Synthesis and hydrolytic degradation behaviour of high-molecular-weight L-lactide and glycolide copolymers

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High-molecular-weight copolymers of L-lactide and glycolide have been synthesized. The influence of the glycolide content on the mechanical and thermal properties of the as-polymerized copolymer was studied. Excellent mechanical properties and a large melting-point depression were observed. The dyad splitting of the carbonyl carbon atoms in the ^{13}C nuclear magnetic resonance spectrum was used to determine the average length of the monomer sequences. It was found that the synthesized copolymers did not reveal a truly random monomer distribution. Hydrolytic degradation of a copolymer containing 27 mol% glycolide showed that large amounts of highly crystalline material were still present after 140 days, and that 10 mol% glycolide has been incorporated in the poly(L-lactide) lattice.

(Keywords: biomaterials; copolymers; melting-point depression; sequence analysis; hydrolytic degradation)

INTRODUCTION

Because of the biocompatible and biodegradable properties of poly(L-lactide) (PLLA), much interest has been displayed in the polymerization and degradation behaviour of L-lactide and glycolide homo- and copolymers[1–6]. These polymers have been used for a variety of biomedical applications, ranging from surgical sutures[7–12] and drug release systems[13] to osteosynthetic devices[14–19] and vascular prostheses[20–22].

It has already been shown that the polymerization of L-lactide in the monomer melt at relatively low temperature results in the formation of very high-molecular-weight PLLA[1]. The as-polymerized material is semi-crystalline and possesses excellent mechanical properties. Therefore, it seemed a suitable material for use as resorbable internal fracture fixation devices.

Primary bone healing without callus formation was seen to occur when these bone plates were used to stabilize mandibular fractures in sheep[16]. The favourable results made it possible to explore the use of PLLA devices in man. A series of bone plates and screws were implanted in 10 patients for the internal fixation of zygomatic fractures[23]. Again, fracture healing was shown to be excellent.

However, in a parallel study poly(L-lactide) samples were implanted subcutaneously in rats. It was observed[24] that after 143 weeks an increased foreign-body reaction had developed, where foamy macrophages surrounded the implant-derived PLLA particles. The tissue reaction caused by the presence of crystalline PLLA debris might eventually result in granulomas comparable to Teflon granuloma[25].

Similar foreign-body reactions were found when poly(ε-caprolactone) was degraded *in vivo*[26]. A vascular granulation tissue containing macrophages, giant cells and fibroblasts was seen to develop upon fragmentation of the brittle, crystalline polyester.

In order to prevent these side-effects from taking place, the synthesis of high-molecular-weight L-lactide and glycolide copolymers was attempted. The crystallinity of these copolymers is expected to decrease with glycolide content, while the rate of degradation will increase simultaneously due to the more hydrophilic nature of the glycolide counterpart[5,27,28].

In this paper, results of the copolymerization of L-lactide with glycolide in the monomer melt are presented. The influence of the L-lactide/glycolide ratio on the mechanical, thermal and hydrolytic degradation properties of the as-polymerized material will be discussed.

EXPERIMENTAL

Copolymer synthesis

Copolymers of L-lactide and glycolide were prepared on a 30–300 g scale by ring-opening polymerization in the L-lactide/glycolide melt at 110°C in the presence of stannous octoate as catalyst[1].

L-Lactide and glycolide (CCA, Gorinchem, The Netherlands) were purified by recrystallization from dry toluene and a 1:0.9 toluene/1,2-dimethoxyethane mixture, respectively. 1,2-Dimethoxyethane was distilled from $LiAlH_4$; stannous octoate (Sigma Corp.) was used without further purification.

The copolymerization reactions took place under high vacuum in sealed silanized glass ampoules at 110°C. The polymerization time used was one week. The catalyst concentration was 1×10^{-4} mol/mol monomer.

The intrinsic viscosities $[\eta]$ were measured in chloroform at 25°C with an Ubbelohde viscosimeter, type OA.

