Copolymers of 1,5-Dioxepan-2-one and L- or D,L-Dilactide: Hydrolytic Degradation Behavior

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SYNOPSIS

The degradation of two series of copolymers made of 1,5-dioxepan-2-one (DXO) and L- or D,L-dilactide has been investigated. *In vitro* degradation of the six copolymers with different ratios of the ingoing components was followed using size exlusion chromatography (SEC), nuclear magnetic resonance (NMR) spectrometry, Fourier transform infrared (FTIR) spectroscopy, and differential scanning calorimetry (DSC). The copolymers with a high content of lactic acid units showed a higher rate of hydrolysis than the DXO-rich copolymers. The copolymer morphology also affects the rate of degradation as seen in the differences between amorphous and semicrystalline samples. The effect of electron beam sterilization was studied as well as the degradation products formed using the gas chromatography–mass spectrometry (GC–MS) technique. The major degradation products resulted from ester bond cleavage. Kinetics of the *in vitro* degradation indicate a complex hydrolysis, probably a mixture of an uncatalyzed and catalyzed mechanism. © 1994 John Wiley & Sons, Inc.

INTRODUCTION

Hydrolysable polymers are an important group of materials that are finding an increasing number of applications. The materials should have ample shelf-life, degrade with an appropriate profile, and cause no adverse effects by doing so. Different applications naturally demand different properties. In some applications, for example many medical devices, it is vitally important that these properties are well-known and can be modified in a controlled way, should it be necessary. One of the best methods of modifying the properties of polymers, especially in medical polymers where low-molecular-weight modifiers can cause harm, is copolymerization. The most frequently used class of polymers in this area is probably the aliphatic polyesters. Polymers like poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(β-hydroxy-butyrate) (PHB), and poly(β-propiolactone) (PPL) have been extensively studied,[1–4] in many cases as a component in a copolymer system. The way chosen to produce these polymers is almost exclusively ring-opening polymerization or, in the case of PHB, production by bacteria.[5]

One of the most important properties of hydrolysable or degradable polymers is the rate of degradation, which is determined by several factors, the most important being chemical composition and degree of crystallinity. Both these properties can easily be modified by copolymerization. Many studies have been devoted to the polymers of glycolic or lactic acid and their corresponding copolymers.[6] These studies have shown that a larger proportion of lactic acid in the polymer results in a slower degradation rate, due to the more hydrophobic character of the lactic acid than of the glycolic acid. In poly(L-lactic acid) PLLA homopolymers, the crystalline domains have shown high resistance toward degradation, probably due to difficulties of water penetration.[7] The results of this work are in agreement with these observations.

Copolymers of glycolic and lactic acid have a glass transition temperature (T_g) above body temperature except for low-molecular-weight samples.[8] This fact and the usually crystalline character makes this copolymer stiff at body temperature with little elasticity. By copolymerizing monomers that yield polymers with large differences in T_g and/or crystallin-

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ity, copolymers with vastly different properties may be obtained. One example of such a system is the 1,5-dioxepan-2-one/lactic acid (DXO/LA) copolymer.[9] Lactic acid yields a homopolymer with a T_g around 55°C and has an amorphous or semicrystalline character depending on the stereoisomer used.[10,11] DXO, on the other hand, gives an amorphous homopolymer of low T_g (−36°C).[9] In the present work, we have investigated DXO/L-LA and DXO/D,L-LA copolymers of compositions (in mol %) 20/80, 50/50, and 80/20. An *in vivo* study of a selected number of these copolymers has also been completed and will be published elsewhere.[12]

EXPERIMENTAL

Materials

The synthesis of 1,5-dioxepan-2-one (DXO) has been described elsewhere.[13] DXO was recrystallized twice in anhydrous diethyl ether. Stannous-2-ethylhexanoate was used as received. D,L- and L-dilactide (Boehringer GmbH, Ingelheim, Germany) were recrystallized twice in toluene before use. Toluene was distilled over a Na/K-benzophenone complex under an Ar(g) atmosphere before use.

Polymerizations

A 20-mL serum bottle with a magnetic stirrer was sealed with a rubber septum and used as the reaction vessel. L- or D,L-dilactide and DXO (1–6 g of each) were mixed in the bottle and the initiator, stannous-2-ethylhexanoate was added ([M]/[I] = 500–800). The reaction vessel was closed with the rubber septum, flushed with inert gas (N_2 or Ar) through a syringe and immersed in a thermostated oil bath (115°C). After 20 h the serum bottle was rapidly cooled, the contents were dissolved in chloroform, and then precipitated in cold methanol. The copolymer was isolated by filtration and dried at room temperature *in vacuo*. The yield was above 95% in all cases and the purified copolymers were characterized by ^{1}H-NMR, differential scanning calorimetry (DSC) and size exclusion chromatography (SEC) measurements as described below.

In vitro Hydrolysis

Hydrolysis studies were carried out using melt-pressed films of the copolymers, 0.5 mm in thickness. Circular discs with a diameter of 13 mm were punched from the films. The discs were immersed in a phosphate buffer of pH 7.4 in 20-mL serum bottles. The bottles were stored in 37°C without any stirring or shaking motions. Two samples of each copolymer were analyzed on each occasion and the mean value was calculated and used.

Copolymer Composition

^{1}H-NMR spectra were taken to check whether the composition of the copolymers changed with time *in vitro*. Assignments of the chemical shifts have been reported in an earlier work[9] and a more thorough NMR analysis will be published in the near future.[14] Spectra were obtained using a Bruker AC-250 or AC-400 FT-NMR spectrometer. Samples were dried *in vacuo* and then dissolved in deuterochloroform or deuterated DMSO in 5-mm-diameter sample tubes. The relative intensities of the peaks representing the two different constituents were measured and used in the calculations.

Surface Changes

Reflection infrared (IR) measurements were made to detect any changes on the surface of the test specimens. Analyses were made with a Perkin-Elmer 1725X spectrometer using the attenuated total reflection (ATR) technique. Thin films were attached to a KRS-5 prism having an incident angle of 45°.

