined by moisture diffusion rates which are molecular weight dependent, and therefore property changes with the higher molecular weight material are more limited.

1. Introduction

Polymers based on lactic and glycolic acids have been widely investigated for applications requiring controlled bio-degradation [1]. The *in vivo* degradation mechanism is probably a random hydrolytic scission ultimately leading to lactic or glycolic acids, and because the degradation products are natural metabolites the polymers are particularly attractive as bio-engineering materials. Additionally, rates of degradation are such that products can be engineered to give reductions in mechanical integrity which match the rates of natural tissue re-building processes.

Products must be sterilized but steam sterilization is clearly precluded, leaving ethylene oxide (ETO) and γ-irradiation as the two possible alternatives. Both procedures are potentially capable of degrading the polymer: γ-irradiation through promotion of scission, crosslinking or photo-oxidation reactions and ETO through hydrolysis as a controlled amount of moisture must be present during sterilization to render the technique effective. In this work the effects of these two sterilization procedures on the properties of compression moulded samples of poly-d,l-lactide have been examined. The objectives were to quantify the extent to which the two available procedures degrade compression moulded samples and to investigate the fundamentals of the degradation processes. A further important part of the investigation was to establish what effects the sterilization procedures had on hydrolytic stability. Most published work on the effects of sterilizing radiation on lactide and glycolide polymers, for example [2–4], has been concerned with suture materials which have a high surface to volume ratio, and moulded materials have received much less attention. Increasing interest in the use of these materials for such devices as intramedullary bone plugs and fracture fixation plates provoked this investigation.

2. Experimental results

The materials used were commercial poly-d,l-lactides ex Boehringer, and were designated as Batch 1, which after moulding had M_w and M_n values of 105 200 and 60 000, and Batch 2, with M_w and M_n values of 206 700 and 114 200. Plaques 150 × 150 × 2 mm were compression moulded, from pre-dried material, at 110 °C and a pressure of 2.59 MPa. Test specimens of the appropriate dimensions were then machined from the mouldings and stored in darkness over silica-gel.

Molecular weight distribution was determined by size exclusion chromatography with THF as solvent and the polystyrene calibration was applied. Intrinsic viscosity, measured in chloroform at 25 °C, was also used to indicate average molecular weight. Mark–Houwink constants used were $K = 6.6 \times 10^{-4}$ and

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$\alpha = 0.67$ [5]. Throughout the work the two methods were found to give good agreement.

Irradiation was carried out in air with a cobalt 60 source at a dose rate of 0.156 Mrad h^{-1} to give received doses between zero and 10 Mrad. Although normal sterilization procedures use between 2.5 and 5.0 Mrad, previous work on other materials has shown [6] that higher dose levels can be useful in highlighting property change. A similar approach was used with the ethylene oxide sterilization where up to three repeat cycles were used. For each cycle preconditioning involved 17 h dwell at 50 °C ± 5 °C and a relative humidity of 60% ± 10%. The active gas mixture used in the exposure stage was 10% ETO, 90% CO_2 at a pressure of 2.84×10^5 Pa and the exposure time was 180–200 min. A humidification pressure of 0.11×10^5 Pa and a humidification dwell of 60–70 min were used.

Mechanical properties measured included tensile strength, flexural strength and modulus and fracture toughness. Standard procedures after ASTM D638 were used for the tensile testing and D790 for flexural testing. Fracture toughness was assessed using a single edge notch three point bend specimen, dimensions $75 \times 10 \times 2$ mm, and K_{IC} calculated assuming linear elastic fracture mechanics [7, 8]. The dynamic mechanical response was recorded using a Du Pont 982 resonant frequency instrument between − 100 °C and 100 °C. As some polymers are known to show significant post-irradiation ageing effects [6], tests were also carried out on irradiated materials stored in darkness over silica-gel for time periods of up to 100 weeks.