Tensile testing

The mechanical properties of the copolymers were measured at room temperature on an Instron 4301 tensile

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tester. Rectangular bars, $4 \times 6 \times 50\,mm^3$, were machined from the as-polymerized material and subjected to tensile testing. The distance between the clamps was 25 mm and the crosshead speed was $10\,mm\,min^{-1}$.

Thermal analysis

D.s.c. measurements were carried out on a Perkin–Elmer DSC-7 differential scanning calorimeter. The sample size was 5–10 mg and the heating rate was $10°C\,min^{-1}$.

Wide-angle X-ray scattering

Wide-angle X-ray diffraction patterns were obtained on a Statton camera with pinhole collimation using Cu Kα radiation produced by a Philips X-ray generator operating at 45 kV and 45 mA. Samples were 1 mm thick and the sample–film distance was 5.375 cm.

Dynamic mechanical thermal analysis

Rectangular bars, $1 \times 6 \times 50\,mm^3$, were machined from the as-polymerized copolymers and tested in dual cantilever mode on a Rheometrics RSA II DMTA. The strain amplitude was 0.5% and the testing frequency was 1 Hz. Glass transition temperatures were determined from the maxima in the tan δ *versus* temperature curves.

Nuclear magnetic resonance

N.m.r. measurements were performed on a Varian 300 n.m.r. spectrometer. The ^1H n.m.r. spectra were obtained from copolymer solutions in deuterated chloroform in 5 mm tubes. Monomer conversion and L-lactide/glycolide ratios in the copolymers were calculated from these spectra. Spectra of copolymers not soluble in chloroform were obtained from solutions in deuterated chloroform to which small amounts of hexafluoro-2-propanol were added.

^{13}C n.m.r. spectra were obtained from copolymer solutions in hexafluoro-2-propanol ($10\,mg\,ml^{-1}$). Tubes of 10 mm diameter, with a coaxial inner tube containing deuterated benzene for the lock signal, were used. The number of transients was 5000, with a relaxation delay of 10 s. Average sequence lengths were calculated from the dyad splitting of the carbonyl signals.

Hydrolytic degradation

Bars ($4 \times 6 \times 50\,mm^3$) of the copolymer containing 27% glycolide were machined from the as-polymerized material and placed in screw-capped test tubes containing 15 ml of buffer solution of pH 6.9 (Titrisol, Merck). Buffer solutions were changed regularly and the temperature was maintained at $37 \pm 1°C$. After hydrolytic degradation, samples were carefully rinsed with demineralized water and dried over Sicapent (Merck) under vacuum. When constant weight was achieved, the remaining mass, intrinsic viscosity, tensile strength, copolymer composition and thermal characteristics were determined.

RESULTS AND DISCUSSION

Copolymerization and material properties

A series of copolymerizations of L-lactide and glycolide was carried out under identical conditions with respect to polymerization time, temperature and catalyst concentration. The effect of the amount of glycolide in the as-polymerized copolymer on the mechanical and thermal properties was studied. The results are summarized in *Table 1*.

In all cases monomer conversion was nearly complete. Unreacted glycolide could not be detected by ^1H n.m.r., but L-lactide conversion was more than 96% in every case, except in the copolymer containing 53.7% glycolide, where the L-lactide conversion was 80%. The higher reactivity of glycolide in comparison with L-lactide, as previously reported[3,29,30], accounts for the larger fraction of glycolide in the copolymer than charged in the monomer feed.

As shown in *Table 1*, the large values of the intrinsic viscosity, measured in chloroform, indicate that high-molecular-weight polymer has been formed. The decrease in intrinsic viscosity with increasing glycolide content may be due to the insolubility of glycolide sequences in chloroform. With higher glycolide contents and longer glycolide sequences, the relative quality of the solvent for the copolymer deteriorates, resulting in a smaller hydrodynamic volume and a lower intrinsic viscosity. The intrinsic viscosities of a number of copolymer samples were determined more than three weeks after synthesis. As the samples were stored in an ambient atmosphere and temperature, significant degradation had taken place, resulting in much lower values of $[\eta]$ than was to be expected. These measurements are indicated by dashes in *Table 1*. The copolymer with the highest glycolide