Molecular Weight Changes

Size exclusion chromatography (SEC) was used to monitor the molecular weight decrease and molecular weight distribution. The molecular weight determination must be looked upon in relative terms since this is not an absolute method. Earlier studies show, however, that values determined by light scattering do not differ greatly from values determined by the SEC method for these types of copolymers.[9] SEC measurements were made at 30°C with five μ-styragel columns (500, 10^3, 10^4, 10^5, 100 Å). THF was used as solvent, with a flow rate of 1.0 mL/min. A Waters model 510 was used with a differential refractometer (Waters 410) as detector. For data recording and calculations, a Copam PC-501 Turbo unit was used. SEC analyses with $CHCl_3$ as solvent (used in the case of PLLA and PDLA homopolymers) were carried out at 26°C with three SHODEX columns of mixed porosity and a Waters 6000A pump and R-400 RI-detector. The flow rate was 1.0 mL/min. Narrow PS standards were used for calibration in all cases.

Thermal Analysis

Differential scanning calorimetry (DSC) was used to follow variations in crystallinity during degradation of the semicrystalline copolymers. In the DSC analysis a Perkin-Elmer DSC-7 with a Perkin-Elmer 7700 computer was used. The heating rate was 10°C/min. The first scan was used for the calculations.

Electron Beam Treatment

Electron beam treatment was carried out with a 6.5-MeV source, pulsed at 75 Hz and 15 μA. Radiation took place on a cooling plate at +3°C, each passage giving a dose of 2 Mrad. The copolymers were irradiated either in air or in an $Ar_{(g)}$ atmosphere with doses between 0 and 15 Mrad.

pH Changes in Buffer Solution

The pH of buffer solutions was measured in order to monitor the production of carboxylic acids formed by hydrolysis of the copolymers. A Metrohm 632 pH meter with a Metrohm combined pH glass electrode was used.

Sample Weight Changes

The dry weight of the test specimens was determined by drying them *in vacuo* to constant weight and was compared with that of the original test piece. The weight loss was calculated as a percentage of the original test specimen weight. $W = (W_1/W_0)\ 100$, (W = % remaining of original weight, W_1 = dry weight, W_0 = original weight).

Degradation Products

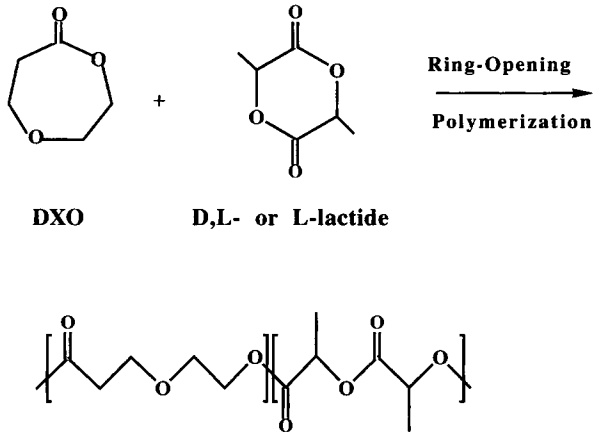
Gas chromatography–mass spectrometry (GC–MS) was used to identify degradation products in the phosphate buffer solutions. The following procedure was used for sample preparation: The acidified (pH = 2–3) *in vitro* solutions were extracted with diethylether (pro analysi) which was thereafter evaporated by a stream of nitrogen gas. iso-Octane, as received, was added and the solution was treated with a large excess of (*N*-(tert-butyldimethylsilyl)-*N*-methyl trifluoroacetamide (MTBSTFA) at 50°C for approximately 1 h. The derivatized degradation products were analyzed by GC–MS using a Perkin-Elmer Ion Trap Detector and a Perkin-Elmer GC 8500 with a fused silica column, Chrompack 25MX 0.32 mm CB43.

RESULTS AND DISCUSSION

Six different types of copolymers were investigated. Three of them consisted of DXO and L-lactic acid in the molar ratios 80/20, 50/50, and 20/80, respectively, and the other three of DXO and D,L-lactic acid in the same compositions. The copolymerization is schematized in Scheme 1. The copolymers of DXO and L-lactic acid exhibited crystallinity except for the one with 80 mol % DXO, which had too short L-lactic acid sequences to be able to crystallize. All copolymers of DXO and D,L-lactic acid were amorphous.[9] Table I summarizes some important properties of the pristine materials.

The test specimens were all treated in the same way to avoid discrepancies. However, as the molecular weight diminished with degradation time, treatments such as washing and specimen recovery from the phosphate buffer solution became difficult due to fragmentation of the test pieces. The test results from the end of the study therefore involve a higher degree of uncertainty than the earlier results.

When the test specimens were immersed in the phosphate buffer solution immediate water absorption was observed in the amorphous copolymer samples, whose appearance changed from transparent to white, opaque. The samples containing 80% DXO also changed in shape. Later, the 50/50 DXO/L-LA copolymer also became opaque but it retained its shape for at least 65 days. The 20/80 DXO/L-LA copolymer showed a marginal water uptake up



Scheme 1 Schematized copolymerization procedure of DXO and dilactide monomers.

Table I Copolymers before Immersion in Buffer Solution

Composition (Mol %) (DXO/L-LA)	[M]/[I]	M_w[a] (g/mol)	M_w/M_n	ΔH (J/g)	T_g (°C)
80/20	810	76000	1.72		−30
50/50	770	70500	1.90	3.3	−18
20/80	830	68000	1.94	24.5	22
(DXO/D,L-LA)					
80/20	540	70300	2.02		−30
50/50	640	66700	1.90		−11
20/80	770	68100	2.00		18

[a] SEC, PS-standard calibration. Weight-average molecular weight after melt-pressing.

to 35 days and very good dimension stability. This behavior was expected and can be explained by the different morphologies of the copolymers.

