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Changes in chemical and thermal properties of the tri-block copolymer poly(L-lactide-*b*-1,5-dioxepan-2-one-*b*-L-lactide) during hydrolytic degradation

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Abstract

Hydrolysis of the novel tri-block copolymer poly(L-lactide-*b*-1,5-dioxepan-2-one-*b*-L-lactide) of different compositions has been studied in buffered salt solution at 37°C and pH 7.4. Specifically, polymer weight loss, composition changes, molecular weight changes, thermal properties and release of lactic acid and 3-(2-hydroxyethyl)-propanoic acid have been detected. The degradation was found to start immediately after the sample was immersed into the aqueous buffer solution. The rate of degradation was influenced only by the original molecular weight, the copolymer composition had no significant effect. The heat of fusion and T_g increased with degradation time due to an increased amount of L-lactide (L-LA) in the polymer matrix. The GC–MS analysis showed that up to 70% of the theoretical amount of 3-(2-hydroxyethyl)-propanoic acid and 10–20% of lactic acid was released after 23 weeks of degradation.

Keywords: Tri-block copolymer; L-lactide; 1,5-dioxepan-2-one

1. Introduction

Poly(hydroxy acid)s are an important class of degradable polymers for biomedical applications due to their biocompatibility and physiologically tolerable degradation products. Polylactide is one of the most intensively studied biodegradable synthetic materials because of its beneficial mechanical properties and adjustable hydrolyzability [1–3]. The homopolymer of L-lactide is highly crystalline and stiff. Copolymerisation of L-lactide with different types of cyclic monomers provides an important contribution to the already existing materials, since it combines the inherent properties of each homopolymer [4–6]. Presently, polylactide, polyglycolide and poly(ϵ-caprolactone) homo- and copolymers constitute the most promising materials in the field of surgery and pharmaceutics [3,7,8].

In many medical applications there is a need for degradable materials that are similar to human tissue with respect to tensile strength and elasticity [9]. Block copolymerisation is recognised as an interesting possibility to create new, highly flexible materials. Block copolymers often have unique morphology and physical properties, due to microphase separation. In a previous paper we have reported the synthesis of the tri-block copolymer poly(L-lactide-*b*-1,5-dioxepan-2-one-*b*-L-lactide) by controlled ring-opening polymerisation [10]. The blocks exhibited different physical properties, poly(1,5-dioxepan-2-one) [11] formed a soft, amorphous block and poly(L-lactide) formed a hard, semicrystalline segment. The combination of different properties resulted in thermoplastic elastomeric behaviour.

Degradation of poly(L-LA) and copolymers in an aqueous environment occurs through hydrolysis of the ester group in the main-chain. The in vitro degradation has been investigated thoroughly [2,12,13]. The molecular weight, molecular weight distribution [14], ionic strength of the degradation medium [15] and the size and shape of the devices [16] subjected to degradation are factors that influence the rate of degradation. The purpose of this work is to study the effects of copolymer composition and molecular weight on the in vitro hydrolysis. In the present study we have monitored the hydrolytic degradation of solution cast films of poly(L-lactide-*b*-1,5-dioxepan-2-one-*b*-L-lactide) in terms of change in composition, weight loss, molecular weight, release of degradation products and change in crystallinity. SEC, NMR and DSC have been utilised to follow the degradation. The formation of degradation products has been analysed by gas chromatography–mass spectroscopy.

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Table 1
Molecular characteristics and thermal properties of the tri-block poly(L-lactide-*b*-1,5-dioxepan-2-one-*b*-L-lactide) prior to hydrolysis

Polym. no.	DXO/L-LA[a] (%)	$\bar{M}_n$[b]	$\bar{M}_w$[b]	T_g[c] (°C)	T_m[c] (°C)	ΔH[c] (J/g)
1	93/7	65 100	88 900	−32.8	–	–
2	89/11	74 900	97 700	−32.6	123.4	4.52
3	87/13	64 900	80 800	−32.7	130.3	7.67
4	80/20	68 400	88 900	−33.9	143.7	10.9
5	77/23	77 300	96 100	−33.8	152.3	15.2
6	75/25	65 400	84 900	−33.0	154.0	16.7
7	75/25	53 700	70 100	−33.6	149.8	15.5

[a] Molar composition of the copolymer as determined by ^{1}H NMR.
[b] Molecular weight of the tri-block copolymer as determined by SEC, chloroform used as eluent.
[c] Determined by differential scanning calorimetry, heating rate 10°C/min.

2. Experimental

2.1. Materials

Different tri-block poly(L-lactide-*b*-1,5-dioxepan-2-one-*b*-L-lactide) used in this work was synthesised from 1,5-dioxepan-2-one [17] and L-lactide and purified as described in a previous paper [10,18]. Molecular characteristics and physical properties of poly(L-LA-*b*-DXO-*b*-L-LA) obtained by controlled ring-opening polymerisation are listed in Table 1. Dichloromethane (KEBO Lab, Sweden) was used as received.

2.2. Film preparation

Films were prepared as follows: dichloromethane solutions of different tri-block copolymers were prepared to have a total polymer concentration of 0.16 g/ml and cast onto flat glass plates followed by solvent evaporation at room temperature. The resulting films were dried under reduced pressure for 2 weeks. The thickness of the films was 10–20 μm.