Table 1 Mechanical and thermal properties of as-polymerized copolymers of L-lactide and glycolide initiated by stannous octoate in the melt at 110°C

Glycolide (%)		σ	ΔH	T_m	T_g	$[\eta]$
in monomer feed	in polymer	(MPa)	($J\,g^{-1}$)	(°C)	(°C)	($dl\,g^{-1}$)
0	0	59.5	76.0	192.1	*a*	9.6
4.7	5.7	66.4	55.5	178.5	58.5	9.6
4.9	7.9	68.2	50.3	174.1	56.5	–
9.1	9.6	66.4	46.0	169.9	52.7	9.2
10.6	12.3	64.5	40.4	166.4	55.9	–
16.8	19.3	64.3	31.1	156.5	50.1	8.1
18.6	22.9	64.3	20.3	154.8	49.1	–
25.7	26.6	65.9	20.0	147.0	45.5	6.7
44.6	53.7	49.6	*a*	*a*	36.5	*b*

[a] Not detectable in d.s.c. scan
[b] Insoluble in chloroform at 25°C

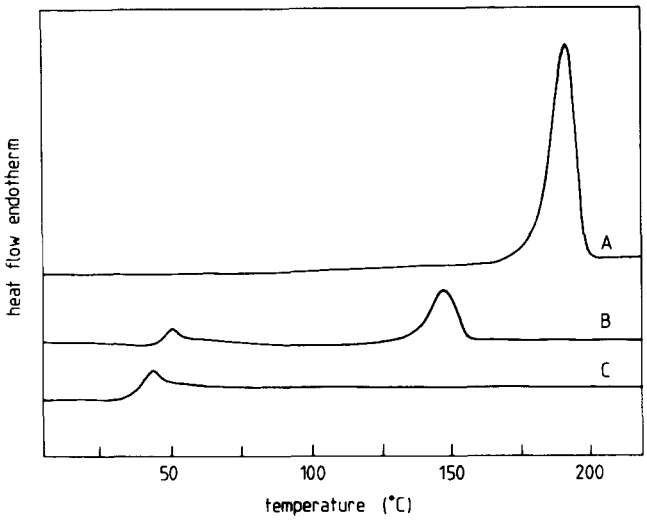

Figure 1 Characteristic d.s.c. thermograms of as-polymerized high-molecular-weight L-lactide homopolymer and L-lactide/glycolide copolymers: (A) poly(L-lactide); (B) 73/27 L-lactide/glycolide copolymer; (C) 47/53 L-lactide/glycolide copolymer

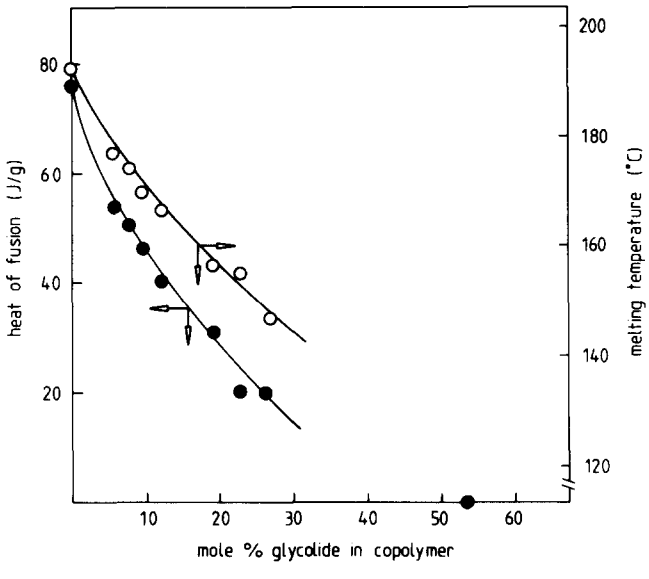

Figure 2 Dependence of the heat of fusion and the melting temperature of as-polymerized L-lactide/glycolide copolymers on the copolymer composition: (○) melting temperature; (●) heat of fusion

content was found to be insoluble in chloroform.