Kinetics of Hydrolysis

The molecular weight decrease starts immediately *in vitro* and is evident after 7 days in all the different copolymers except DXO/L-LA: 80/20. The dependence of degradation rate on the copolymer composition is illustrated in Figure 1. The higher the content of lactic acid units in the copolymers the faster is the degradation.

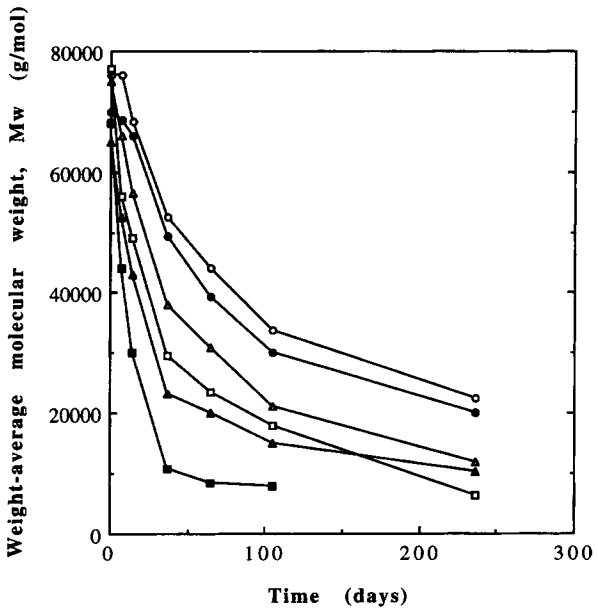


Figure 1 Molecular weight changes *in vitro* of DXO/L or D,L-LA copolymers. Molar ratios: DXO/L-LA: (○) 80/20; (△) 50/50; (□) 20/80. DXO/D,L-LA: (●) 80/20; (▲) 50/50; (■) 20/80.

The kinetics of the degradation were investigated by applying the approach of Pitt and Gu.[15] They derived two equations based on uncatalyzed and autocatalyzed hydrolysis. In this model, an autocatalytic hydrolysis follows the equation:

$$d[\mathrm{COOH}]/dt = k_1[\mathrm{COOH}][\mathrm{ester}][\mathrm{H_2O}] \quad (1)$$

The process generates carboxylic acid end groups that further catalyse the hydrolysis.
For a small degree of hydrolysis, one can assume that [ester] = [H_2O] = constant which gives

$$d[\mathrm{COOH}]/dt = k_2[\mathrm{COOH}] \quad (2)$$

Integration assuming [COOH] = $1/M_n$ yields

$$\ln(M_n) = \ln(M_{n^0}) - k_2 t \quad (3)$$

where M_{n^0} = number-average molecular weight before hydrolysis, k_2 is the rate constant, and t the degradation time.
If the hydrolysis is uncatalyzed, the equation is modified to

$$d[\mathrm{COOH}]/dt = k[\mathrm{ester}][\mathrm{H_2O}] \quad (4)$$

Assuming a high degree of polymerization, [ester] and [H_2O] may be considered to be initially constant. With the same substitution, integration yields

$$1/M_n = 1/M_{n^0} + k_3 t \quad (5)$$

By plotting the experimental data from the degradation study according to Eqs. (3) and (5), using data only before the onset of the major weight loss ($t < 63$ days), the prevailing mechanism can be elucidated. Figures 2 and 3 show plots of $\ln(M_n)$ and

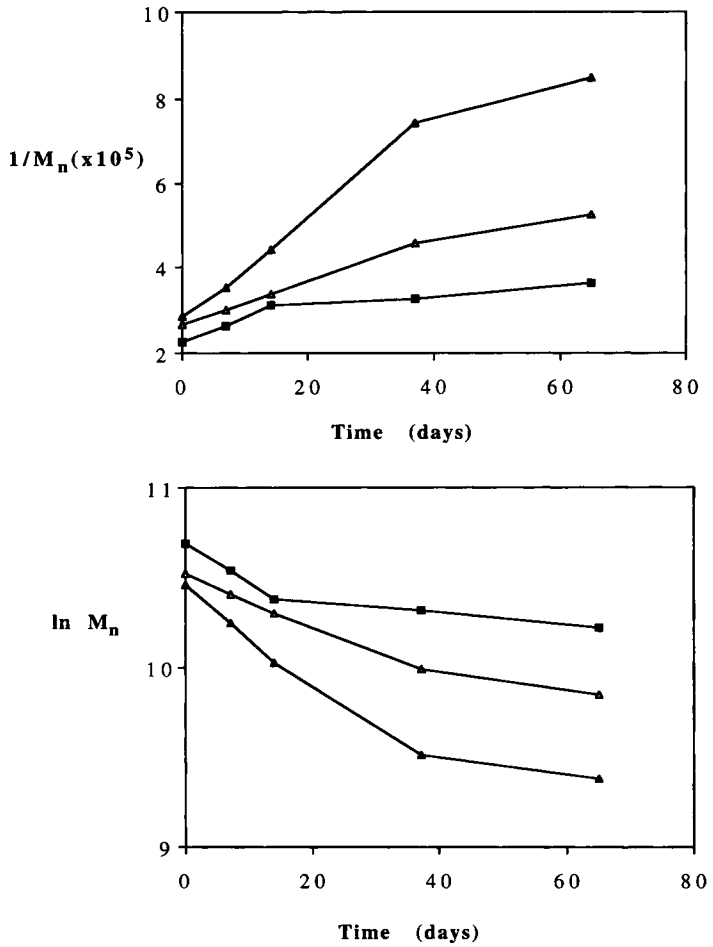


Figure 2 $1/M_n$ (top) and ln $M_n = f$(time) (bottom) for the DXO/L-LA copolymers. Molar ratios: DXO/L-LA: (■) 80/20; (△) 50/50; (▲) 20/80.