2.3. In vitro degradation

For degradation studies, circular plates of 12 mm diameter of approximately 0.02 g were prepared from the solution cast films. Samples were subjected to hydrolytic degradation in a saline buffer of pH 7.4 at 37°C. The saline buffer contained per litre of water the following: 9 g NaCl, 10.73 g $Na_2HPO_4 \cdot 7H_2O$, 2.12 g NaH_2PO_4. The pH of the buffer solution was adjusted to 7.4 by the addition of NaOH. The degradation experiments were performed in 10 ml of the saline solution. In order to prevent microbial growth 100 μl 0.04 wt% NaN_3 solution was added to the solution. Sample tubes were placed in a thermostatically controlled chamber, temperature set to 37°C, test tubes were subjected to a gentle shaking motion. Samples were drawn from the test environment after 1, 2, 5, 10, 15 and 23 weeks of degradation and washed with deionised water before drying under vacuum.

2.4. Measurements

2.4.1. Nuclear magnetic resonance

Proton nuclear magnetic resonance (^{1}H NMR) was utilised to determine the composition of the polymer subjected to hydrolysis. ^{1}H NMR-spectra were obtained using a Bruker AC-400 Fourier-Transform Nuclear Magnetic Resonance Spectrometer (FT-NMR) operating at 400 MHz, $T = 25$°C, with chloroform-d_1 ($CDCl_3$) as solvent. The polymer sample was dissolved in 0.5 ml $CDCl_3$ in a 5 mm diameter sample tube. The non-deuterated chloroform was used as an internal standard ($\delta = 7.26$ ppm).

2.4.2. Size exclusion chromatography

Size exclusion chromatography (SEC) was used to monitor the molecular weight change during degradation. Polymers were analysed using a Waters 717plus autosampler and a Waters model 510 apparatus equipped with two PLgel 10 μm mixed-B columns, 300 × 7.5 mm (Polymer Labs., UK). Spectra were recorded with a PL-ELS 1000 evaporative light scattering detector (Polymer Labs., UK) connected to an IBM-compatible PC. Millennium[32] version 3.05.01 software was used to process the data. Chloroform was used as the mobile phase, at a flow rate of 1.0 ml/min. Narrow MWD polystyrene standards were used for calibration, range 1700–706 000 g/mol.

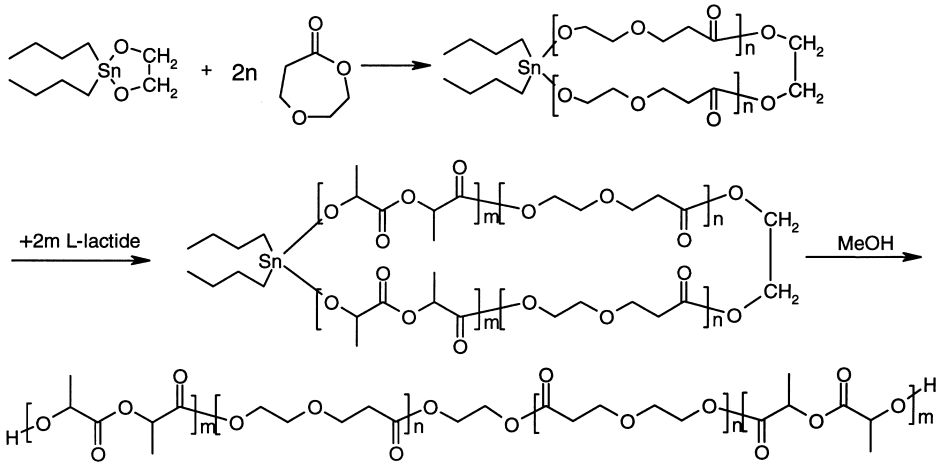
2.4.3. Residual weight

The residual weight of the samples was determined gravimetrically. The percentage residual weight was calculated by comparing the dry weight, $w(t)$, at a given hydrolysis time with the initial weight $w(0)$ according to the following equation:

$$\% \text{ residual weight} = 100 \times w(t)/w(0) \quad (1)$$

2.4.4. Thermal analysis—differential scanning calorimetry (DSC)

Thermal properties of the tri-block copolymer films were determined by differential scanning calorimetry (DSC) utilising a Mettler-Toledo 820 connected to a RP100 cooling unit (Labplant, England). For DSC measurements,



Scheme 1.

degraded samples were heated in 40 μl Al pans at a rate of 10°C/min under nitrogen gas flow. Calibration was performed with Zn and In. The melting point of the block copolymer was defined as the peak temperature.

2.4.5. Scanning electron microscopy

The morphology of the original films was examined by scanning electron microscopy (SEM) using a JEOL JSM-5400 scanning microscope using acceleration voltage of 15 kV. The samples were mounted on metal studs and sputter coated with gold–palladium utilising a Denton Vacuum Desk II cold sputter etch unit for 3×15 s.

2.4.6. Extraction of degradation products

The degradation products were isolated and concentrated from the aqueous degradation medium by solid phase extraction (SPE). The degradation products were isolated according to the following procedure: A SPE ENV + column (100 mg, Sorbent AB) was pre-washed with one equivalent of methanol (HPLC-grade, Kebo Lab AB), and then with 1 equiv of acidified buffer solution. The internal standard 2-hydroxyvaleric acid sodium salt (Sigma, Germany) was added to 2 ml of the aqueous sample solution. The mixture was acidified to pH 1–2 with conc. HCl (Kebo Lab, Sweden) and applied on the column immediately after pre-washing. After subsequent drying of the column the degradation products were eluted with 0.5 ml of acetonitrile (HPLC-grade, Kebo Lab, Sweden).

2.4.7. Gas chromatography–mass spectroscopy (GC–MS)

The identification and quantification of degradation products formed during hydrolysis was performed by GC–MS. The samples were analysed with a Finnigan SSQ 7000 mass spectrometer connected to a Varian 4000 GC. The GC was equipped with a DB-5MS capillary column from J&W ($30\ m \times 0.25$ mm i.d.). Helium was used as the carrier gas. The samples was analysed with the following temperature program of the column: the temperature was held at 40°C for 10 min and then increased to 250°C with a heating rate of 10°C/min. The injector was maintained at a temperature of 200°C.

