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High molecular weight copolymers of L-lactide and ε-caprolactone as biodegradable elastomeric implant materials

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Summary

High molecular weight copolymers of L-lactide and ε-caprolactone have been synthesized by ring opening copolymerization with stannous octoate as catalyst. The good mechanical properties of the 50/50 copolymers make it a suitable material for biomedical applications such as nerve guides etc., where degradation of the elastomeric implant is required. In contrast to the frequently used MDI containing polyurethanes, degradation products of the P(LLA-ε-CL) are non toxic. The use of such a material is therefore preferable.

Introduction

In medicine, biodegradable polyurethanes are widely used as elastomeric biomaterials (1). Examples of applications are veins (2,3,4), nerve guides (5,6), artificial skin (7) and meniscus prostheses (8). However, segmented medical grade polyurethanes like Estane, Pellethane, Biomer and Mitrathane contain aromatic diphenylmethane diisocyanate (MDI) in the hard segments. It has been shown (9,10,11) that upon processing and degradation of the polymer, the toxic and carcinogenic methylenedianiline is formed and released. A degradable elastomeric biomaterial, without these serious side effects is highly desirable.
We have synthesized a biocompatible, high molecular weight copolymer of L-lactide and ε-caprolactone with good mechanical properties. Hydrolysis of this polymer will yield L-lactic acid and ω-hydroxy hexanoic acid as the degradation products.

Experimental

Materials

L-lactide (CCA, The Netherlands) was purified by recrystallization from dry toluene. ε-caprolactone (Janssen Chimica, Belgium) was purified by drying over CaH_2 and distillation under reduced nitrogen atmosphere. The catalyst stannous octoate (Sigma Corp., USA) was used as received.

Polymerizations

Copolymers of L-lactide and ε-caprolactone were prepared in silanized glass ampoules. To the mixture of freshly purified monomers an amount of 1.10^{-5} mole catalyst per mole of monomer was added, after which the ampoules were evacuated and heat sealed. After thorough homogenization at the polymerization temperature, the polymerization reaction was set to take place at 110 to 120

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°C for the required time period.

Polymer Processing

The synthesized polymers were purified and freed from unreacted monomer and low molecular weight polymeric material by precipitating chloroform solutions into 40/60 mixtures of acetone/hexane. P(LLA-ε-CL) films were prepared by casting copolymer solutions in chloroform. Estane films were cast from dioxane solutions. The nerve guides were prepared by dipcoating glass rods with a diameter of 1.25 mm.

Polymer Characterization

Intrinsic viscosities were measured in chloroform at 25 °C with an Ubbelohde viscosimeter. Gel permeation chromatography of polymer samples was carried out at 30°C on a Waters GPC 150 with chloroform as the eluens. An estimate of the molecular weight was obtained by using the Mark-Houwink constants for PLLA ($K=5.45\ 10^{-4}$ dl/g and a=0.73).
Thermal characteristics were measured on a Perkin-Elmer DSC-7. 5-10 mg samples were heated at a rate of 10 °C/min.
The mechanical properties of polymer films were measured on a 4301 Instron tensile tester. Stress-strain diagrams of the films were obtained at a crosshead speed of 12 mm/min at room temperature.
X-ray diffractograms were measured on a Philips PW 28 diffractometer using Cu-Kα radiation. Of the as-polymerized homo polymers round disks were machined and used for the diffraction experiments. In the case of copolymers, a film on glass was measured.
Copolymer solutions in deutero chloroform were measured on a Varian XR-300 spectrometer. 300 MHz ^{1}H NMR was used to determine monomer conversion and copolymer compsition. Average monomer sequence lengths were determined by 75 MHz ^{13}C NMR.

Results and Discussion

A number of 50/50 mole per mole L-lactide and ε-caprolactone copolymers were synthesized by ring opening polymerization. When careful purification and polymerization procedures are applied, it is possible to synthesize very high molecular weight copolymers as shown in Table 1. Under the applied conditions L-lactide conversion was essentially complete in all cases. At 110 °C, 98 to 99 mole % of ε-caprolactone had been converted into polymeric material, at 120 °C ε-caprolactone conversion was 91 %.

