Biodegradable polymers for use in surgery—polyglycolic/poly(actic acid) homo- and copolymers: 1

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The historical development of polyglycolic acid (PGA) and polylactic acid (PLA) polymers and copolymers for use in surgery is set down. Details of the synthesis of PGA and PLA polymers from their cyclic diesters are described, as well as a series of glycolide/lactide copolymers. The reactions were followed by time sampling techniques. The resulting samples were characterized by gel permeation chromatography (g.p.c.), differential scanning calorimetry (d.s.c.), thermogravimetric analysis (t.g.a.) and 220 MHz proton nuclear magnetic resonance spectroscopy (n.m.r.). Details of these analytical technicques are given. The respective reactivity ratios of glycolide and lactide are elucidated. The effect of ^{60}Co γ radiation on the molecular properties of PGA is also shown.

INTRODUCTION

Polyglycolic acid (PGA) has been known since 1954 to be a potentially low cost tough fibre forming polymer[1–4], but has one major limitation, i.e. hydrolytic instability. Many comonomers[4–7] have been used in an attempt to increase the hydrolytic stability, but have always produced materials with inferior properties to the homopolymer. Advantage has been taken of the hydrolytic instability, by copolymerizing small quantities of glycolic acid with polyethylene terephthalate (PET) in order to introduce weak linkages in the (PET) chain which can be used to change the surface finish of fibres[8].

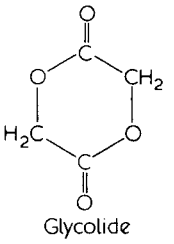
In 1962, PGA was developed as the first synthetic absorbable suture, Dexon®, by American Cyanamid Co.[9–12]. Du Pont[13] considered the polymer of the homologous α-hydroxy acid, polylactic (PLA), for the same application. Since 1970, PGA has been commercially available as the surgical suture Dexon®[14–19], and the copolymer of 92 m % GA/8 m % LA[20] has had a limited application as the competitive suture, Vicryl[21–22], since 1975.

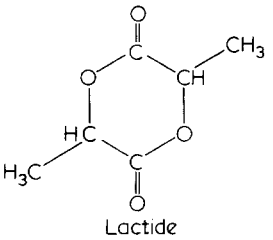
Over the past eight years there has been considerable interest in PGA, PLA and GA/LA copolymers as biodegradable materials in dental[23,24], orthopaedic[25] and drug delivery[26–30] applications, which have arisen out of the suture development. Although there are undoubtedly data within the classified literature of the suture companies, there is no basic information in the open literature on the molecular, compositional and morphological structure of this family of polymers.

We are particularly interested in the use of these materials as potential biocompatible hard blocks in biodegradable elastomers based on polyethylene oxide (PEO), as replacements for (PET) blocks described in our previous papers[31–33]. This paper describes the synthesis, characterization methods, and structure/property relationships of the family as a whole. We have studied those details of the synthesis which allow us to define the structure of the resulting polymers.

SYNTHESIS

Although the synthesis of PGA (PLA) is possible by the simplest polycondensation of glycolic (lactic) acids with antimony trioxide[4] the resulting polymer has low *MW*, and optimum properties are not obtained. The preferred method for producing high *MW* polymers is the ring opening polymerization of the cyclic diester, glycolide (lactide) using antimony[1,34], zinc[1], lead[35], or preferably tin[4,9,12,22] catalysts.


Glycolide


Lactide

Glycolide

Glycolide was synthesized by the method described in Sorenson and Campbell[36]. 1000 g of glycolic acid (Aldrich Gold Label) was placed in a three necked flask fitted with a stirrer, distillation head and condenser, a thermometer for monitoring the temperature of the melt, and a nitrogen bleed. The vessel was heated with an isomantle. 1 g of Sb_2O_3 was added and the temperature raised to 120°C. Polycondensation began and as the rate of water elimination fell, the temperature was increased to 180°C and pressure reduced gradually from 760–5 mm Hg over a period of 4–6 hours. (Thermogravimetric analysis (t.g.a.) of Dexon® (PGA) sutures had shown that 255°–270°C was the optimum range for the thermal unzipping reaction under vacuum to form glycolide monomer).