The mechanical properties at room temperature, as shown by the tensile strength measurements, are hardly dependent on the amount of glycolide in the polymer and on the degree of crystallinity. As long as the temperature is below the glass transition temperature of the polymer (T_g), polymer chains in the amorphous regions will be fairly immobile, and able to contribute to the strength of the material. The tensile strength for most of the copolymers even exceeds the value of the PLLA homopolymer. As a result of stress concentrations, fracture of the specimens in the tensile tests often occurred at the clamps. In spite of that, the mechanical properties appear to be outstanding.

Table 1 also shows the effects of copolymerization on the thermal properties, as characterized by differential scanning calorimetry (d.s.c.). The heat of fusion, melting temperature and the glass transition temperature are strongly affected by copolymerization.

Figure 1 shows typical d.s.c. scans for the studied system. The PLLA homopolymer shows a sharp melting endotherm peaking at 192°C, while a T_g value cannot be discerned. Copolymerizing with glycolide results in the lowering of the melting temperature and in a decrease in the heat of fusion; a glass transition also becomes apparent. The copolymer containing 53.7% glycolide shows the characteristics of an amorphous polymer; a melting endotherm is absent, and the glass transition temperature has shifted to even lower temperatures.

Glycolide units in the copolymer will tend to be excluded from the crystallites, resulting in a decrease in overall crystallinity and in smaller lateral crystallite dimensions, with a lower melting temperature. Besides this, partial incorporation of glycolide in the lattice structure of poly(L-lactide) will give rise to defects in the crystalline regions, also lowering the heat of fusion and the melting temperature. The magnitude of these effects is more clearly illustrated in *Figure 2*.

For random copolymers of crystallizable A units and B units that are not able to crystallize in the lattice characteristic of A, Flory derived the following equation for the melting-point depression[31]:

$$\frac{1}{T_m} - \frac{1}{T_m^\circ} = -\frac{R}{\Delta H} \ln(x) \qquad (1)$$

where T_m is the melting temperature of the polymer, T_m° is the equilibrium melting temperature of the defect-free polymer, R is the gas constant, ΔH is the heat of fusion per crystallizable unit and x is the fraction of the crystallizable comonomer. In this case, a plot of $1/T_m$ *versus* $\ln(x)$ will give a straight line. In *Figure 3* such a plot is given; it is clear that the Flory equation is not applicable to the L-lactide/glycolide copolymer. Incorporation of glycolide units in the L-lactide crystal lattice seems possible[32] and also a non-random comonomer distribution due to the difference in reactivity can be expected[3,29,30].

Average sequence lengths of L-lactide and glycolide in the copolymer can readily be determined by ^{13}C n.m.r. Carbonyl carbon atoms have been shown to be sensitive to

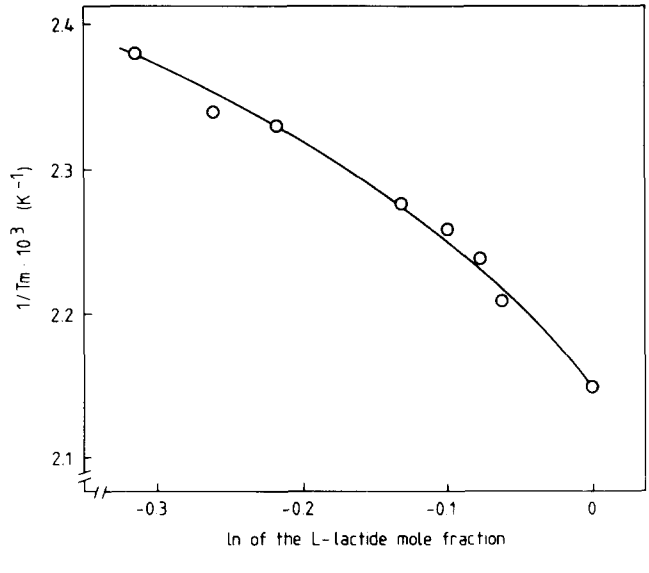

Figure 3 The variation of the reciprocal value of the melting temperature with the logarithm of the L-lactide mole fraction in the copolymer