TABLE I Effect of γ-irradiation on the molecular weight of poly-d,l-lactide

Dose (Mrad)	M_w	M_n	M_w/M_n	M_v	η*
Batch 1					
0	86400	43300	1.99	79600	0.743
2.5	68000	31100	2.19	61400	0.630
5.0	55100	22200	2.49	49100	0.546
10	42000	18600	2.26	36600	0.452
Batch 2					
0	206700	114200	1.81	204400	1.358
2.5	116700	59800	1.95	106000	0.893
5.0	81000	34400	2.36	73000	0.703
10	66100	31200	2.12	59500	0.617

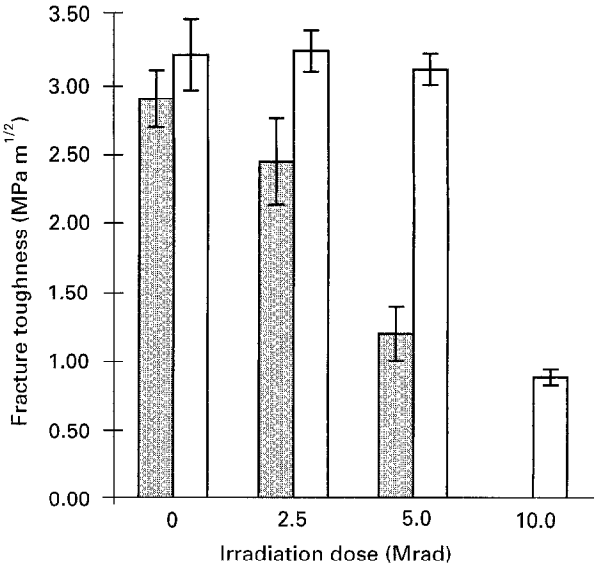

Figure 1 Effect of irradiation dose on fracture toughness: ▨ batch 1; □ batch 2. Standard deviations indicated by bars.

Table I details the effects of increasing radiation dose on the molecular weight of material from the compression moulded plaques of the two materials and Table II gives the corresponding tensile information. Fig. 1 shows the radiation induced changes in fracture toughness and Fig. 2 shows the effect of storage time on flexural strength. All results are the average of at least five tests.

The effects of repeated ethylene oxide sterilization on molecular weight is detailed in Table III. Specimens used were $75 \times 10 \times 2$ mm. Table IV shows how tensile properties change with ETO exposure and Fig. 3 shows the change in fracture toughness.

Rates of degradation *in vivo* are obviously of prime concern and to obtain some indication of the likely response both as-moulded and sterilized samples were stored in phosphate buffered saline of pH 7.4 at 37 °C. Mechanical properties were assessed over a period of 12 weeks and Fig. 4 compares the effects of the two sterilization techniques on the flexural strength of the low molecular weight Batch 1 material. Batch 2 materials showed much less relative change. The dynamic modulus of samples of irradiated Batch 1, material extracted from saline buffer after various time intervals, is shown in Fig. 5.

TABLE II Tensile properties of irradiated materials

Dose (Mrad)	Stress at yield (MPa)	Elongation at yield (%)	Stress at break (MPa)	Elongation at break (%)	Modulus (GPa)
Batch 1					
0	–	–	48.0	1.4	3.7
2.5	–	–	40.8	1.2	3.7
5.0	–	–	24.6	0.7	3.5
10	–	–	7.2	0.2	–
Batch 2					
0	49.1	1.6	41.9	11.7	3.7
2.5	48.9	1.6	43.7	4.0	3.7
5.0	–	–	47.3	1.3	3.7
10	–	–	25.3	0.7	3.6

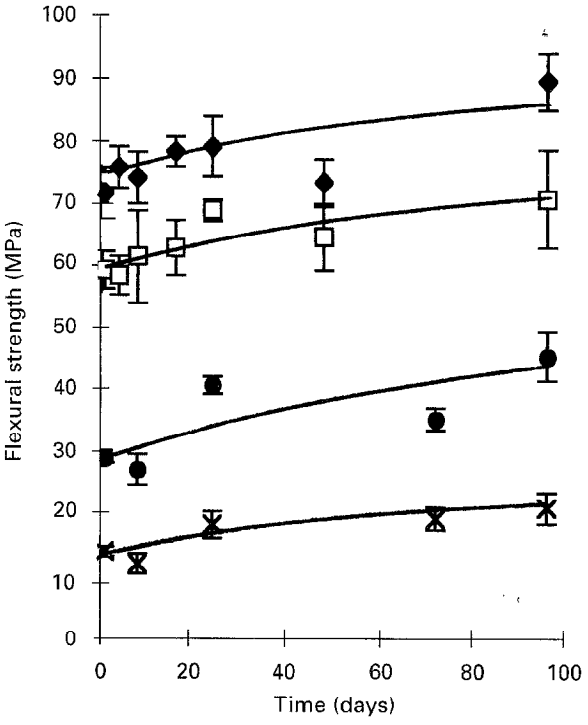

Figure 2 Effect of storage time on the flexural strength of irradiated material (Batch 1). Standard deviations indicated by bars: ◆ 0 Mrad; □ 2.5 Mrad; ● 5 Mrad; × 10 Mrad.