$1/M_n$ versus degradation time for the DXO/L-LA and DXO/D,L-LA copolymers, respectively. It is difficult to decide which of the plots shows the best fit. The correlation coefficients are also very similar; see Table II. In the case of the 50/50 and 80/20 DXO/D,L-LA and DXO/L-LA copolymers, the uncatalysed mechanism fits slightly better. The copolymers with a high content of L-LA have almost identical fits to both models. In the case of lactide homopolymers, the mechanism has earlier been shown to be of an autocatalytic character.[15] A calculation of the hydrolysis behavior of the DXO homopolymer[16] showed very small differences in the fit to both models. After 3 weeks, however, it was observed that the results slightly favored the uncatalyzed mechanism. This together with the results of the copolymer study suggests that there are different hydrolysis mechanisms for the both homopolymers and a mixture of them in the case of the copolymers. Park et al. have postulated that ether functions and carboxylic acid end groups might interact through hydrogen bonding and thus influence degradation kinetics in the case of PLLA/polyether blends.[17] Since the PDXO chain contains an ether function, this might be the reason for the change in hydrolysis mechanism. The rate of hydrolysis is described by the slopes, k_2 and k_3, of the initial linear parts corresponding to Eqs. (3) and (5), respectively. The values of these constants are given in Table II.

The molecular weights of the samples start to decrease immediately after immersion in phosphate buffer solution. The degradation of the DXO-rich copolymer is however slow at first, and the decrease after one week *in vitro* is not significant; see Figure 1. Many *in vitro* studies on aliphatic polyesters show results that indicate a bulk hydrolysis of the material, characterized by an induction period before any significant mass loss is observed. Depending on composition, this induction period for the present

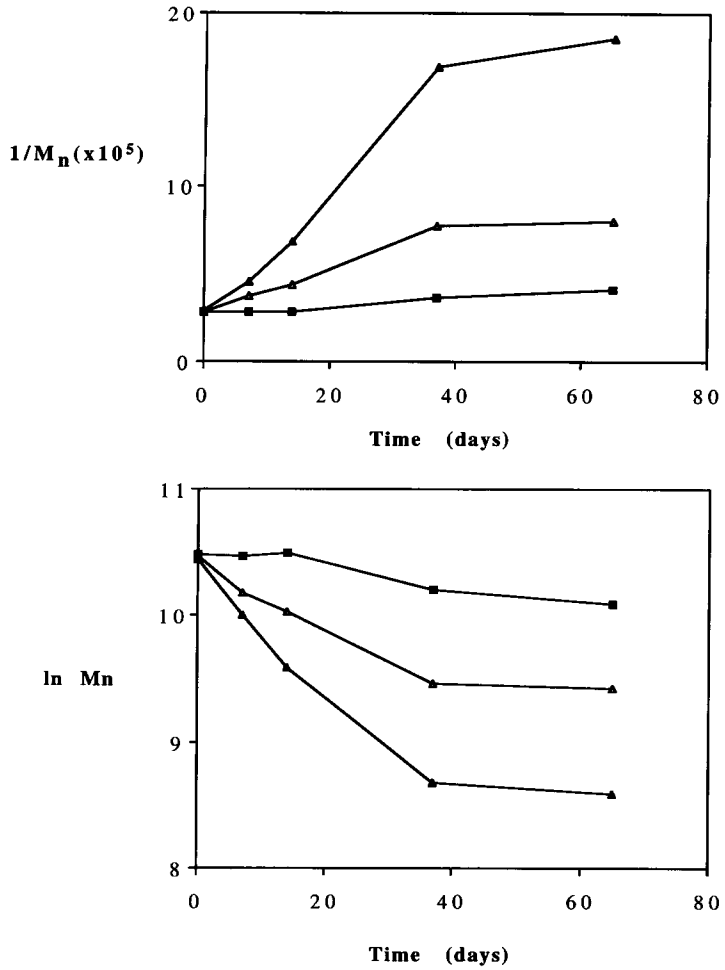


Figure 3 $1/M_n$ (top) and ln M_n = f(time) (bottom) for the DXO/D,L-LA copolymers. Molar ratios: DXO/D,L-LA: (■) 80/20; (△) 50/50; (▲) 20/80.

copolymers ranges between 5 and 9 weeks (more than 5% weight loss); see Figure 4. This can be explained by an initial chain cleavage after water absorption which produces shorter chains and broadens the molecular weight distribution (MWD). When the molecular weights of the chains are sufficiently small, the oligomers can diffuse through the bulk and dissolve, causing mass loss. Later one observes fragmentation especially from the amorphous samples. The MWD becomes again more narrow after the initial increase due to the disappearance of the high molecular weight fraction. A typical behavior of the MWD can be seen in Figure 5.

Table II Kinetic Data for the Hydrolysis of DXO/LA Copolymers[a]

Copolymer (DXO/L-LA)	Slope, $k_2 \times 10^2$ (Days^{-1})	r	Slope, $k_3 \times 10^6$ (Days^{-1})	r
80/20	0.63	0.894	0.19	0.920
50/50	1.0	0.976	0.41	0.986
20/80[b]	2.5	0.997	1.1	0.999
(DXO/D,L-LA)				
80/20	0.68	0.969	0.23	0.973
50/50[b]	2.6	0.994	1.3	0.998
20/80[b]	4.6	0.993	3.9	0.994

[a] Slope and correlation coefficients (r) calculated from mean values of data point in Figure 2 and 3, respectively.

[b] Calculated from the first 37 days *in vitro* only, due to weight loss at 65 days.

Vert et al. have shown in a previous paper[18] that *in vitro* degradation of poly(D,L-lactic acid), for example, gives bimodal SEC chromatograms due to a difference in degradation rate between the bulk and the outer layer of the test specimens. A heterogeneous cross section of the test specimens was also observed. This difference between the bulk and the outer layer was explained by a higher concentration of carboxylic acid end groups in the bulk. It was

more difficult for these end groups, created during hydrolysis, to diffuse away from the bulk than from the material near or at the surface. The resulting higher concentration of carboxylic acid end groups autocatalyzed the hydrolysis of the bulk material.