Table 1
Characteristics of the synthesis of 50/50 P(LLA-ε-CL)

sample	pol. temp. (°C)	pol. time (days)	% ε-caprolactone (mole %)	[η] (dl/g)
1	110	17	51.8	9.9
2	110	17	52.7	9.9
3	110	14	45.5	8.5
4	120	5	51.6	7.8
5	120	8	48.5	8.0

A typical gel permeation chromatogram of a P(LLA-ε-CL) sample synthesized at 110 °C is given in Figure 1. It can be seen that high molecular weight polymer with a relative low polydispersity, D=1.63, has been formed. Previous investigations (12,13) have shown that the synthesis of L-lactide and ε-caprolactone homo polymers with stannous octoate also leads to polymers with low dispersity values.

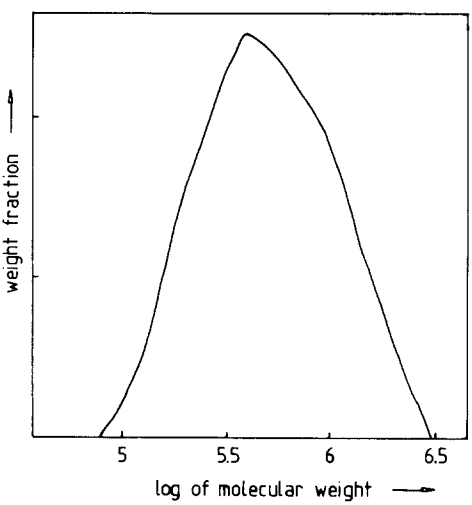

Figure 1:
GPC curve of 50/50 P(LLA-ε-CL) synthesized at 110 °C.

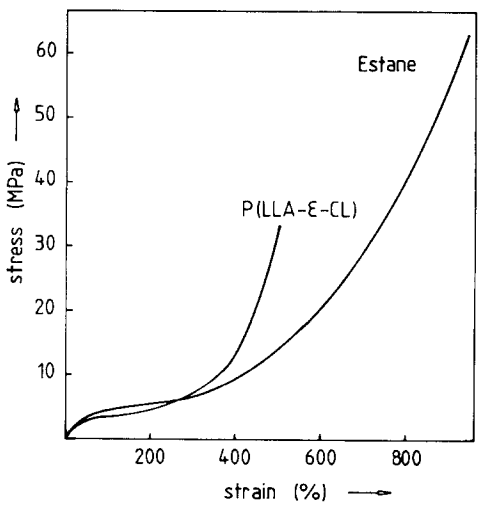

Figure 2:
Stress-strain diagrams of Estane and 50/50 P(LLA-ε-CL) films.

A comparison of the mechanical properties of P(LLA-ε-CL) and Estane is given in Figure 2. This figure shows the stress-strain behaviour of films of both materials at ambient conditions. Estane has a tensile strength of 63 MPa and a strain at break of 950 %. The presence of crystallizable hard segments in the polyurethane chains give it the excellent mechanical properties. P(LLA-ε-CL) shows a similar behaviour to Estane at strains up to 300 %. At higher elongations, strain induced crystallization results in strain hardening of the material and break at 500 %. The tensile strength is 34 MPa.
Thermal analysis by DSC of the precipitated P(LLA-ε-CL) material, Figure 3, shows a Tg at -15 °C. This single Tg, in between the values of Pε-CL -60 °C and PLLA 57 °C, indicates a continuous amorphous phase. The presence of a small melting endotherm (ΔHm = 4.3 J/g) at 71 °C and an even smaller one at 115 °C can be discerned. As the melting temperature of Pε-CL has a value of 64 °C, it follows that the physical crosslinks are small crystalline domains consisting of crystallized L-lactide sequences.