3. Results and discussion

The tri-block copolymer, poly(L-lactide-*b*-1,5-dioxepan-2-one-*b*-L-lactide), was designed to achieve an elastic material with good mechanical properties as well as modified degradation profile. The new semi-crystalline aliphatic tri-block copolyester was prepared by a two-step reaction [18], from 1,5-dioxepan-2-one (DXO) and L-lactide (L-LA) in high yield (>80%). The reaction is schematised in Scheme 1. Properties of the tri-block copolymers subjected to hydrolytic degradation are summarised in Table 1. These samples were selected to provide representative information about the influence of the composition, molecular weight and crystallinity. All polymers except Polym. no. 1 showed some degree of crystallinity, related to the presence of long poly(L-LA) segments, which apparently constitute separate domains. X-ray analysis of the copolymers revealed that the polymers exhibited the same X-ray pattern regardless of the composition, only the intensity of the diffraction pattern increased with increased amount of L-lactide in the copolymer [18]. A scanning electron microscopy examination was performed on the original polymer films before degradation (not shown). The investigation revealed crystal domains, spherulites, varying in size from 10 to 50 μm in the samples containing higher amounts of L-LA. Polym. no. 1 exhibited a totally smooth surface and no spherulites could be detected by SEM.

3.1. Effect of the molecular weight and copolymer composition on the rate of degradation

Size exclusion chromatography was utilised to determine the changes in molecular weight and molecular weight distribution during degradation. Fig. 1 shows the number-average

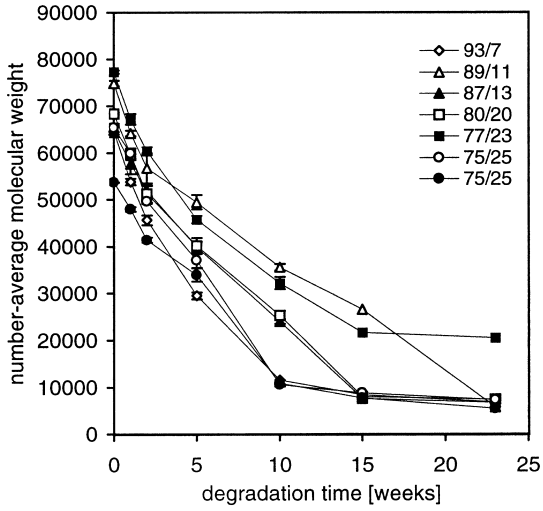


Fig. 1. Number-average molecular weight as determined by SEC as a function of degradation time. Degradation performed at 37°C in saline buffer solution pH 7.4. The standard deviation error bars are shown for the samples degraded for 0, 1, 2, 5 and 10 weeks.

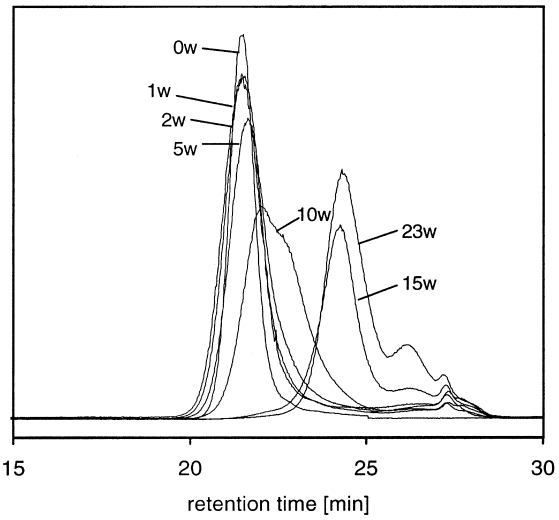


Fig. 2. Evolution of GPC chromatograms of the tri-block copolymer Polym. no. 3 (87/13) at pH 7.4 and 37°C during degradation.

molecular weight, $\bar{M}_n$, as a function of degradation time. The hydrolysis of the tri-block copolymers began immediately upon immersion of the samples into the buffer solution as evidenced by SEC measurements. The increase in amount of L-LA from 7 to 25 mol% in the original polymer films did not show any significant effect on the degradation rate. The important factor determining the rate of degradation was found to be the original molecular weight of the sample. This is in contrast to what has been found for the degradation of random copolymers of DXO and L-LA [19,20]. The in vitro investigation of random copolymers showed that an increase in the amount of lactide in the polymer resulted in a faster degradation. The rate of molecular weight decrease slowed down after 10–15 weeks due to the increase in crystalline poly(L-LA).

Fig. 2 shows the SEC chromatograms of Polym. no. 3 (87/13) after 0, 1, 2, 5, 10, 15 and 23 weeks of degradation. The SEC chromatograms show a broadening of the distribution of polymer chain lengths with a multi-modal tail covering the low molecular weight area. The multi-modal SEC chromatograms are probably due to the different degradation rates in the amorphous and the crystalline domains [21]. Such specific low molecular weight peaks have previously been observed for poly(L-LA) during hydrolysis in alkaline solution [22].