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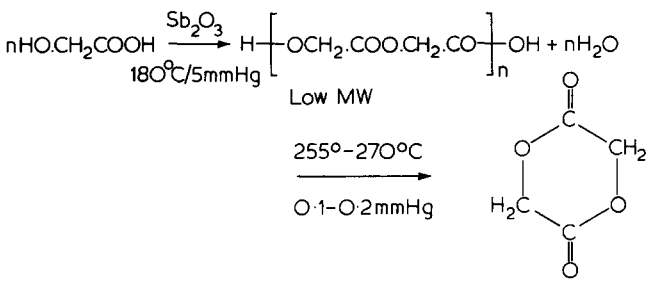
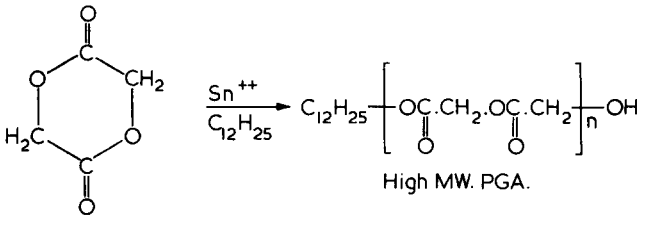


The temperature of the molten dark yellow low *MW* polyglycolic acid was raised to 255°C, an air condenser substituted for the water type, the vacuum increased to 0.1–0.2 mmHg and a clean receiver cooled in methanol/solid CO_2 inserted. Glycolide sublimed and distilled over and was collected initially as white crystals, and later as a pale yellow waxy solid. The yellow colour was removed by washing with chloroform, and after two recrystallizations from ethyl acetate, the pure glycolide remained as a white crystalline solid with a melting point of 80°C by differential scanning calorimetry (d.s.c.) at a heating rate of 10°C/min.

Lactide, obtained from Boehringer in sealed ampoules was recrystallized twice from toluene and had a similar appearance to glycolide with a melting point of 98°C by d.s.c.. Lactide was prepared in a similar manner to glycolide. Both glycolide and lactide were stored over P_2O_5 under vacuum until use.

Polyglycolic Acid

Frazza and Schmitt[11] proposed that the mechanism of polymerization of glycolide (lactide) by tin catalysts in the presence of lauryl alcohol[9] is cationic:



A preliminary comparison of PGA produced by $SnCl_2 \cdot 2H_2O$[9] and stannous octoate catalysts at 220°C showed no significant differences either in *MW* or *MWD*, and the latter catalyst was chosen for the rest of the work because of its acceptance by the FDA as a food stabilizer.

A set of homopolymerizations of glycolide was carried out to gain insight into the rate of conversion, and changes in *MW* and *MWD* with time. Glycolide was contained in evacuated sealed tubes containing 0.03% stannous octoate and 0.01% lauryl alcohol as a catalyst activator and chain control agent. The polymerizations were carried out in a silicone oil bath at 220°C for periods of time ranging from 5 min to 4 h. The reactions were quenched by placing the tubes rapidly onto sheets of aluminium foil in the refrigerator.

Residual monomer was removed by refluxing the crushed polymerization mixture in ethyl acetate, and weighing the insoluble polymer fraction to obtain % conversion, which is shown as a function of time in *Figure 1*. The results show that 80% conversion takes place within the first 30 min, and an additional 3½ h yields a further 16% conversion. After 4 h, 4% monomer remains, i.e. 96% is the limit of the polymerization.

The polymer fraction was molecularly characterized by gel permeation chromatography (g.p.c.) in hexafluoroisopropanol (HFIP). The results are shown in *Figure 2a*, with various *MW* averages as a function of conversion.

Chains of *MW* as large as 2×10^6 are present within the initial 30% conversion, indicating a range of propagation rates, and that the polymerization does not have the classical ionic mechanism where all chains begin at once and grow at a constant rate. Between 80 and 94% conversion the high end of the *MWD* is relatively stable, although the formation of low *MW* species occurs as seen by the fall of M_{n-1}. However, over the 3–4 h period (94–96% conversion) the *MWD* broadens considerably indicating transfer polymerization between polymer chains forming both longer and shorter chains. Sn^{2+} is known to be a depolymerization as well as a polymerization catalyst, and this may be the reason for the observed broadening of *MWD*.