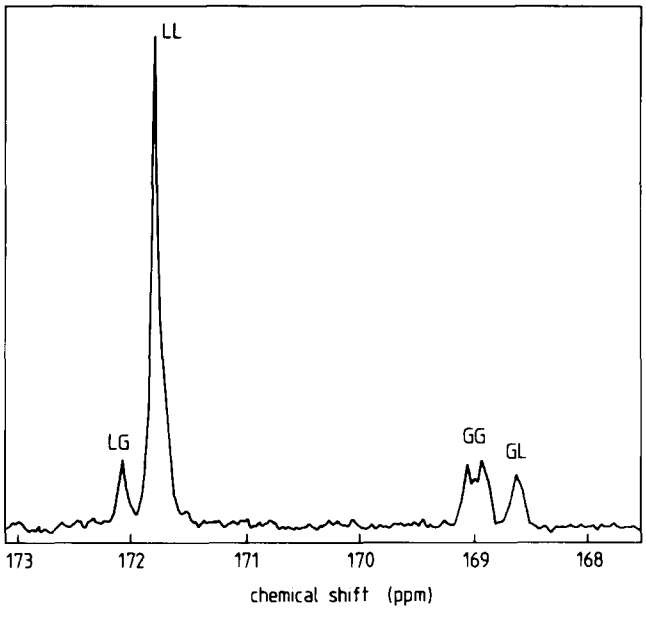

Figure 4 ^{13}C n.m.r. spectrum of a 73/27 L-lactide/glycolide copolymer showing the dyad splitting of the carbonyl carbon atoms

Table 2 ^{13}C n.m.r. sequence analysis of L-lactide and glycolide copolymers initiated by stannous octoate in the melt at 110°C

Glycolide (%) in polymer	$\bar{L}_L$	$\bar{L}_G$	$\bar{L}_G/(\bar{L}_G+\bar{L}_L)$ (%)
19.5	12.0	2.8	18.9
26.6	7.9	3.0	27.5
41.7	5.1	3.7	42.0
53.7	4.8	4.3	47.3

monomer sequences[33], and when hexafluoro-2-propanol is used as the solvent, a dyad splitting of the carbonyl carbon atoms is observed[30]. *Figure 4* shows this dyad splitting in the ^{13}C n.m.r. spectrum. The average sequence lengths in monomer units $\bar{L}$, of the L-lactide and glycolide blocks can be calculated from the relative intensities of the L-lactyl–L-lactyl, L-lactyl–glycolyl, glycolyl–glycolyl and glycolyl–L-lactyl signals:

$$\bar{L}_L = \frac{I_{LL}}{I_{LG}} + 1$$
$$\bar{L}_G = \frac{I_{GG}}{I_{GL}} + 1 \qquad (2)$$

Table 2 shows the average sequence lengths determined by ^{13}C n.m.r. A good correlation between glycolide concentration determined by ^{1}H n.m.r. and the average glycolide sequence length fraction indicates that the calculated values are reasonably accurate.

It is evident that these copolymers do not show a truly random distribution; a random copolymer would yield an average glycolyl sequence length, $\bar{L}_G$, equal to 2. The blocky structures, however, may have been randomized to some extent by transesterification reactions. With increasing glycolide concentration, the average glycolide sequences increase in length. The copolymer with average glycolide sequence length 4.3 was found to be insoluble in chloroform.

In any case, glycolide sequences were not long enough to give rise to crystallization of glycolide blocks. In *Figure 5* the wide-angle X-ray diffraction pattern of the 26.6% glycolide-containing copolymer is presented. The reflections have been calculated to arise from unoriented L-lactide sequences crystallized in the α-structure of poly(L-lactide)[34,35]. No trace of glycolide sequences crystallizing in the planar zig-zag sheet structure of poly(glycolide)[36] is visible, in agreement with the d.s.c. results presented in *Figure 3*. The WAXS diffraction pattern of the copolymer containing 53.7% glycolide revealed a completely amorphous structure.