TABLE III Effect of ETO sterilization on the molecular weight of poly-d,l-lactide

Number of cycles	M_w	M_n	M_w/M_n	M_v	η^*
Batch 1					
0	86 400	43 300	1.99	79 600	0.743
1	91 300	43 300	2.12	82 100	0.758
2	78 800	41 500	1.90	71 900	0.697
3	68 300	36 700	1.86	62 800	0.639
Batch 2					
0	206 700	114 200	1.81	204 400	1.358
1	205 300	101 100	2.03	205 300	1.362
2	196 300	82 000	2.39	196 300	1.324

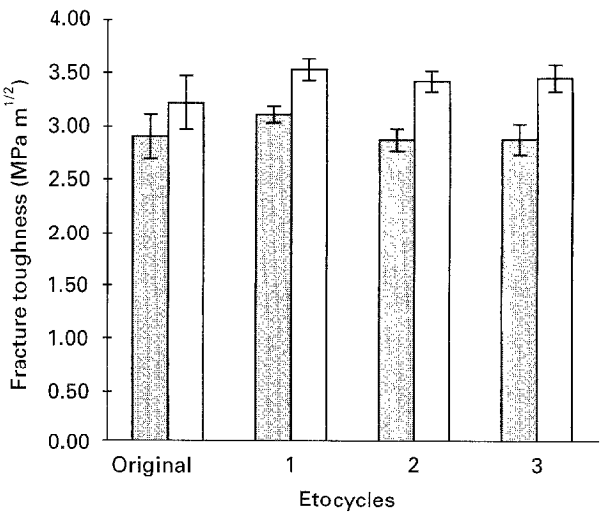

Figure 3 Effect of ETO sterilization on fracture toughness: ▨ batch 1; □ batch 2. Standard deviations indicated by bars.

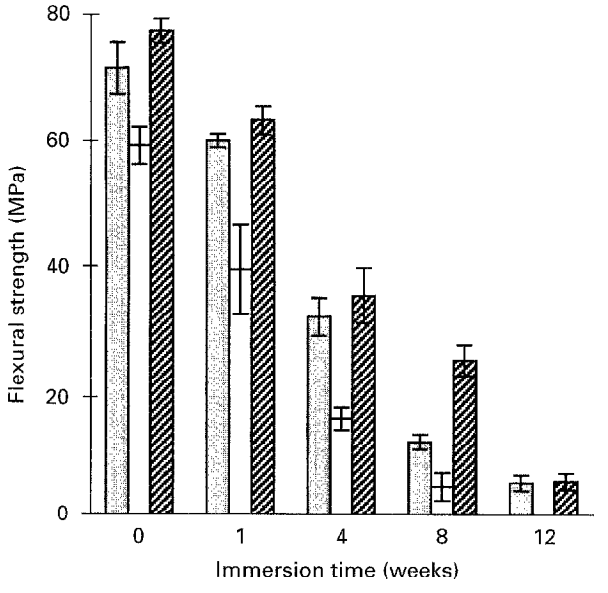

Figure 4 Effect of the two sterilizing techniques on the flexural strength of Batch 1 material: ▨ batch 1; □ batch 1, 2.5 Mrad; ▨ batch 1, ETO 1 cycle. Standard deviations indicated by bars.