The practical significance of the presence of high *MW* chains of PGA at low conversions is that any differences in the reactivities of glycolide and lactide monomers will lead to broad composition ranges not only within a given chain, but between chains produced early or late in the polymerization, due to depletion of the more reactive monomer.

Copolymers of Glycolide/Lactide

A series of copolymerizations were carried out at 200°C for periods of time ranging from 3–5 min with catalyst and activator concentrations as described above. Typical conversion levels were 10–15% which were required in order to calculate reactivity ratios and obtain relative reactivities. The polymerization mixtures were quenched as before, crushed and extracted with 50:50 ethyl acetate/60–80° petroleum ether for 72 h. Copolymer composition and % conversion were obtained on the pre-extracted polymers by t.g.a..

This was accomplished by running the respective polymerization mixture on t.g.a. at a heating rate of 10°C/min. For the copolymer polymerization mixtures a t.g.a. thermogram similar to that shown in *Figure 2b* was obtained. From the respective weight losses seen in these traces and a knowledge of which weight loss band refers to which component of the polymerization mixture one can calculate the % conversion and % composition of the copolymers by using the relevant ratios of A, B, C and D. 220 MHz proton n.m.r. in trifluoro acetic acid was used to determine the composition of the

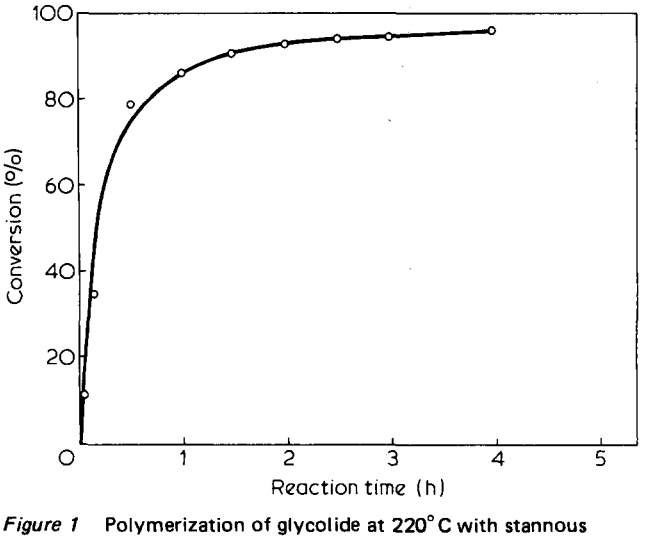


Figure 1 Polymerization of glycolide at 220°C with stannous octoate

polymer fractions. Ratios of absorbances at 5.11 ppm and 4.77 ppm were used to determine composition. The results of this series are shown in *Table 1*.

The results show that the copolymers initially formed are considerably richer in glycolide than the starting monomer mix. The compositions of the polymer relative to the monomer are shown in *Figure 3*. The reactivity ratios r_G and r_L were calculated according to the following equation:

$$\frac{G}{L} = \frac{r_G \frac{g}{l} + 1}{\frac{l}{r_L \frac{l}{g} + 1}}$$

where g and l are the molar concentrations of glycolide and lactide in the monomer mix, G and L the molar concentrations in the copolymer and r_G and r_L reactivity ratios. It was found that $r_G = 2.8$ and $r_L = 0.2$ at 200°C, which states that a chain with a growing glycolide end has a 3:1 preference for adding another glycolide unit, whereas an equivalent chain with a growing lactide end has a 5:1 preference for glycolide. Both conditions lead to blocks of glycolide separated by single lactide units where possible. Copolymers of glycolic and lactic acids will therefore have broad composition ranges, with glycolide always being preferentially polymerized at low conversions with lactide being incorporated to ever-increasing extents as the glycolide is depleted.

Narrow composition ranged samples may be possible using monomer feed techniques[37], however the need for accurate metering of a high temperature >100°C glycolide/lactide mixture, together with the rapidity of conversion, (i.e. 80% in 30 min) makes this prospect very difficult experimentally.