Of major importance in the testing of polymer materials for use in load-carrying biomedical devices is the performance of these materials in the physiological environment. The mechanical and thermal properties after immersion in water at 37°C are not often mentioned in the literature concerning the subject. Dynamic mechanical thermal analysis was used to measure the influence of these effects. The results are listed in *Table 3*. The T_g value was determined from the maximum in the tan δ *versus* temperature curve.

The PLLA homopolymer shows a glass transition temperature of 73.5°C. Copolymerizing with glycolide results in a decrease of T_g, but at 37°C the 26.6% glycolide copolymer still retains the high E' storage modulus value of the PLLA homopolymer. The amorphous copolymer with 53.7% glycolide has a T_g value below body temperature and is therefore not a suitable material for bone fixation devices.

It was also found that immersion of the 26.6% glycolide copolymer in water at 37°C for 60 h resulted in a water absorption of 1.5% by mass. Even though the maximum of the tan δ curve was not shifted, water absorption resulted in the appearance of a shoulder in the broadened tan δ curve, thereby reducing the E' storage modulus value at body temperature. This re-

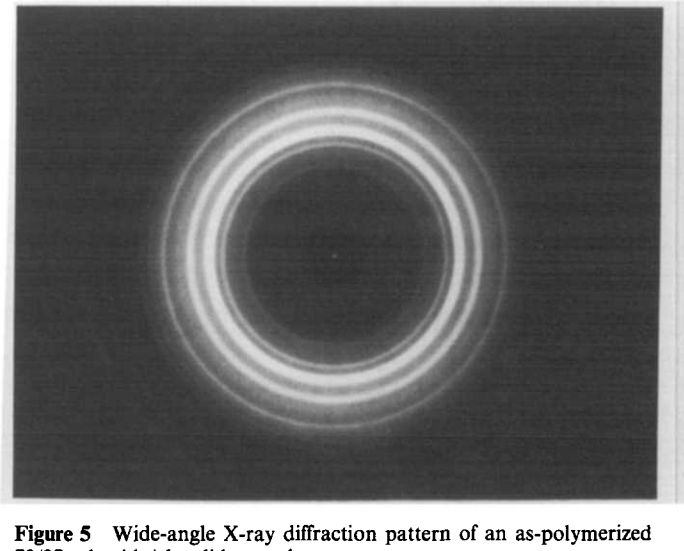

Figure 5 Wide-angle X-ray diffraction pattern of an as-polymerized 73/27 L-lactide/glycolide copolymer

Table 3 Dynamic mechanical thermal analysis of as-polymerized L-lactide and glycolide copolymers

Glycolide (%) in polymer	T_g (°C)	E' (at 37°C) (GPa)
0	73.5	5.8
26.6 (dry)	51.0	5.8
26.6 (wet)	51.0	2.2
53.7	35.8	0.2

duction in modulus might even prove to be too large for the use of this copolymer as a fracture fixation device. Nevertheless, this copolymer was chosen as a starting point to study the *in vitro* degradation behaviour of these as-polymerized copolymers.

Hydrolytic degradation

No significant differences between *in vivo* and *in vitro* degradation of unstressed polylactones have been found[2,4,37], indicating that polymer degradation occurs predominantly via simple hydrolysis of the ester bonds. The degradation behaviour of the as-polymerized copolymer containing 26.6% glycolide was studied by immersing rectangular bars, $4 \times 6 \times 50\,mm^3$, in buffered solutions at pH 6.9 at 37°C. To ensure constant pH, buffer solutions were refreshed regularly. Changes in intrinsic viscosity, tensile strength, mass, polymer composition and crystallinity were monitored as a function of degradation time.