3. Discussion

The mechanical test results demonstrate the importance of molecular weight in controlling the failure mode of these materials. In the as-moulded condition samples produced from the higher molecular weight polymer generally showed a ductile response to stressing whereas those from the lower molecular batch failed in a brittle manner on all occasions. These effects were particularly noticeable in the flexural testing where specimens of higher molecular weight

TABLE IV Tensile properties of ETO sterilized materials

Cycles	Stress at yield (MPa)	Elongation at yield (%)	Stress at break (MPa)	Elongation at break (%)	Modulus (GPa)
Batch 1					
0	–	–	48.0	1.4	3.7
1	–	–	46.6	1.6	3.6
2	–	–	46.2	1.7	3.4
3	–	–	39.7	1.4	3.1
Batch 2					
0	49.1	1.6	41.9	11.7	3.7
1	44.4	1.7	39.5	5.7	3.6
2	41.5	1.6	37.4	13.8	3.7

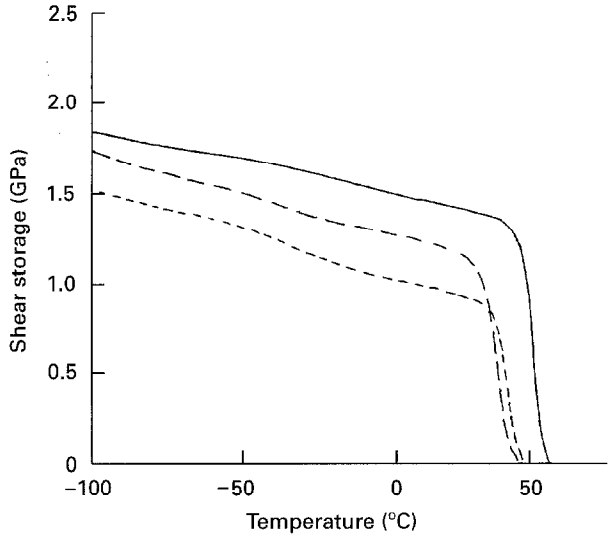

Figure 5 DMA response of 2.5 Mrad Batch 1 material after retrieval from saline buffer: — original; – – – 1 week in buffer; - - - - 4 weeks in buffer.

deformed to such a degree that meaningful flexural strength results could not be obtained. Similar molecular weight effects appear to dominate the response to sterilization.

Previous work [9] had suggested that the primary effect of sterilizing radiation was to reduce molecular weight and thus increase the likelihood of a brittle response to mechanical stressing. The more comprehensive results presented here confirm that observation. The greatest effect is observed with the Batch 2 material between zero and 2.5 Mrad where the molecular weight averages fall by about 45%. Subsequent reductions are proportionately much less and it is presumed that some form of weak link scission is involved in this initial change, perhaps associated with relief of moulding stress. The lower molecular weight Batch 1 material shows a clear dose related reduction in both tensile and flexural strength, but little change in the mode of failure, whereas the tensile response of the higher molecular weight Batch 2 material underwent a "ductile-brittle transition" at a dose of 5 Mrad, which corresponds to a fall in the weight average molecular weight from 206 700 to 81 000. The as-moulded molecular weight of the Batch 1 material was 86 400 and the similarity between the mechanical properties of this material and those of the Batch 2 material that had received 5.0 Mrad provide strong support for the hypothesis that the short term effects of irradiation on poly-d,l-lactide can be explained almost entirely in terms of chain scission processes.

The radiochemical yield for scission and crosslinking, G_s and G_x respectively, can be calculated by using the relationships [10];

$$\frac{1}{M_{n,D}} = \frac{1}{M_{n,0}} + (G_s - G_x)\frac{D}{100N_A}$$

$$\frac{1}{M_{w,D}} = \frac{1}{M_{w,0}} + \left(\frac{G_s}{2} - 2G_x\right)\frac{D}{100N_A}$$

where $M_{w,0}$ and $M_{w,D}$ are the weight average molecular weights at dose zero and dose D, M_n, etc., is the corresponding number average data, D is the received dose, usually in Mrads and N_A is Avogadro's number.

TABLE V Calculated radiochemical yields for scission (G_s), and crosslinking (G_x)

Material	G_s	G_x	G_s/G_x	Correlation coefficient[a]
Batch 1	3.06	0.16	19	0.99
Batch 2	2.34	0.19	12	0.94

[a]The correlation coefficient is obtained from a linear regression fit of the data points.

Table V details the results produced by this approach and they provide further confirmation of the relative importance of scission processes. There is a suggestion that the absolute values for radiochemical yield may be molecular weight dependent.