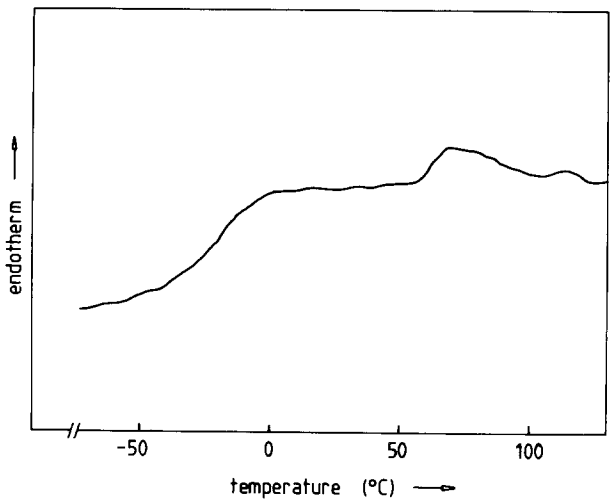

Figure 3:
DSC thermogram of 50/50 P(LLA-ε-CL) after precipitation.

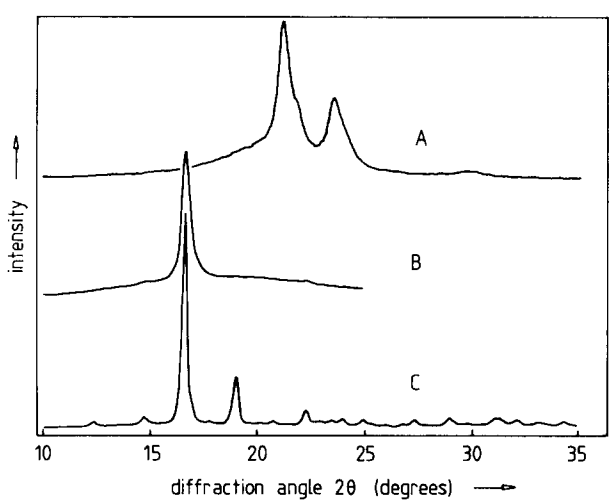

Figure 4:
X-ray diffraction pattern of Pε-CL (A); 50/50 P(LLA-ε-CL) (B) and PLLA (C)

X-ray diffractograms are given in Figure 4. Crystalline Pε-CL (A) shows two

distinctive maxima at diffraction angles of 21.1 and 23.4 degrees 2Θ. The highly crystalline PLLA (C) shows a large number of diffraction peaks. The sharpest and most intense one being the 020 reflection at 16.69 degrees 2Θ. Other peaks can be observed at 14.75, (101 reflection); 19.05, (023 reflection) and at 22.34 (121 reflection) degrees 2Θ. The diffraction spectrum of the P(LLA-ε-CL) (B) film consists of a relatively intense reflection at 16.65 degrees 2Θ and two less resolved peaks at 14.75 and 22.26 degrees 2Θ. These values coincide with the observed values of the PLLA α structure (14). Crystallization of ε-caprolactone sequences could not be detected.
The fact that L-lactide sequences in the 50/50 copolymer are capable of crystallizing, indicates the presence of relatively long L-lactide sequences in the polymer chains. ^{13}C NMR was employed to calculate the average monomer sequence lengths. In Figure 5, the splitting of the carbonyl carbon atom signals of ε-caprolactone and L-lactyl units due to neighbour effects is shown. Measurement of the signal intensities allows the calculation of average sequence lengths (15). A random incorporation of monomers should yield a $\bar{L}c$ of 2 and a $\bar{L}L$ of 4.