In *Figure 6*, the tensile strength and remaining mass are plotted as functions of degradation time. It can be seen that the loss of tensile strength is rapid, and that load-bearing properties have declined to zero within a month. The initial intrinsic viscosity, $6.7\,dl\,g^{-1}$, had also decreased rapidly to a value of $0.8\,dl\,g^{-1}$ in 15 days.

Mass loss was not simultaneous with loss of molecular weight and strength, but lagged behind, indicating bulk erosion of the polymer sample[4,37,38]. Diffusion of water into the amorphous domains will result in the scission of (taught) tie molecules that connect the crystalline regions. A great loss of tensile properties occurs practically without any loss of mass.

The change in appearance of the as-polymerized copolymer during degradation is displayed in *Figure 7*. Initially the copolymer is amber coloured and slightly translucent. Upon hydrolysis, recrystallization takes place and the colour of the material changes to white. Samples that were degraded for periods of time longer than one month needed to be handled very carefully. At this time the material was brittle and fragmented very easily.

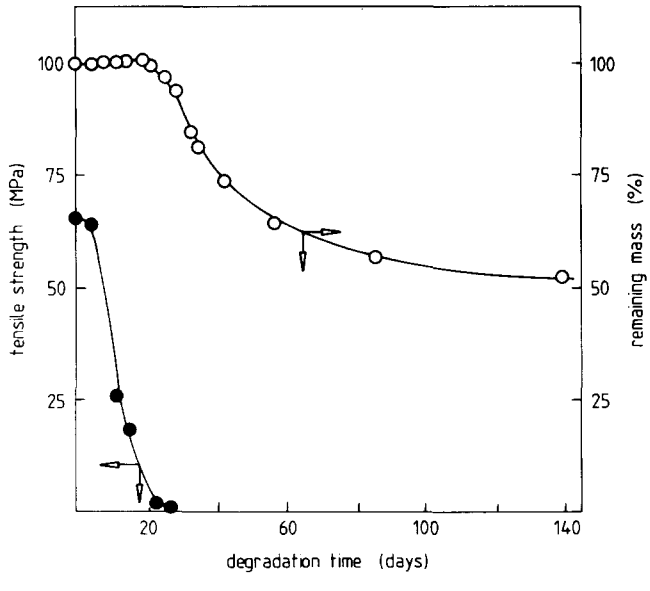

Figure 6 Loss of tensile strength and mass upon hydrolytic degradation of an as-polymerized 73/27 L-lactide/glycolide copolymer at 37°C in a buffered solution of pH 6.9: (○) remaining mass; (●) remaining tensile strength

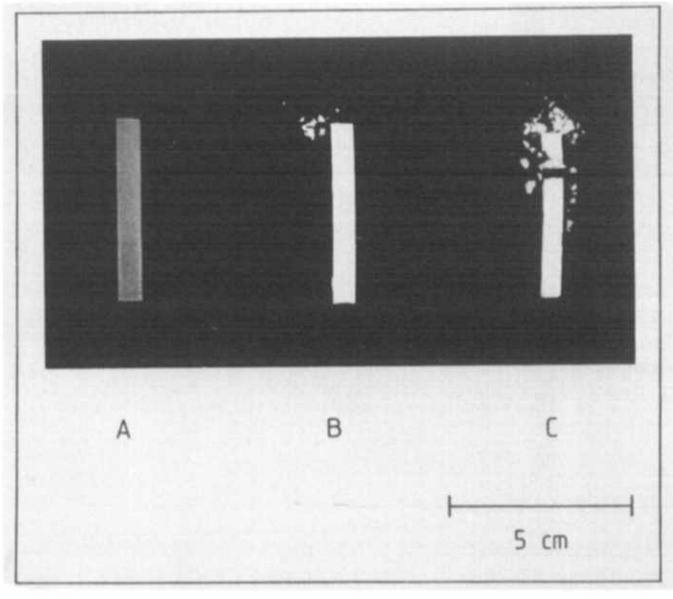

Figure 7 The change in appearance of the as-polymerized 73/27 L-lactide/glycolide copolymer during hydrolytic degradation: (A) copolymer before hydrolysis; (B) copolymer after 33 days of hydrolytic degradation; (C) copolymer after 86 days of hydrolytic degradation

