NOTE

In Vitro Degradation of Lactide–Glycolide Copolymers: PLA35GA30

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Received 11 November 1997; accepted 18 November 1997

INTRODUCTION

Biodegradable polymers such as lactide–glycolide copolymers have been in use for many applications like surgical sutures, encapsulants, and other advanced biomedical or pharmaceutical devices.[1,2] Being a crystalline material, polyglycolide biodegrades rather slowly, whereas its copolymers with lactide, because of lower crystallinity, have higher rates of biodegradation. In general, factors influencing crystallinity and the hydrophobic/hydrophilic balance determine the biodegradation characteristics. Thus, copolymerization with lactide increases the hydrophobicity and lowers the biodegradation rate. Because lactic acid is a chiral monomer, quite a variety of stereopolymers are obtainable by a simple variation in the proportions of D or L configuration of the monomer. Even stereoblock blends of L- or D-polylactides have been shown to possess different properties.[3] Copolymerization of varying proportions of glycolide with L- or D-lactide yields products quite different in their biodegradation behavior. For example, the PLA75GA35 [for nomenclature, see ref. 4(a)] copolymer loses about 70% of its weight after 15 weeks, while PLA37.5GA25 loses 90% of its weight after 3 weeks.[4] In the latter case, the copolymer is nearly amorphous, whereas in the former, both amorphous and crystalline regions are reported to exist. Obviously, amorphous regions hydrolyze faster. Extensive studies by Vert et al.[4] have shown that the core of the specimens hydrolyze faster than do the surface regions, indicating the heterogeneous nature of the bulk degradation. In an attempt to extend these investigations, we studied the synthesis and *in vitro* hydrolytic degradation of PLA35GA30 (70LA/30GA, mol %).

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Journal of Applied Polymer Science, Vol. 69, 627–630 (1998)
 CCC 0021-8995/98/030627-04

EXPERIMENTAL

Materials

DL-Lactide was prepared from a DL-lactic acid solution (85%) (Hopkin & Williams, Essex, UK) and recrystallized three times from ethyl acetate.[5] Glycolide was prepared from glycolic acid (Merck, Darmstadt, Germany) and the crude extract was washed with chloroform and recrystallized twice from ethyl acetate.[6] Due to the instability of glycolide, it is used fresh just after preparation. Tin–2-ethyl hexanoate, $Sn(Oct)_2$ (Sigma, St. Louis, MO) was purified by vacuum distillation. Chromotropic acid sodium salt (dihydrate, analytical grade) was from Merck. All solvents (Merck) were purified, if necessary, by the standard procedures.[7]

Polymerizations

DL-Lactide and glycolide were charged into a polymerization tube together with 0.1 mL of the catalyst (3% solution in toluene). The tube was kept under a high vacuum at 80°C for 2 h, subsequently heat-sealed, and kept at 129°C for 1 week. After this period, the tube

was broken and the crude polymer was dissolved in dichloromethane, filtered, and precipitated by hexane.

Film Preparation and Degradation

Films were prepared by solvent casting from a 25% solution of the polymer in dichloromethane and dried in a vacuum. Degradation studies were performed on square samples (1×5 cm, nearly equal weight) placed in 7 mL phosphate buffer (pH 7.35) at 37 ± 0.1°C in sealed tubes. At time intervals, one of the tubes was removed and broken, and the weight loss, amount of glycolic acid released, intrinsic viscosity, and ^{1}H-NMR spectra of the remaining speciemens were determined.