3.2. The influence of molecular weight decrease on the weight loss

The hydrolytic degradation was followed by determination of the weight loss of the samples. Fig. 3 shows the percentage residual weight and weight-average molecular weight, $\bar{M}_w$, as a function of degradation time for a range of poly(L-LA-*b*-DXO-*b*-L-LA)s with different composition in the polymer backbone. A decrease in the residual weight was observed in the first week due to diffusion of low molecular weight compounds, e.g. residual monomer or solvent, into the buffer solution. However, the in vitro hydrolysis results indicate that relatively little weight loss occurred during the first 5 weeks of degradation. After this initial retention in weight the rate increased substantially and some of the samples became brittle and started to disintegrate. The rate of weight loss decreased again during the later stages of degradation. The lowered rate of weight loss at the later stages of degradation was due to the increase in amount of semi-crystalline poly(L-LA), the amorphous poly(DXO) phase degraded first. The weight loss was clearly dependent on the molecular weight. The decrease in residual weight started when the weight-average molecular weight had reached a value lower than approximately 40 000.

3.3. Influence of copolymer composition on the formation of low molecular weight degradation products

Degradation products formed during hydrolysis of poly(L-LA-*b*-DXO-*b*-L-LA) were monitored as a function of degradation time. The detection and identification of low molecular weight compounds diffusing out from the polymer matrix into the buffer solution was performed by GC–MS. The degradation products were separated from the buffer solution utilising solid-phase extraction techniques and subsequently eluted with an organic solvent suitable for analysis, e.g. acetonitrile.

Identification of the degradation products was performed by comparing the actual mass spectrum with library spectra. Fig. 4 shows the GC chromatograms of the isolated degradation products from Polym. no. 4 after 1, 10 and 23 weeks of degradation and the peak assignment. The major degradation products formed during hydrolysis of the tri-block copolymer were lactic acid and 3-(2-hydroxy-ethoxy)-propanoic

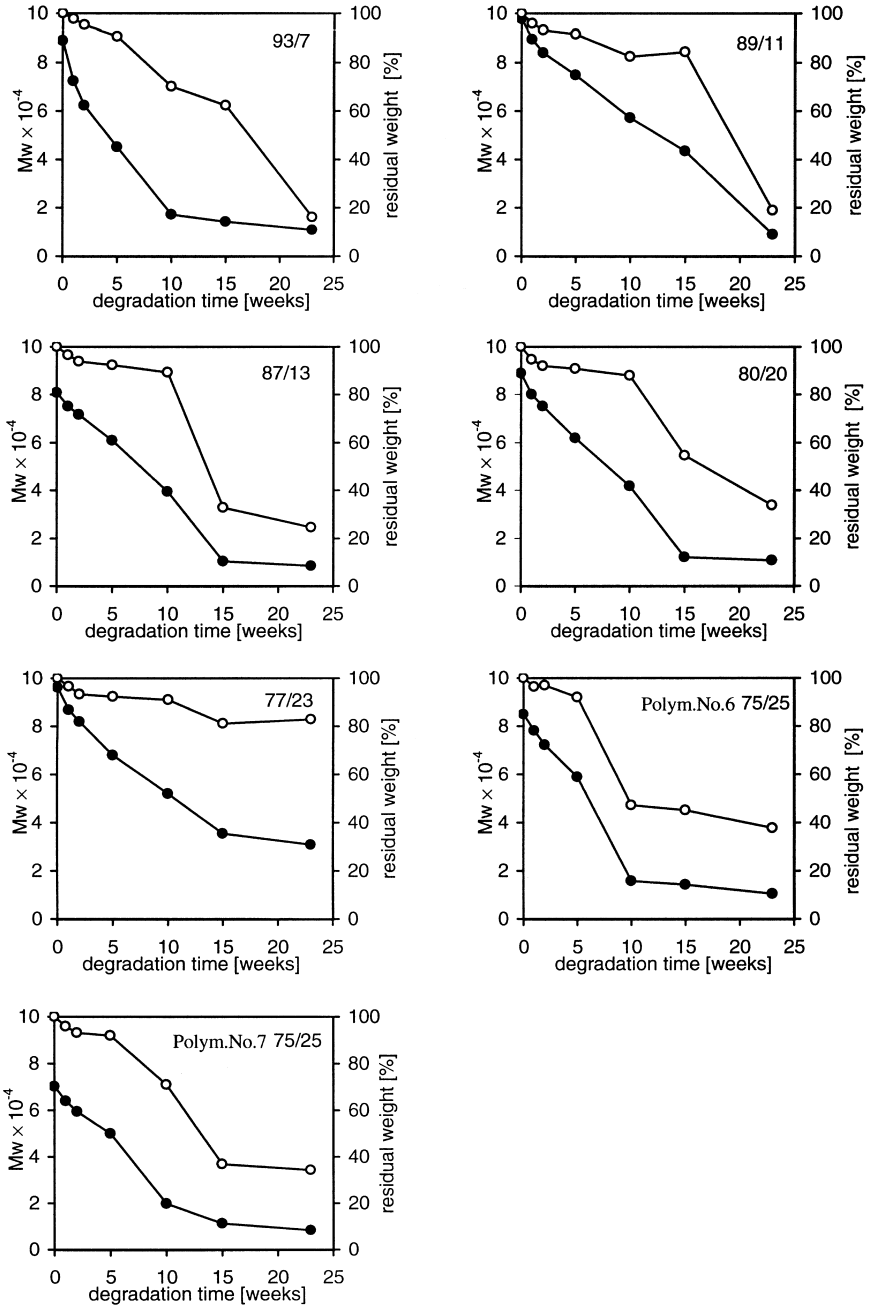


Fig. 3. Relationship between the decrease in weight-average molecular weight (●) and residual weight (○) for a range of poly(L-LA-*b*-DXO-*b*-L-LA), during degradation in saline phosphate buffer solution for 23 weeks at 37°C.

acid. This result has also been established for the hydrolytic degradation of random copolymers of L-LA and DXO [19]. The structure of the degradation products indicated that hydrolytic cleavage occurred at the ester bond, the ether bond in the DXO repeat unit remained unattacked.