In our study only one out of the six copolymers displayed bimodal SEC chromatograms, namely the 20/80 DXO/L-LA copolymer. This bimodal distribution began emerging after 15 weeks *in vitro*. In some of the samples heterogeneous cross sections were observed. This was best seen in the 50/50 copolymers where the test specimen seemed to swell and when cut showed a skinlike surface layer with a more granular morphology in the bulk. Because of the thin samples and difficulties in physical separation no separate SEC measurements were made on the surface layer and the bulk. The SEC chromatograms of these samples showed a unimodal distribution. In the 20/80 DXO/L-LA copolymer no heterogeneity could be seen in the cross section. The material became very brittle only as the degradation progressed. It should be realized that because of the sample geometry (very thin discs) it should be difficult to observe any difference between surface and bulk material.

pH of Buffer Solution

The pH of the phosphate buffer solution was followed during the *in vitro* degradation. A constant pH was observed during the first two weeks in all samples; see Figure 6. Then the fast degrading lactic-acid-rich copolymers produced acidic hydrolysis products, in excess of the buffer capacity and lowered the pH of the phosphate buffer solution. The pH change was in good agreement with other observations made on the hydrolysis of the copolymers, e.g., the degradation rate.

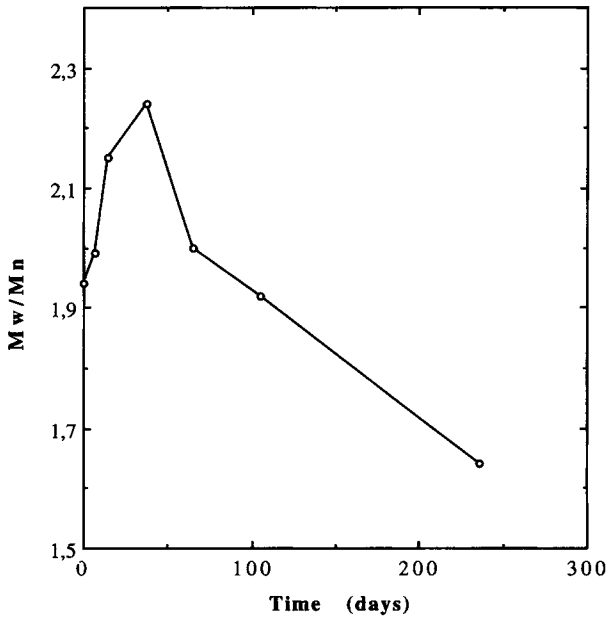


Figure 5 MWD of DXO/L-LA: 20/80 copolymer as function of time *in vitro*.

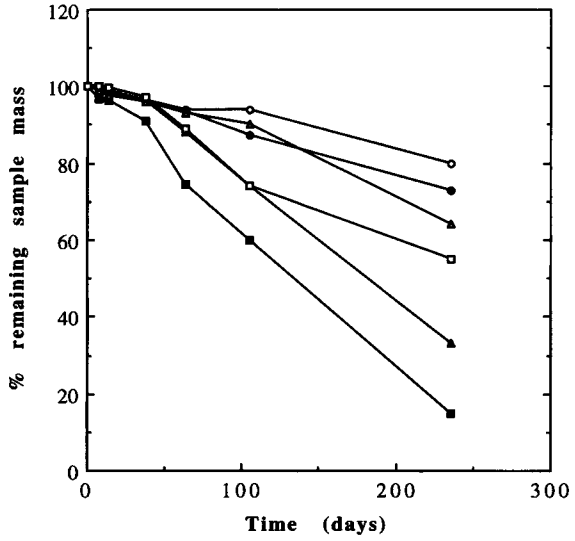


Figure 4 Sample mass loss of DXO/L or D,L-LA copolymers. Molar ratios: DXO/L-LA: (○) 80/20; (△) 50/50; (□) 20/80. DXO/D,L-LA: (●) 80/20; (▲) 50/50; (■) 20/80.

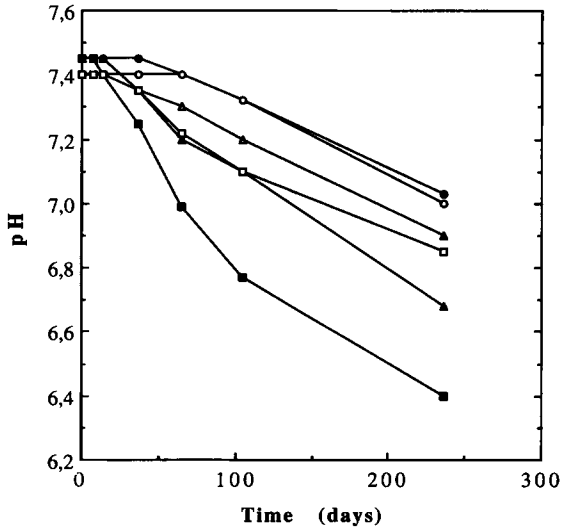


Figure 6 pH = *f*(time), *in vitro* buffer solution of DXO/L- or D,L-LA copolymers. Molar ratios: DXO/L-LA: (○) 80/20; (△) 50/50; (□) 20/80. DXO/D,L-LA: (●) 80/20; (▲) 50/50; (■) 20/80.

Copolymer Composition

NMR measurements were made on the test samples at different degradation times to see whether the compositions of the different copolymers changed with time. Regardless of composition, the amorphous copolymers became progressively enriched in the slower degrading DXO (though this was not significant in the 20/80 DXO/D,L-LA copolymer). This is in line with an ester hydrolysis taking place preferentially at the lactide ester linkages throughout the bulk. The semicrystalline copolymers (DXO/L-LA: 20/80 and 50/50) showed the opposite behavior, becoming enriched in L-LA units with time; see Figure 7. The reason is probably that the hydrolysis-resistant crystalline material is made up of L-LA units. This emphasizes the importance of taking into consideration both the chemical composition and the morphology of copolymers when predicting degradation times.