The composition ranges calculated for the 50:50 and 90:10 GA/LA copolymers, based on $r_G = 2.8$ and $r_L = 0.2$ are shown in *Figure 4*. The results show that for the 50:50 average composition, the range extends from 78% GA to pure PLA (at 80% conversion theoretically). Experimentally, no residual glycolide was detectable at 96% conversion. For the 90:10 GA/LA monomer mixture, the composition range is 97–45 m% GA, with the maximum of the distribution being 95.5 m% GA and the final overall average composition

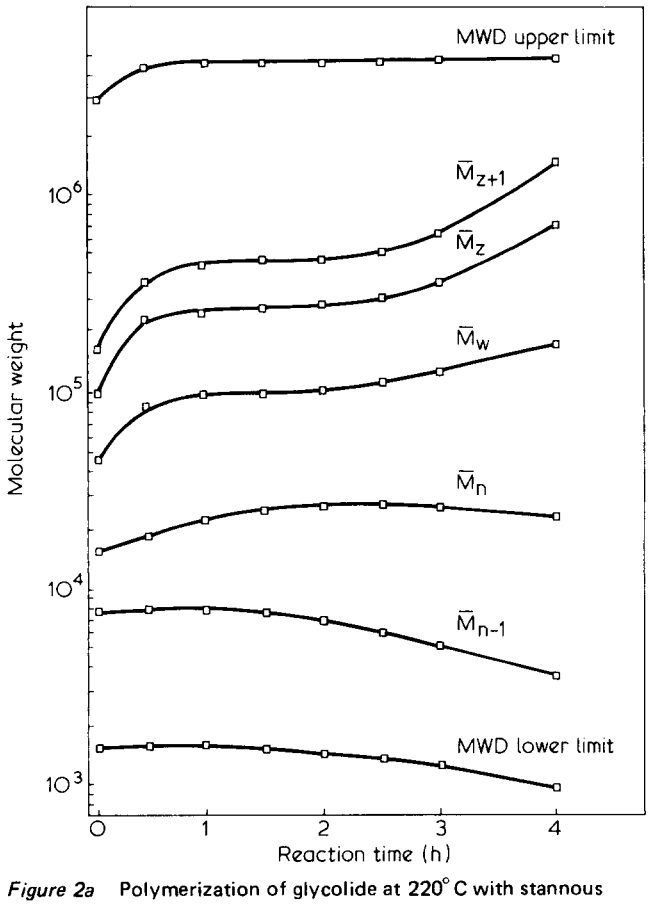


Figure 2a Polymerization of glycolide at 220° C with stannous octoate

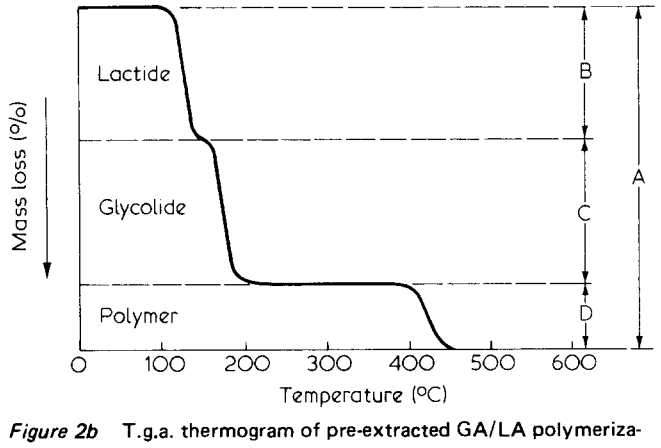


Figure 2b T.g.a. thermogram of pre-extracted GA/LA polymerization mixture

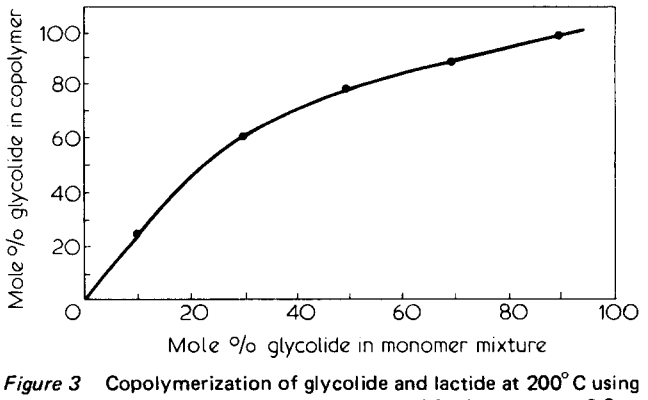


Figure 3 Copolymerization of glycolide and lactide at 200° C using stannous octoate as catalyst, reaction times of 3–5 min. $r_G = 2.8$; $r_L = 0.2$