In order to determine the amount of monomer released into the aqueous phase, an internal standard was added to the sample solution before GC–MS analysis. The 2-hydroxy valeric acid sodium salt was selected as internal standard due to its resemblance with the analysed products and favourable retention time. Fig. 5 shows the release of 2-hydroxy propanoic acid (e.g. lactic acid) and 3-(2-hydroxy-ethoxy)-propanoic acid and the residual weight as a function of degradation time. The amount of lactic acid and 3-(2-hydroxy-ethoxy)-propanoic acid released from the polymer matrix were determined by comparison with the amount of internal standard. The release of degradation products started after 5 weeks of degradation, which coincide with the onset of weight loss. The release of 3-(2-hydroxy-ethoxy)-propanoic acid showed a progressive increase after onset. The amount of released degradation products correlates very well with the weight loss. The

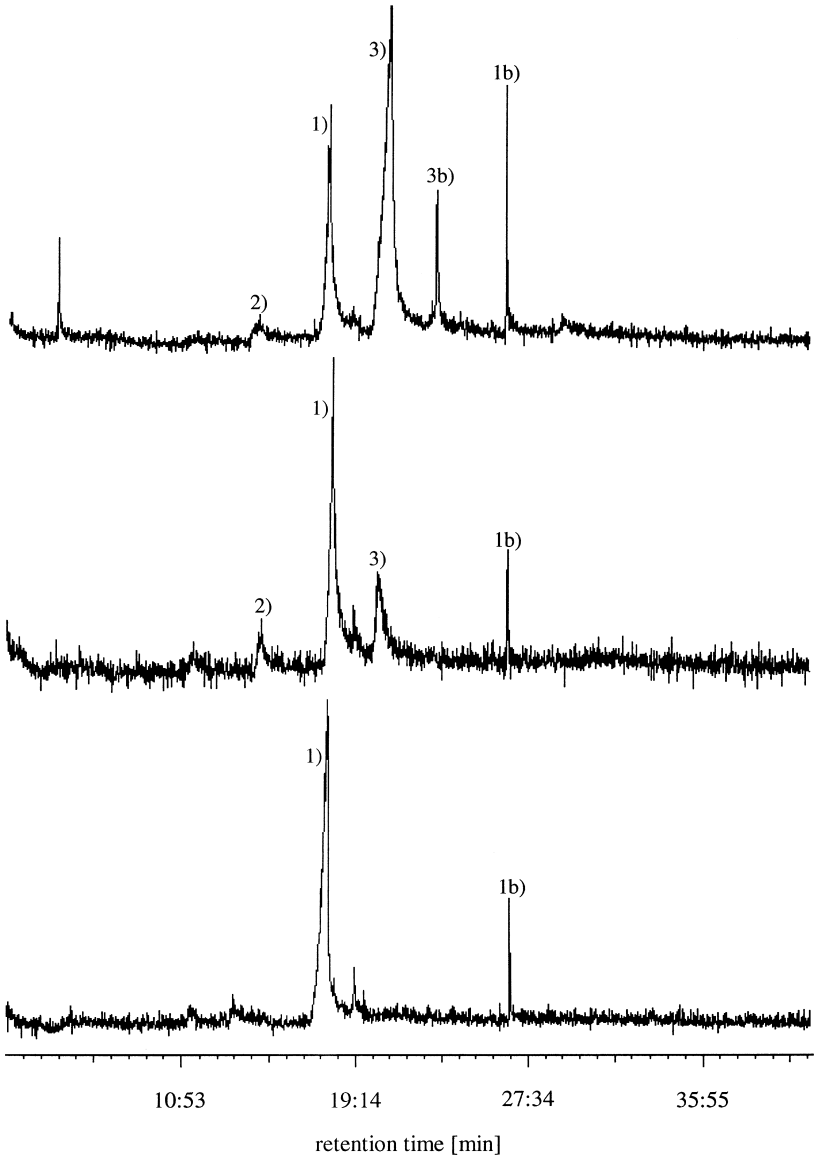


Fig. 4. GC chromatogram showing the degradation products formed during hydrolysis of Polym. no. 4 after 1, 10 and 23 weeks in buffer solution at 37°C. Peak notation: (1) 2-hydroxyvaleric acid (internal standard), (1b) methyl ester of 2-hydroxyvaleric acid; (2) 2-hydroxypropanoic acid; (3) 3-(2-hydroxyethoxy)-propanoic acid, (3b) methyl ester of 3-(2-hydroxyethoxy)-propanoic acid.

release of lactic acid first showed an increase and then a decrease. This might be due to the formation of dimers and trimers of lactic acid in the buffer solution at the later stages of degradation due to the more acidified solution. The pH of the buffer solution was followed during the course of degradation. The pH of the degradation medium decreased only slightly until the later stages of degradation when the weight loss became significant. The decrease in pH from 7.4 to 6.6 at the later stages of hydrolysis, was due to the diffusion of acidic degradation products out of the polymer matrix. No clear trend in the amount of released degradation products with the copolymer composition was observed. This was probably due to the influence of several factors such as original molecular weight and degree of crystallinity.

3.4. The effect of copolymer composition and molecular weight on the thermal properties of the poly(L-LA-b-DXO-b-L-LA) films

The thermal properties of the degraded samples were detected by DSC. DSC analysis of the degraded films revealed one distinct melting peak (T_m) and one glass transition (T_g) which indicates that the block copolymer formed a homogeneous amorphous and crystalline phase, this indicate a compatibility of the polymers at the molecular level. Fig. 6 shows the DSC scans of the tri-block copolymer Polym. no. 6 (75/25) film at various degradation times. The glass transition (T_g) changed from a distinct transition to a vague, uncertain transition. The crystalline melting peak became multi-modal in shape as the degradation proceeded.