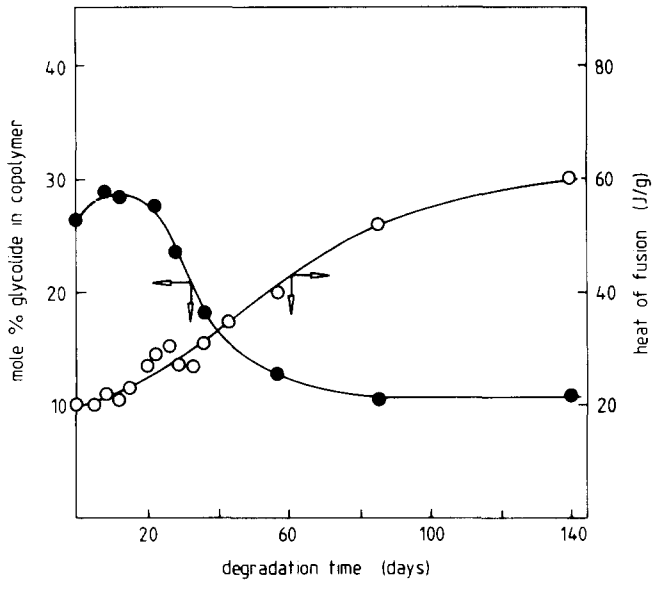

Figure 8 Variation of the heat of fusion and the copolymer composition of an as-polymerized L-lactide/glycolide copolymer of initial composition 73/27 with degradation time at 37°C in a buffered solution of pH 6.9: (○) heat of fusion; (●) glycolide concentration in the copolymer

Figure 8 shows the variation of the glycolide content and the heat of fusion of the copolymer with time. When water diffuses into the amorphous regions, the glycolide ester bonds will be scissioned most rapidly, as indicated by the decrease in glycolide concentration in the copolymer. The initial increase in glycolide content may be caused by diffusion of oligomeric or low-molecular-weight poly(L-lactide) chains out of the bulk of the material. The constant glycolide concentration at longer immersion times shows that a definite amount of glycolide is incorporated into the poly(L-lactide) lattice.

Partially degraded tie chains become more mobile due to a less entangled conformation and recrystallize, resulting in an increase in crystallinity. This effect has been observed for several polyesters[2,38,39]. The decrease

in rate of mass loss, as observed by the levelling off of the remaining mass profile in *Figure 6*, can be correlated with the decrease in glycolide content in the copolymer and the increase in crystallinity.

It can be seen that, after long degradation periods, 50% of the initial mass is still present in a highly crystalline form. Because of the incorporation of 10% glycolide in the poly(L-lactide) lattice, however, hydrolysis upon phagocytosis by macrophages might be more rapid than in the case of the PLLA homopolymer. This effect may be even more pronounced in the case of random copolymers with shorter L-lactide sequences.

The use of other catalysts[30] and other comonomers, such as D-lactide or D,L-lactide with a reactivity comparable to L-lactide, are currently being investigated.

CONCLUSIONS

High-molecular-weight copolymers of L-lactide and glycolide can be synthesized by ring-opening polymerization in the monomer melt at relatively low temperatures with stannous octoate as catalyst. The mechanical properties are excellent, comparable to those of the PLLA homopolymer. Tensile strengths of 64–68 MPa were measured for copolymers containing up to 26.6% glycolide.

When used in biomedical devices, plasticization effects due to water absorption in the physiological environment can result in lowering of the mechanical properties at body temperature.

Degradation experiments showed that, after long hydrolysis periods, 50% of the initial mass was still present, the material was highly crystalline and the rate of mass loss was quite low. The constant glycolide concentration at high immersion times indicates that an amount of 10% glycolide is incorporated in the poly(L-lactide) lattice.

True random copolymers with shorter L-lactide sequences should prevent the large increase in crystallinity and the slow mass loss upon hydrolytic degradation experienced with the copolymers investigated in this study.

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