Table 1 Relative reactivity studies for glycolide/lactide copolymerization

% Glycolide in monomer	Copolymerisation time in minutes	% Conversion	w% Residual Glycolide	% Glycolide in copolymer (t.g.a.)	% Glycolide in copolymer (n.m.r.)
10	5	12.9	6	24	23
30	4.5	13.6	19	62	60
50	4	12.4	35	81	78
70	3.5	16.4	56	82	84
90	3	14.6	71	98	97

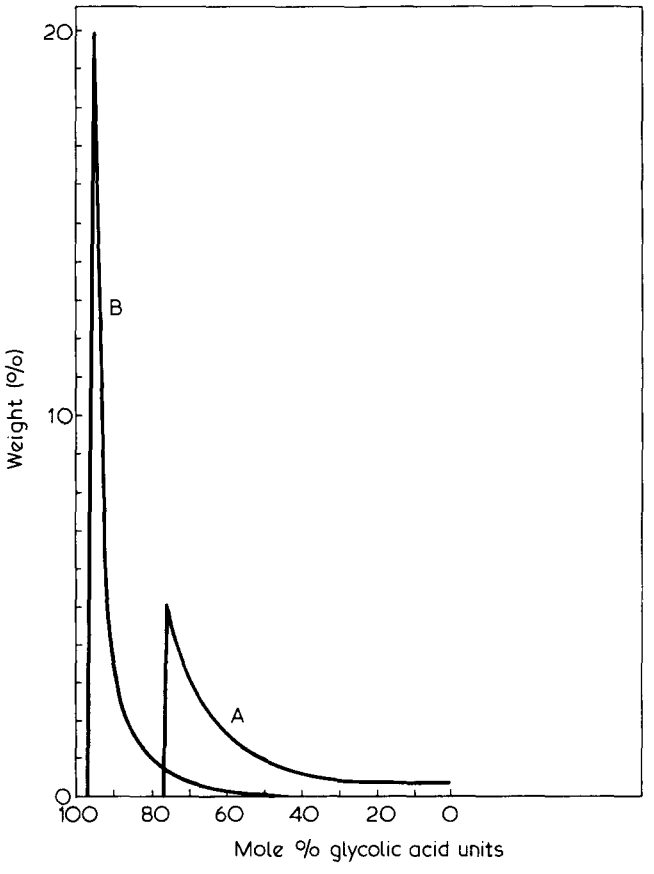


Figure 4 Composition distribution for (A) 50/50 and (B) 90/10 GA/LA copolymers

Table 2 Molecular characterization of low conversion copolymers by g.p.c.

% Glycolide in monomer	% Glycolide in polymer	$\bar{M}_n \times 10^{-3}$	$\bar{M}_w \times 10^{-3}$	M_w/M_n
10	23	20	80	4.0
30	60	24	82	3.4
50	78	28	86	3.1
70	84	32	92	2.9
90	97	37	98	2.7

being 92 m% GA at 96% conversion. The 4% residual monomer in the 90:10 copolymerization consists of 2% glycolide, 2% lactide which correlates well with the mean polymer composition.

The copolymers produced at low conversions were characterized by g.p.c. using 10^5 and 10^3 Å Styragel columns with HFIP at 1 ml/min. The results in *Table 2* show that *MW* increases and polydispersity, $\bar{M}_w/\bar{M}_n$, falls with increased glycolide content.

Homopolymers of P-l-LA, and P-dl-LA together with copolymers of the same monomer compositions as above were synthesized on 100 g scale in sealed tubes using 0.03% stannous octoate, 0.01% lauryl alcohol and taken to 96% conversion over 4 h at 200°C. Monomer residuals were extracted by refluxing with 50:50 ethyl acetate/60–80° petroleum ether. Films were cast from 20% solutions in HFIP and chloroform. Although the prior solvent is expensive, it is preferable as a casting solvent as final traces are more easily removed from the films than $CHCl_3$. The homo- and copolymers produced at 96% conversion had typical $\bar{M}_n$ of 2.5–4 x 10^4, $\bar{M}_w$ of 6–9 x 10^4 and $\bar{M}_w/\bar{M}_n$ of 3–4, which compare favourably with Dexon® and Vicryl®.