Crystallinity

To measure changes in crystallinity of the semicrystalline copolymers, differential scanning calorimetry (DSC) was used. The heat of fusion of the melting endotherm (ΔH) and the peak maximum temperature were measured as a function of time *in vitro*. The 50/50 DXO/L-LA copolymer has a very low crystallinity with a broad melting endotherm, spanning from 40–45°C to 85–90°C. At 0 or 1 week *in vitro*, a definite peak maximum is seen at low temperatures (around 55°C). With time, this maximum is transferred to higher temperatures as seen in Figure 8. The melt region is otherwise not shifted on the temperature scale. Crystal formation in this copolymer is probably very slow due to the small amount of L-lactic acid with presumably short sequences. In the 20/80 DXO/L-LA copolymer, the crystallinity is much higher and the peak maximum stays constant with time (Fig. 8).

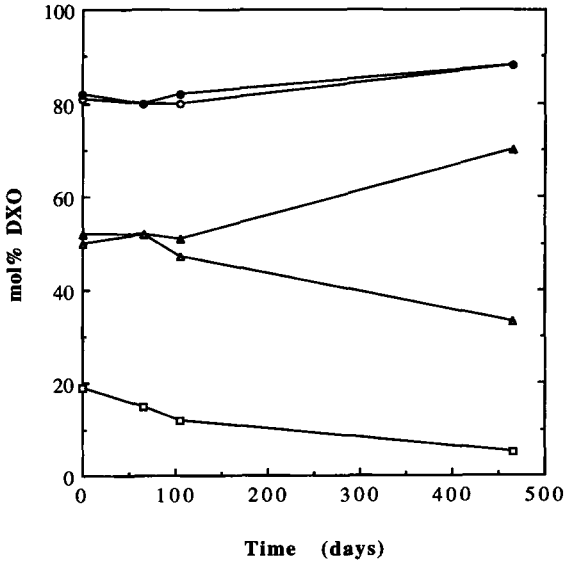


Figure 7 Mol % DXO in DXO/L- or D,L-LA copolymers vs. time. Molar ratios: DXO/L-LA: (○) 80/20; (△) 50/50; (□) 20/80. DXO/D,L-LA: (●) 80/20; (▲) 50/50.

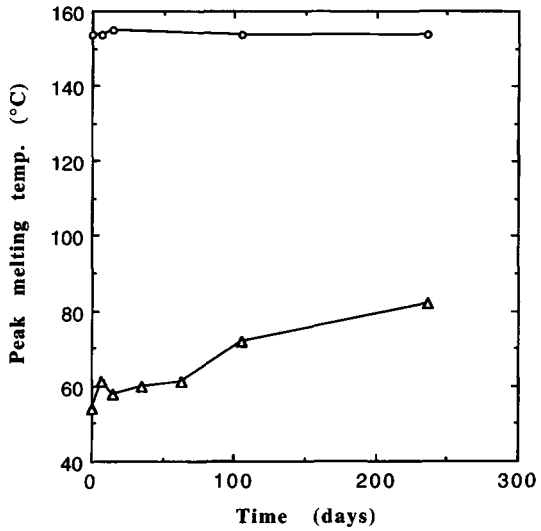


Figure 8 Peak melting temperature of DXO/L-LA copolymers. Molar ratios: DXO/L-LA: (○) 20/80; (△) 50/50.

Figure 9 shows that ΔH of the 20/80 DXO/L-LA copolymer increases with hydrolysis time, whereas it stays relatively constant for the 50/50 copolymer. The middle curve in Figure 9 shows the expected increase in ΔH for the 20/80 DXO/L-LA copolymer assuming mass loss only from the amorphous phase. The discrepancy is due to crystallization of previously amorphous material. It is evident that the total increase in heat of fusion cannot be the result of mass loss alone.

When the films are melt pressed, the copolymers are probably quenched to some extent. When they are immersed in the 37°C buffer solution, the higher mobility due to elevated temperature and plastization from absorbed water might influence annealing motions. The water probably does not penetrate the highly crystalline material of the 20/80 DXO/L-LA copolymer, and thus no shift in peak maximum is observed. In the case of the 50/50 copolymer, the less ordered, low crystalline material is more susceptible to water absorption, and the higher chain mobility causes a crystal thickening, resulting in a shift in the peak maximum temperature.

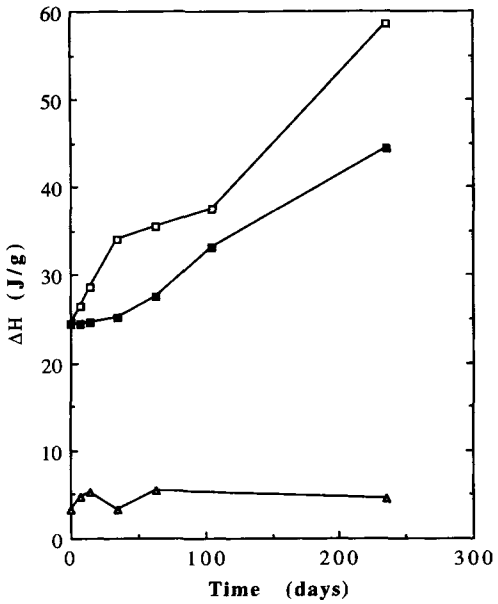


Figure 9 Melting enthalpy of crystalline fraction of DXO/L-LA copolymers vs. time. Molar ratios: DXO/L-LA: (□) 20/80; (△) 50/50; (■) calculated increase of ΔH due to mass loss alone in 20/80 copolymer.

The increase in ΔH of the 20/80 copolymer is a result of the formation of a fraction melting at a lower temperature. This is probably due to the crystallization of shorter chain segments, which become more mobile for the same reasons as stated above, or to the crystallization of chain ends liberated by chain scisson from entanglements. ΔH of the 50/50 copolymer remains relatively constant, but an increase would in fact be difficult to observe due to the low ΔH values and the smaller mass loss compared to the 20/80 copolymer. The less ordered system is also more susceptible to hydrolysis and will thus degrade with time.