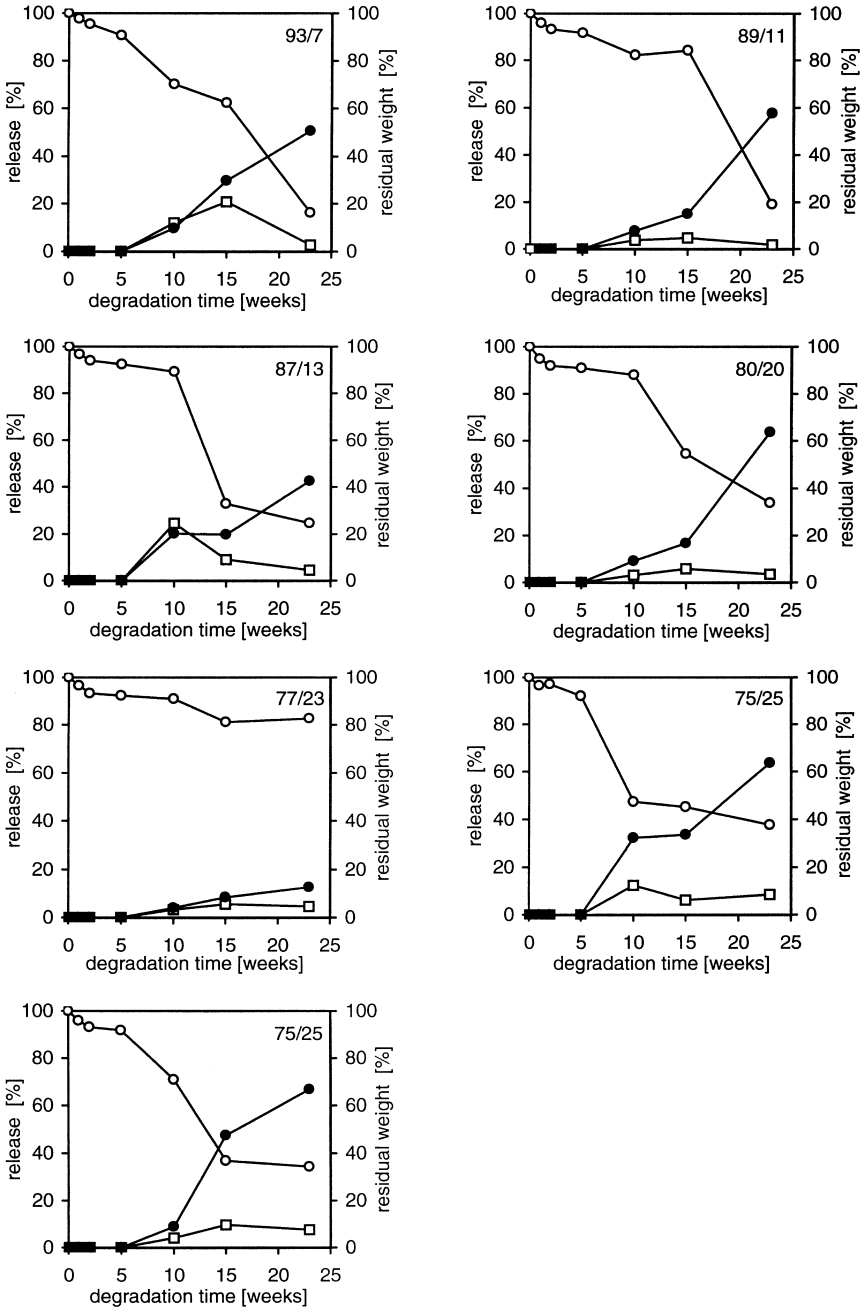


Fig. 5. Residual weight (○) ($w(t)/w(0) \times 100$) and release of 2-hydroxypropanoic acid (□) and 3-(2-hydroxy-ethoxy)-propanoic acid (●) as a function of degradation time during degradation in a phosphate buffer solution at 37°C.

Fig. 7 shows the T_g of the block copolymers as a function of the degradation time. An increase in T_g was observed at the later stages of degradation for all polymer samples. This phenomenon was due to the increase in the amount of poly(L-LA) in the remaining copolymer films as the degradation proceeded. Poly(L-LA) exhibits a much higher T_g than poly(DXO), $T_g \approx 55$–58°C [23,24] and −36°C [11], respectively.

Fig. 8 shows the melting temperature as a function of the degradation time. The melting point of the original material was affected by the amount of L-LA in the copolymer. DSC analysis revealed that the melting point increased with the increased amount of L-LA in the copolymer. However, Polym. no. 7 exhibited a slightly lower melting point than expected from the copolymer composition, this was due to the lower molecular weight of the sample i.e. shorter poly(L-LA) blocks. It has been reported that the melting point is largely affected by the molecular weight of poly(L-LA) [24].