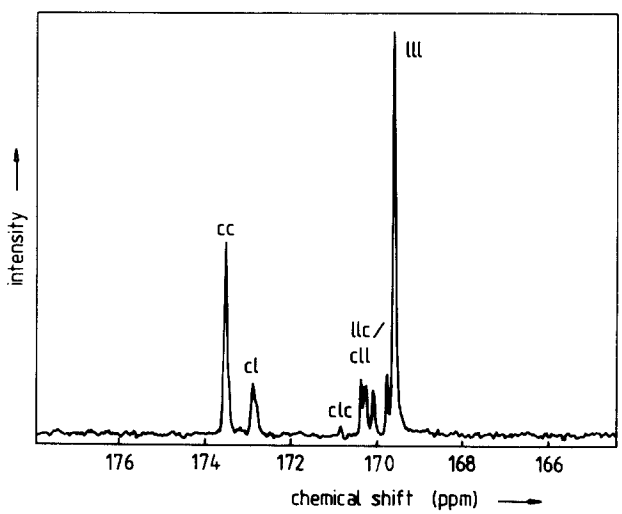

Figure 5:
Splitting of the L-lactyl and ε-caprolactone carbonyl signals due to sequence effects in the ^{13}C NMR spectrum of 50/50 P(LLA-ε-CL).

The calculated average sequence length values for copolymers synthesized at different temperatures are given in Table 2. Higher polymerization temperatures result in smaller average sequence lengths due to possible transesterifications and a less pronounced difference in reactivity ratios of L-lactide and ε-caprolactone at higher temperatures. The table indicates that the monomers are not randomly incorporated in the polymer chain. Due to the difference in reactivity of both monomers, a broad distribution of monomer sequence lengths can be expected (16). At low conversions L-lactide is polymerized preferentially, while at longer polymerization times ε-caprolactone will be built in as L-lactide is depleted.

Table 2
Average sequence lengths of 50/50 P(LLA-ε-CL) determined by ^{13}C NMR

sample	pol. temp. (°C)	% ε-caprolactone (^{1}H NMR)	$\bar{L}c$	$\bar{L}L$	$\frac{\bar{L}c}{\bar{L}c + \bar{L}L/2}$
3	110	45.5	3.7	8.5	46.5
5	120	48.5	2.5	6.5	48.5

This 50/50 copolymer can be used for the preparation of a large number of degradable elastomeric implants. As an example, a two-ply biodegradable nerve guide is shown in Figure 6. The inner layer provides a barrier for the ingrowth of perigraft scar tissue into the lumen. The macroporous outer layer permits capillary and fibrohystiocytic tissue ingrowth, and gives the necessary mechanical strength. A two-ply nerve guide of which only the inner layer was made of P(LLA-ε-CL) has already been described (6). Further details on the preparation and the in vivo performance of a complete P(LLA-ε-CL) nerve guide will be published soon (17).

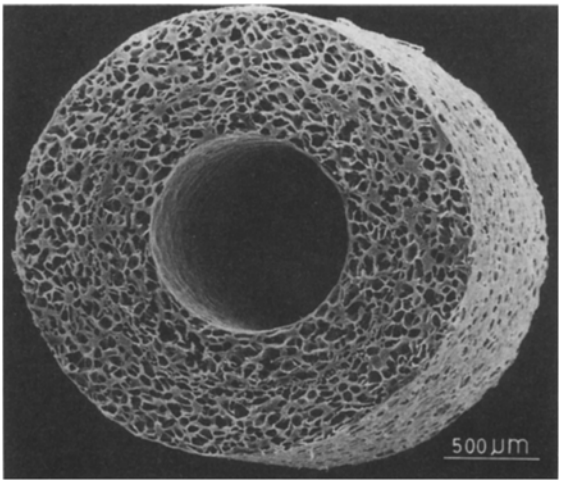

Figure 6:
Degradable nerve guide prepared by a dipcoating technique of solutions of the copolymer in chloroform and DMF/dioxane mixtures.

Conclusions

Very high molecular weight copolymers with intrinsic viscosities [η] up to 9.9

dl/g can be synthesized by ring opening polymerization of 50/50 L-lactide and ε-caprolactone monomer mixtures. The copolymers show a non random distribution of monomer, resulting in the presence of long crystallizable L-lactide sequences. These crystalline domains account for the good mechanical properties of the material, and make it suitable for use as a strong, degradable, biomedical elastomer.

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