Copolymer Surface

Reflection FTIR on the surfaces of the test specimens at different times showed small differences compared to the reference material. After 9 weeks *in vitro,* two new bands were visible at 1545 and 1650 cm^{-1}, in the 20/80 DXO/L-LA copolymer (Fig. 10), whereas the 50/50 copolymers showed only one new band at 1615 cm^{-1} and the 80/20 copolymers showed a very small, new peak at 1630 cm^{-1}. These new bands are most certainly due to the formation of salts of carboxylic acid end groups during hydrolysis of the copolymers.

Electron Beam Treatment

To investigate the possibility to sterilize these types of copolymers, experiments conducted with electron beam treatments were made. Birkinshaw et al. showed that irradiation of PLLA homopolymers

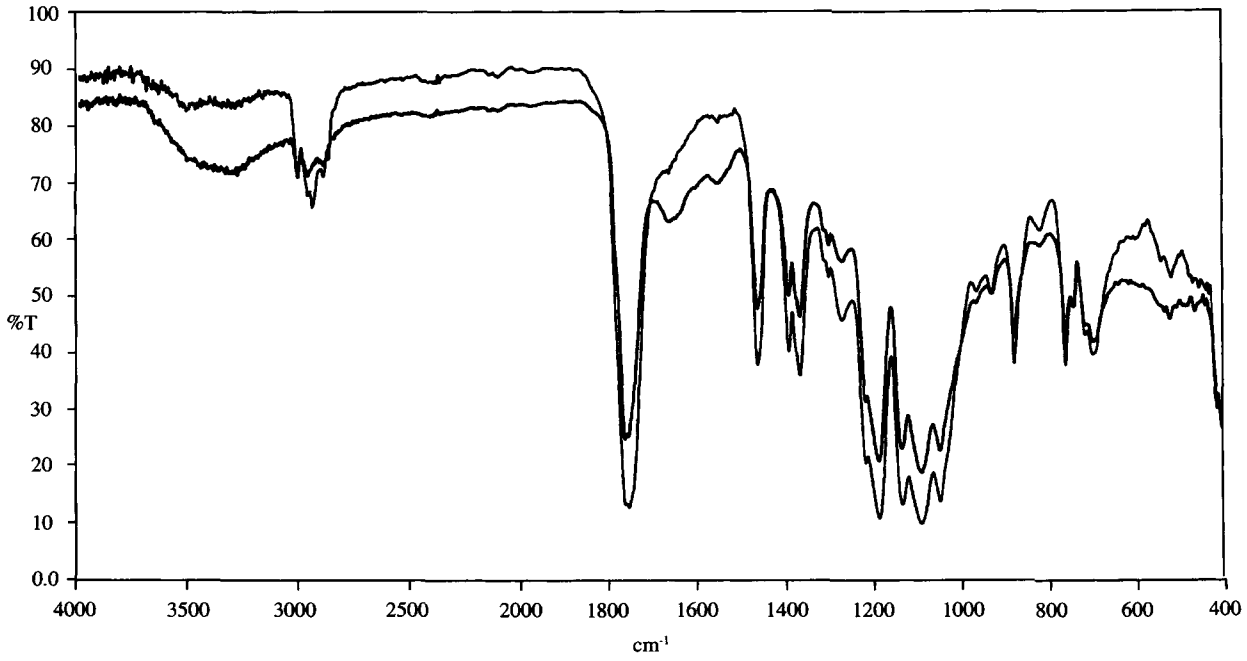


Figure 10 ATR-FTIR of DXO/L-LA: 20/80 copolymer surface at 0 (upper) and 9 weeks (lower) *in vitro.*

Table III Electron Beam Treatment in Ar(g) and Air for DXO/L-LA : 20/80 Copolymer

Dose (Mrad)	M_w	M_n	M_w/M_n
0	51600	24300	2.12
2.5	45700	22100	2.07
5.0	43100	21300	2.03
10	41200	19600	2.10
15	35000	17200	2.03
2.5[a]	49000	24200	2.02
5.0[a]	43200	21200	2.06
10[a]	32100	16000	2.01
15[a]	35500	15700	2.27

[a] Treatment in air.

with doses of up to 10 Mrad induced a major decrease in the initial molecular weight.[19] In our case, melt-pressed films of the copolymers were exposed to between 2.5 and 15 Mrad in air or an Ar-gas atmosphere. The molecular weight decrease and molecular weight distribution were determined by SEC. The results are given in Table III. A relatively small decrease in molecular weight is seen up to 10 Mrad, which is more than enough for sterilization purposes. MWD stays relatively constant. In air, the sample exposed to 15 Mrad showed a higher molecular weight than the sample exposed to 10 Mrad. Whether this is due to incipient grafting reactions or merely to experimental variation is difficult to say. The increase in M_W was accompanied by a slight increase in MWD.

In vitro Degradation Products

When designing materials for use in biological systems, it is naturally important to know what potential degradation products may be released. In order to obtain an idea of this, we made a GC–MS study of the *in vitro* solutions left after withdrawal of the test specimens of the DXO/L-LA and DXO/D,L-LA 20/80, 50/50, and 80/20 copolymers. The expected products should be those formed by hydrolysis of the ester bonds, i.e., hydroxyacids of the corresponding monomers. These products were found in the solutions, being the major peaks; see Figure 11. Other peaks in the chromatogram are either solvent stabilizers or are of uncertain origin. The mechanism is schematized in Scheme 2. Data for