Following irradiation there is very little change in the dynamic stiffness even after 10 Mrad, but a clear dose related downward movement of T_g occurs. With Batch 1 material this involved a shift from 53.0 °C, as-moulded, to 49.0 °C after 10 Mrad and the halving of molecular weight provides a ready explanation.

It is more difficult to explain the time-dependent changes. Flexural strength increases with storage time with the greatest relative strength recovery occurring at the higher dose levels. Possible contributory mechanisms include physical ageing and chain recombination processes, although molecular weight measurement did not confirm the latter. For chain recombination to occur reactive end groups would have to be present, presumably those capable of ester formation, or perhaps trapped free radicals arising from the irradiation.

The results obtained from ETO sterilization also show the importance of initial molecular weight, but for rather different reasons. Here moisture diffusion rate appears to be the dominant factor. Batch 1 material is clearly more sensitive to ETO treatment with small but significant reductions in molecular weight and a matching reduction in tensile strength. In amorphous polymers the permeability coefficient decreases with increasing molecular weight [11] because of reductions in the chain end contribution to free volume. The effects observed here imply that water is obtaining easier ingression into the bulk of the lower molecular weight sample and subsequent degradation is then likely to be simple hydrolysis. The DMA results show that this material undergoes significant softening and a reduction in the glass transition temperature from 53 °C to 49 °C over the course of three ETO sterilization cycles, presumably reflecting both molecular weight reduction and water plasticization. By comparison the higher molecular weight polymer showed no change in the DMA behaviour under the same experimental conditions.

In the hydrolysis experiments material subject to a single 2.5 Mrad dose showed a significantly greater rate of stiffness and strength loss than similar specimens subject to a single ETO cycle. Table VI lists the corresponding hydrolytic degradation rates calculated from the relative change in molecular weight,

TABLE VI Hydrolytic degradation rates

Material	Rate (day^{-1})	Correlation coefficient[a]
Batch 1		
Unirrad.	1.46×10^{-2}	0.96
2.5 Mrad	1.45×10^{-2}	0.98
ETO (1 cycle)	1.10×10^{-2}	0.95
Batch 2		
Unirrad.	0.21×10^{-2}	0.90
2.5 Mrad	0.51×10^{-2}	0.96
ETO (1 cycle)	0.13×10^{-2}	0.77

[a] The correlation coefficient is obtained from a linear regression fit of the data points.

$\ln(M_{no}/M_{nt}) = kt$. The differences are presumed to be a consequence of the greater reduction in molecular weight which occurs on irradiation, with an immediate reduction in the measured mechanical properties and then an increased water absorption rate. If the hydrolytic degradation rate was controlled by a random scission process then molecular weight dependence should not be expected. The observed results confirm the suggestion that diffusion, either of water into the matrix or lactic acid out of the matrix, is the controlling factor.

An interesting possibility, suggested by the irradiation results, is the use of partial shielding during irradiation to provide variation in molecular weight throughout a moulded product. Given that rates of hydrolysis are controlled by molecular weight such a procedure offers the possibility of quite subtle control of the bio-degradation rate of the different parts of a single product.

4. Conclusions

The most important general observation is the critical importance of initial molecular weight in controlling the behaviour of these materials. Sterilization, by either γ-irradiation or ETO, has the ability to influence molecular weight, and can therefore have significant consequences for material properties. The irradiation induced change in failure mode is also an important observation as brittleness is likely to be a significant disadvantage in most practical applications of this polymer. Under the particular testing conditions used here the ductile–brittle transition appears to occur at a weight average molecular weight of about 100 000.

ETO treatment has less severe immediate consequences, but does expose the material to moisture with the potential for hydrolytic degradation. Molecular weight appears to control the rate of diffusion during the ETO sterilization process and therefore the materials susceptibility to property change during sterilization is again a function of the grade of polymer used. Long-term stability tests of ETO treated materials did not form part of this work but would be useful.

Both sterilization methods have clearly identified effects on the polymer but it is apparent that γ-irradiation has a significantly greater ability to inflict immediate damage. Initial molecular weight is important with both procedures. Factors affecting choice of polymer grade would normally include rates of *in vivo* degradation and consequent mechanical property change, and the ease of processing, but the results presented here suggest that the consequences of the sterilization procedure should also be taken into account.

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Received 6 February
and accepted 14 March 1996