An increase in T_m was observed immediately after immersion of the samples into the buffer solution. This might be due to several factors, the penetration of water into the polymer might act as a plasticising agent which allowed

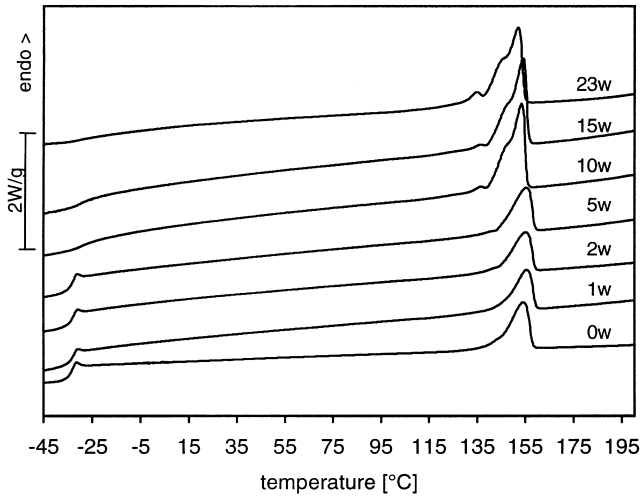


Fig. 6. DSC spectra of poly(L-lactide-*b*-1,5-dioxepan-2-one-*b*-L-lactide) after 0, 1, 2, 5, 10, 15 and 23 weeks of degradation; Polym. no. 6, Table 1.

recrystallisation to take place. Also, the weight loss curve showed a decrease during the first week probably due to release of low molecular weight products originally found in the film, i.e. residual monomer or solvent, which influence the thermal behaviour. After the initial increase in melting temperature, a decrease was observed when the molecular weight of the polymers decreased due to hydrolytic chain cleavage. When the polymers became enriched in L-LA the melting temperature increased again due to the high melting point of pure poly(L-LA), $T_m = 215$°C, [25].

After 10 weeks of degradation, the second run gave a multi-modal crystallisation peak. This indistinct melting peak might reflect the fact that polymers and oligomers of different molecular weight, which were detected to be present by SEC, tend to form crystallites of different sizes. Pure poly(L-LA) degrades in a similar manner resulting in a double melting peak at 154 and 164°C [23].

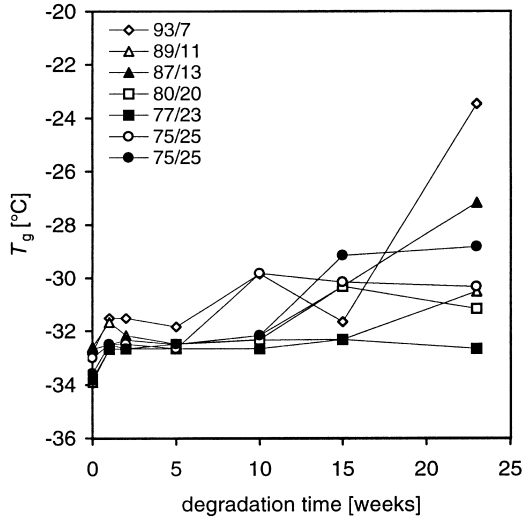


Fig. 7. Glass transition temperatures (T_g) of the poly(L-lactide-*b*-1,5-dioxepan-2-one-*b*-L-lactide) films as a function of the degradation time.

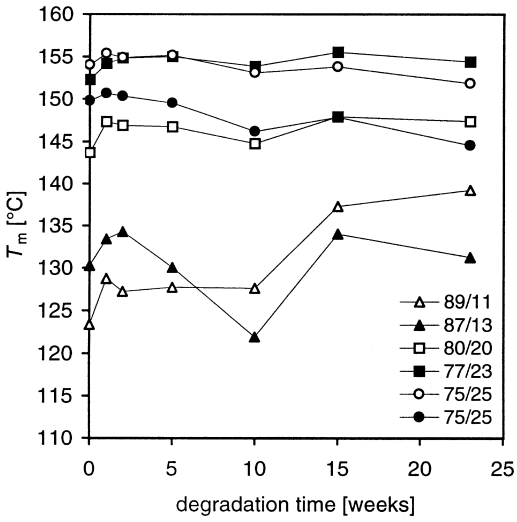


Fig. 8. Melting point (T_m) of the poly(L-lactide-*b*-1,5-dioxepan-2-one-*b*-L-lactide) as a function of degradation time.

All copolymers showed significant increases in the heat of fusion (ΔH_m) upon degradation. The variation of ΔH_m with the degradation time is shown in Fig. 9. The increase in heat of fusion was found to almost exactly follow the increase in amount of L-lactide in the remaining polymer. A similar increase in heat of fusion was also found for the copolymers of L-LA with ϵ-caprolactone, due to the loss of the amorphous phase [26].

3.5. Degradation mechanism

Composition changes in the tri-block copolymers during degradation were monitored by ^{1}H NMR analysis. Fig. 10 shows the amount of DXO and L-lactide in the copolymers subjected to hydrolytic degradation as a function of degradation time. The NMR study showed that the remaining polymer films were enriched in poly(L-LA) during

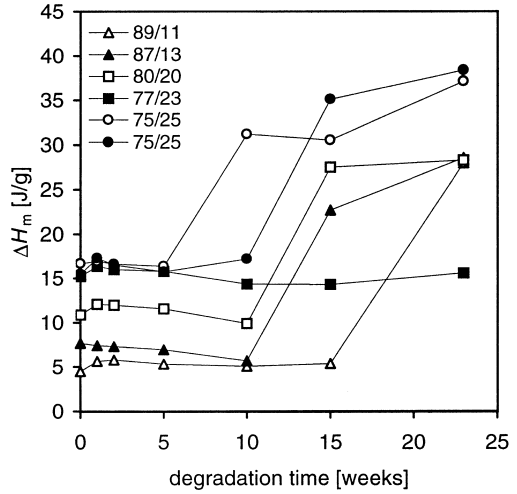


Fig. 9. The heat of fusion (ΔH_m) of the poly(L-lactide-*b*-1,5-dioxepan-2-one-*b*-L-lactide) as a function of the degradation time.