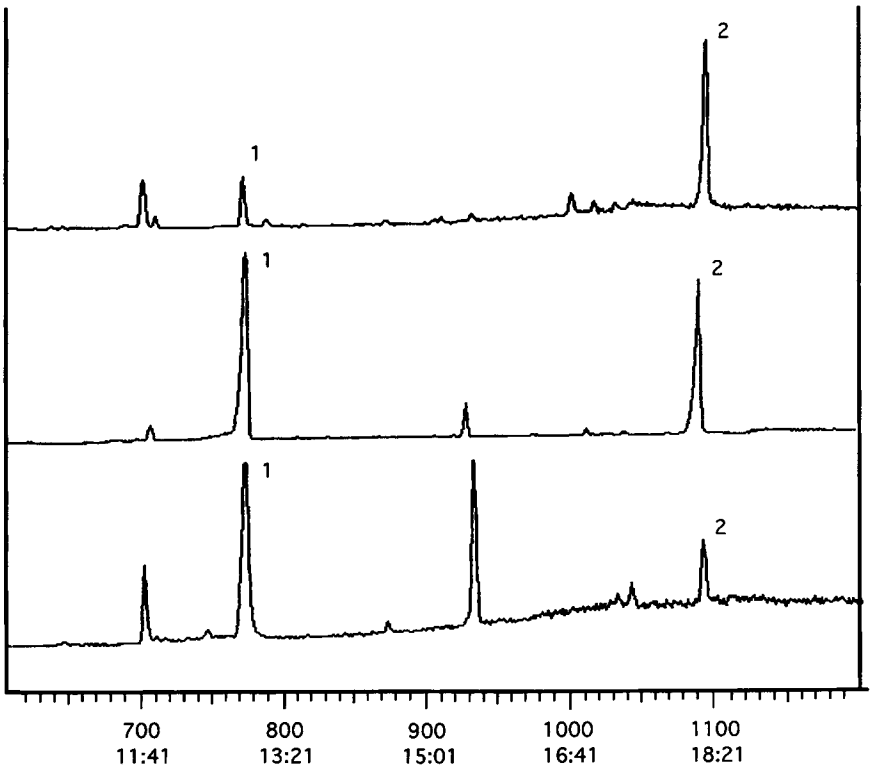
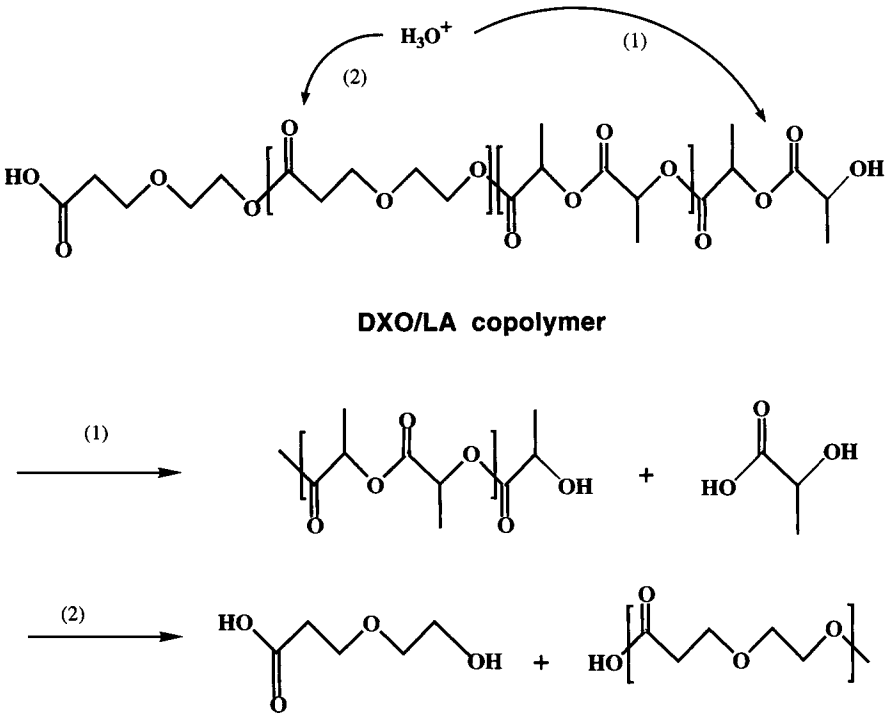


Figure 11 GC–MS chromatogram of (a) 80/20 DXO/D,L-LA copolymer (upper), (b) 50/50 DXO/D,L-LA copolymer (middle), and (c) 20/80 DXO/D,L-LA copolymer (lower), after 20 months *in vitro*. Peak 1, Lactic acid, and peak 2, 2-Hydroxyethoxypropanoic acid (derivatized).



Scheme 2 Proposed hydrolysis mechanism of DXO/LA copolymers, *in vitro*.

the two major products found in the buffer solutions can be seen in Table IV. A more thorough study of the degradation products is currently in progress and will be published in the near future.

CONCLUSIONS

Copolymers of DXO and L- or D,L-dilactide show very different properties depending on the molar ra-

Table IV GC–MS Data of Degradation Products

Compound	Retention Time (Min)	*m/z*	Relative Intensity	Fragment
Lactic acid	12.4	318		M
		303	5	M-15
		261	72	M-57
		233	71	
		189	38	
		147	99	
		133	24	
		75	22	
		73	100	
2-Hydroxyethoxypropanoic acid	18.0	362		M
		347	8	M-15
		305	92	M-57
		187	60	
		159	40	
		103	48	
		99	41	
		89	78	
		75	21	
		73	100	

tios of the corresponding monomers. With a high degree of DXO, an amorphous copolymer with low glass transition and slow rate of degradation is obtained. The copolymers containing a large amount of L-dilactide are semicrystalline and show a rapid decrease in molecular weight *in vitro*. The most rapid degradation rate is observed for the 20/80 DXO/D,L-LA copolymer, which is amorphous.

The degradation kinetics of these copolymers are probably a mixture of a catalyzed and uncatalyzed hydrolysis of ester bonds. The degradation products identified by GC–MS analysis are consistent with an ester hydrolysis mechanism. Changes in the composition of the copolymers can be observed during the last part of the *in vitro* study. An increase in crystallinity with degradation time is evident for the semicrystalline copolymers. Sterilization of the copolymers using electron beam treatment can be done without any severe decrease in the molecular weight.

The DXO/lactic acid copolymers make up an interesting class of materials. The wide variety of properties obtained, combined with the ease of producing high-molecular-weight copolymers and the possibility of sterilizing them should make them favorable candidates in certain biomedical applications. Further studies concerning DXO copolymers are currently taking place and will be published in the near future.

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