The materials were characterized morphologically by X-ray diffraction and d.s.c. at a heating rate of 10°C/min. Typical crystallinities for Dexon®, PGA surgical sutures were 46–52%, while poly-l-lactic acid (PLA) had crystallinities of 37%. Poly-dl-lactic acid (P-dl-LA) is amorphous.

D.s.c. is particularly important in studying the morphology of the GA/LA family of polymers. All compositions can be made amorphous by melting and quenching the d.s.c. pan on a cold aluminium block. This technique was used to provide a standard thermal history for each sample. Typical thermograms at a standard heating rate of 10°C/min., are shown for PGA, PLA and the 50:50 and 90:10 GA/LA copolymers in *Figure 5*. As can be seen, the PGA, PLA and 90:10 GA/LA copolymers show glass transitions T_g of 36°, 57° and 37°C respectively, followed by crystallization exotherms and high temperature melting endotherms. The 10:90 GA/LA copolymer is similar. The 30:70, 50:50 and 70:30 GA/LA copolymers produced in this study are amorphous, with d.s.c. thermograms similar to the 50:50 GA/LA in *Figure 5*, i.e. they exhibit only T_g.

T_g, melting and crystallinities are shown as a function of composition in *Figures 6a* and *6b*. These results show that the range of compositions from 25–70 m% GA are amorphous for GA/L-LA copolymers. If the dl-LA isomer is used, the amorphous region extends from 0–70 m% GA.

The practical significance of this phase diagram, *Figure 6a*, is that the amorphous range is ideal for applications where it is necessary to have mass loss simultaneous with molecular

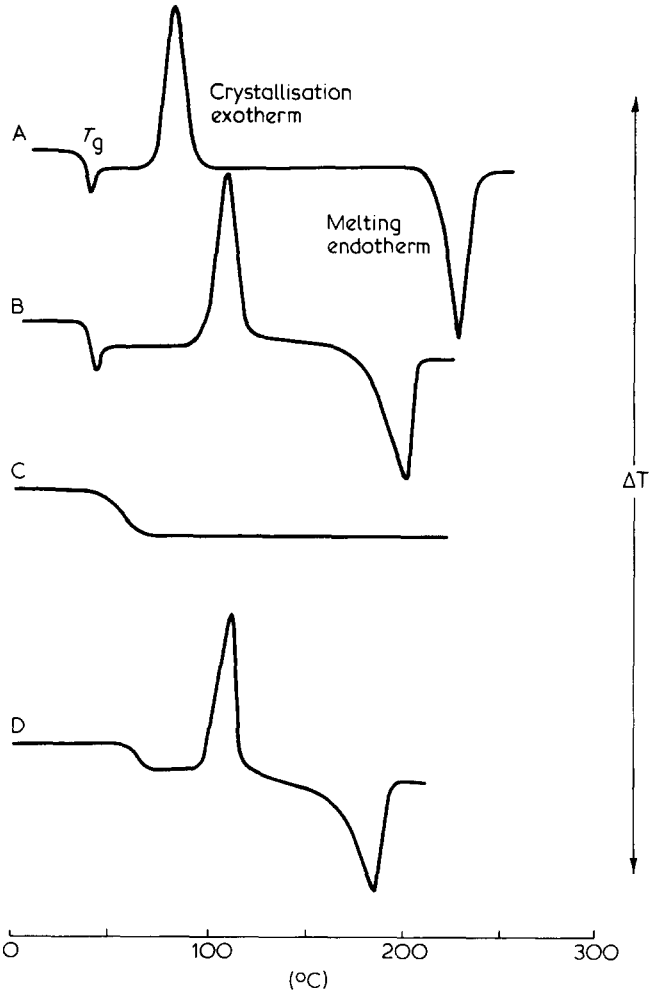


Figure 5 D.s.c. thermograms of GA/LA polymers. A, PGA; B, 90:10 GA/LA; C, 50:50 GA/LA; D, P-1-LA