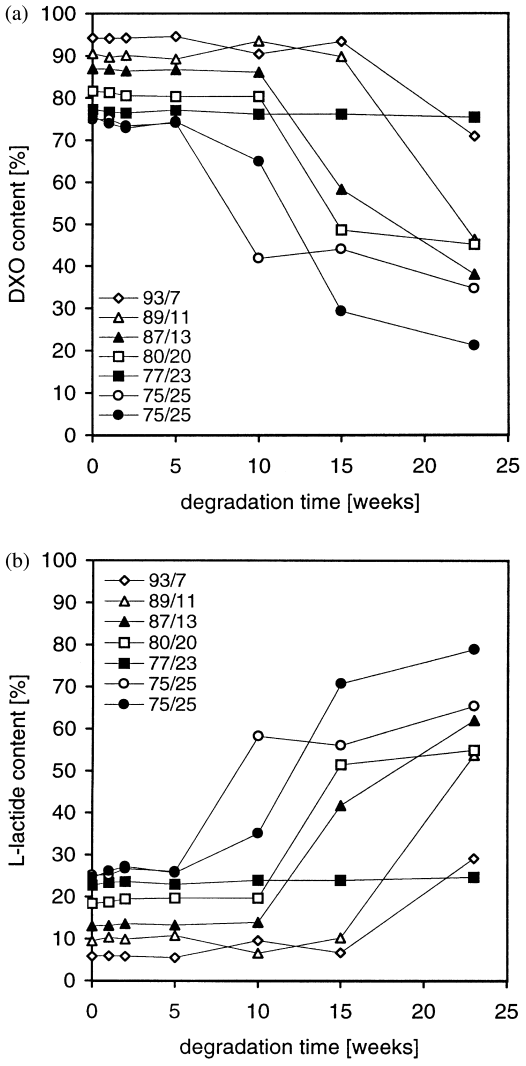


Fig. 10. The composition of the tri-block copolymer as a function of degradation time: (a) amount of L-lactide; (b) amount of 1,5-dioxepan-2-one. Composition determined by ^{1}H NMR. Degradation performed at 37°C in saline buffer solution pH 7.4.

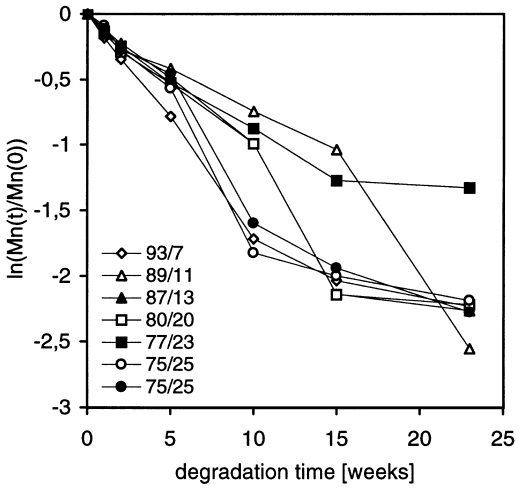


Fig. 11. ln $[M_n(t)/M_n(0)]$ as a function of the hydrolysis time for the poly(L-lactide-*b*-1,5-dioxepan-2-one-*b*-L-lactide) during degradation in a phosphate buffer solution, pH 7.4 at 37°C.

degradation. The onset of the increase in amount of L-LA in the polymer occurred at the same time as the weight loss. Due to the amorphous structure of poly(DXO), water can diffuse easily into the polymer and degradation is therefore very fast. The poly(L-LA) exhibited crystalline domains, which show a higher resistance to degradation, probably due to difficulties of water penetration, resulting in a progressive increase of L-LA in the polymer. The NMR spectra of the degraded block copolymer were very similar to those of the original polymer. Only small peaks originating from end groups were detected in some cases. The results indicate that chain cleavage was a result only of hydrolysis of ester bonds in the main chain.

In a polymer degradation process involving main-chain scission, the scissions can be either random or non-random along the back-bone. In the first case, each bond of the polymer chain has the same probability of cleavage, regardless of the chain length. It has been proposed that simple aqueous hydrolysis proceeds mainly by a random process. The linearity of the plot of ln $[M_n(t)/M_n(0)]$ versus time implies a random chain scission process. Fig. 11 shows the semi-logarithmic plot of ln $[M_n(t)/M_n(0)]$ as a function of time, *t*, for poly(L-lactide-*b*-1,5-dioxepan-2-one-*b*-L-lactide) degraded in phosphorous buffer solution at 37°C. The hydrolysis of poly(L-LA-*b*-DXO-*b*-L-LA) in aqueous medium followed a first-order kinetics as long as the weight loss was below 5%. This implies that hydrolysis proceeded by random chain scission while the weight loss could be neglected. It has been reported that all degradation products have to be included in the calculation of ln $[M_n(t)/M_n(0)]$ in order to achieve a linear plot characteristic for the first order kinetics [27,28]. The onset of deviation in Fig. 11 coincides with the onset of fragmentation and release of degradation products as detected by GC–MS.

4. Conclusions

The hydrolytic degradation of the tri-block copolymer was performed by a simple hydrolysis of ester bonds in the main chain. Hydrolysis was characterised by rapid decrease in molecular weight and a mass loss starting when sufficiently low molecular weight had been achieved. The polymer composition did not influence the rate of degradation. Degradation products formed during hydrolysis were identified as lactic acid and 3-(2-hydroxyethoxy)-propanoic acid. The ether bond in the DXO repeat unit was not affected by hydrolytic degradation. The crystalline phase appeared to be very resistant to degradation and resulted in a multi-modal SEC chromatogram and an increase in the L-LA content in the remaining polymer films. Kinetics of degradation indicated that the hydrolysis of the polymer back-bone was followed a random

chain scission process until the sample started to fragmentise.

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