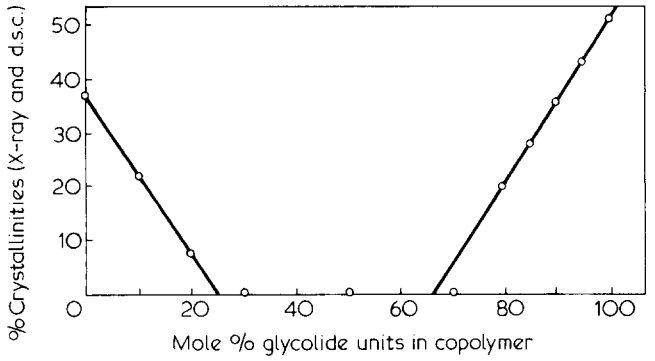


Figure 6a % crystallinities for GA/LA copolymers as a function of composition determined by X-ray and d.s.c. measurements

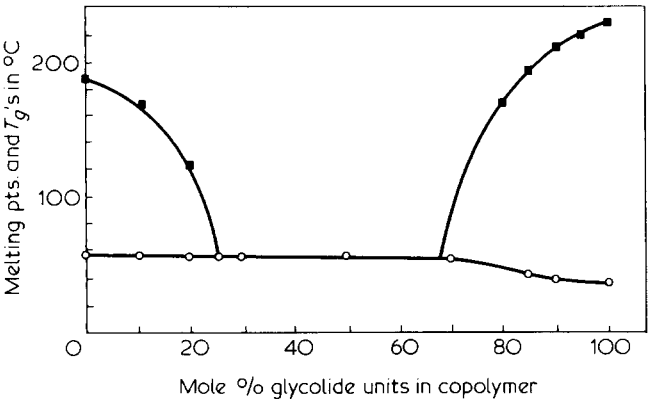


Figure 6b Melting points and glass transition temperatures for GA/LA copolymers measured by d.s.c. ■ melting points; ○ glass transition temperature

weight loss, or for applications (e.g. drug delivery) where it is necessary to have a monophasic matrix with a homogeneous dispersion of the active species. In cases where mechanical integrity needs to be sustained, e.g. sutures, orthopaedic or dental applications, partially crystalline compositions are necessary. It was found that amorphous PGA, P-L-LA, 10:90 and 90:10 GA/L-LA when implanted in the physiological environment or palced in water (or buffer) crystallized, partially, over 24–72 h, hence it is not possible to maintain quenched conditions over extended periods under physiological conditions.

The thermal stability of this family of copolymers was measured by t.g.a. under N_2 at a heating rate of 10°C/min: the thermograms are shown in *Figure 7*. Each composition can be melt-processed without thermal degradation, providing water is absent. Under N_2 or vacuum, the products of thermal degradation are glycolide and/or lactide.

^{60}Co γ-radiation is known to cause deterioration of Dexon® and Vicryl® sutures, at sterilizing doses of 2.5 Mrads. *Figure 8* shows the effect of γ-ray dosage on the *MW* averages of a particular sample. The unexpected more rapid fall of $\bar{M}_n$ than $\bar{M}_w$ suggests that random chain scission is not the primary mechanism. The $\bar{M}_{n-1}$ average which is most sensitive to the low *MW* tail of the *MWD* shows a dramatic fall even at doses as low as 1 Mrad, which indicates that large quantities of low *MW* material are formed by unzipping. This dramatic fall in *MW* explains why the initial strength of PGA sutures is unchanged by γ-sterilization and yet tensile strength falls to zero in 10 days of implantation. The mechanical integrity of the suture is maintained by the crystalline regions, but as soon as hydrolysis begins to disrupt the grain boundaries, a catastropic mechanical failure occurs in days rather than weeks.

Water uptake data were obtained on weighed 250 μ film samples by equilibration in 0.2 M pH7 phosphate buffer, for 3–4 days i.e. constant weight attainment. Water uptake as a function of composition is shown in *Figure 9*. Equilibrium water levels are low for the hydrophobic and crystalline PLA and low GA content copolymers. Water contents increase rapidly to 20–30%in the amorphous range, as hydrophilicity (GA content) increases. However above 70 m% GA, water levels again decrease with the onset of crystallization. Copolymers of 70 m% GA are expected to be the most hydrophilic, and hydrolysis, pH, temperature and enzyme effects would be expected to be most dramatic at this composition since this structure is under conditions of maximum hydration.

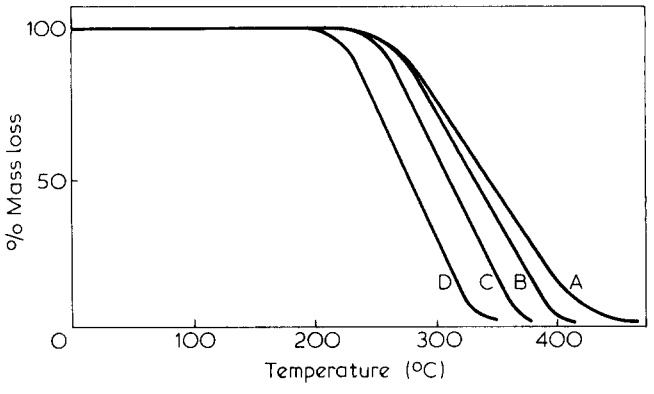


Figure 7 T.g.a. thermograms of GA/LA copolymers. Key as *Figure 5*

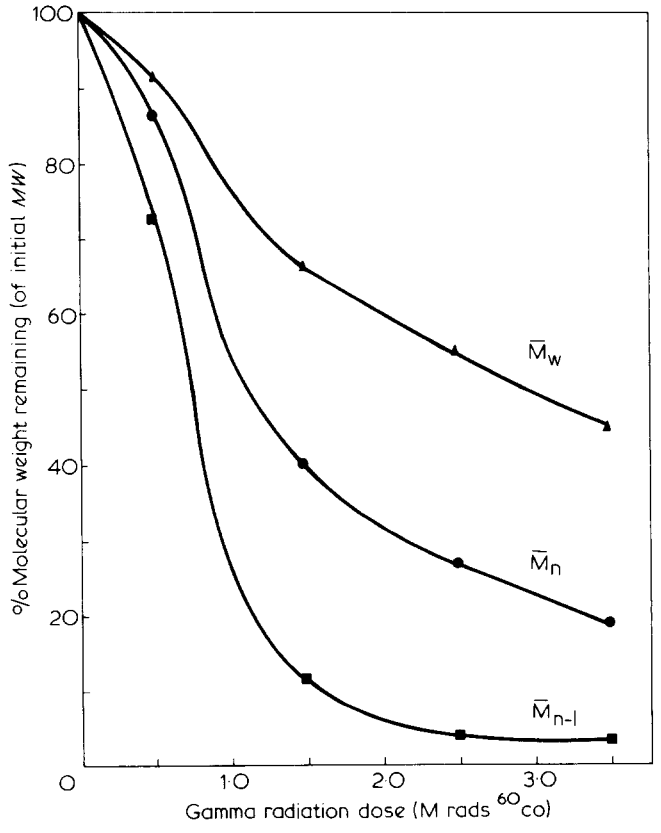


Figure 8 Effect of Gamma sterilization on the molecular weight distribution of Dexon® sutures, (PGA)

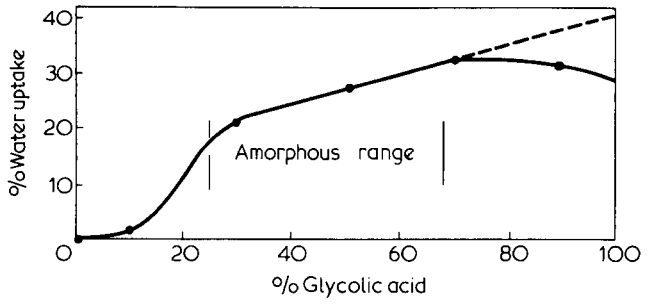


Figure 9 Water uptake data for glycolide/lactide copolymers

CONCLUSION

We have shown that homo and copolymers of glycolic and lactic acids can be made by the ionic polymerization of the cyclic diesters glycolide and lactide with tin-containing catalysts. These polymers have $\bar{M}_n \sim 2.5–4 \times 10^4$ and $\bar{M}_w \sim 6–9 \times 10^4$ and have broad composition ranges. 220 MHz proton n.m.r. in CF_3COOH is an easy and accurate method for compositional analysis. PGA has a typical crystallinity of ~50% whereas P-L-LA is ~37%. GA/LA copolymers are amorphous between 25 and 70 m% GA. γ-irradiation causes degradation by an unzipping mechanism. We were particularly interested in the possibility of replacing the PET hard block in PEO/PET copolymers[31,33] with PGA, PLA or GA/LA blocks. Studies of these copolymers are in progress and will be reported shortly.

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