Instruments and Measurements

^{1}H-NMR spectra of the copolymer and its successive degradation products were obtained on a Bruker AC-80 (Germany). Chloroform-d_1 and TMS were used as the solvent and internal standard, respectively. The intrinsic viscosity of the copolymer and degradation products were measured in a dilute chloroform solution at 25°C, using an Ubbelohde viscometer. The molecular weight and molecular weight distribution of the copolymer samples were determined by gel permeation chromatography (Shimadzu-LC9A, Tokyo, Japan) on a 10^4 Styragel column, (refractive index detector), using tetrahydrofuran as the solvent, a flow rate of 1 mL/min at 40°C, and polystyrenes of low polydispersity as standards. The concentration of the glycolic acid released at different intervals was determined by measuring the UV absorbance in the presence of chromotropic acid at 578 nm (using a Shimadzu-240A UV-vis spectrophotometer) and extrapolation through a calibration curve.[8]

RESULTS AND DISCUSSION

The GPC weight-average molecular weight ($\bar{M}_w$) of the copolymer used in this study was 100,000 and its polydispersity was ($\bar{M}_w/\bar{M}_n$) = 1.7. Figure 1(a) shows the change in viscosity versus time. The reduction in molecular weight is quite drastic as evidenced by the fact that after 20 days the intrinsic viscosity reaches to within 10% of its initial value. The initial composition of the copolymer as determined by ^{1}H-NMR was lactide/glycolide 70/30. The onset of measurable weight loss is at day 20, and 20 days later, it reaches 90% of its initial weight [Fig. 1(b)]. The small initial weight losses may be attributed to the release of glycolic acid as evidenced by ^{1}H-NMR. A major release of glycolic acid takes place after 20 days, being intense at first and leveling off afterward [Fig. 1(c)]. As shown in Table I, little variation in the composition occurred during degradation. This shows that degradation occurs with equal ease at glycolic and lactic units in the copolymer chains. After 4 weeks, insoluble low molecular weight

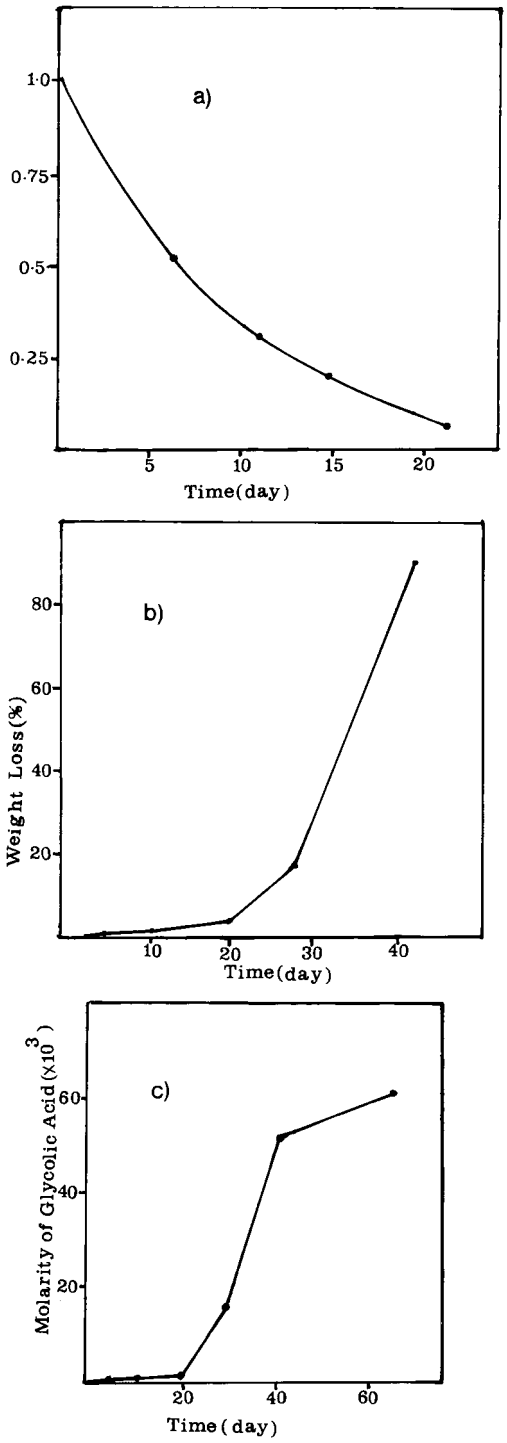

Figure 1 Changes in properties as a function of degradation period: (a) intinsic viscosity; (b) weight loss; (c) glycolic acid released, in phosphate buffer (pH 7.35) at 37°C.

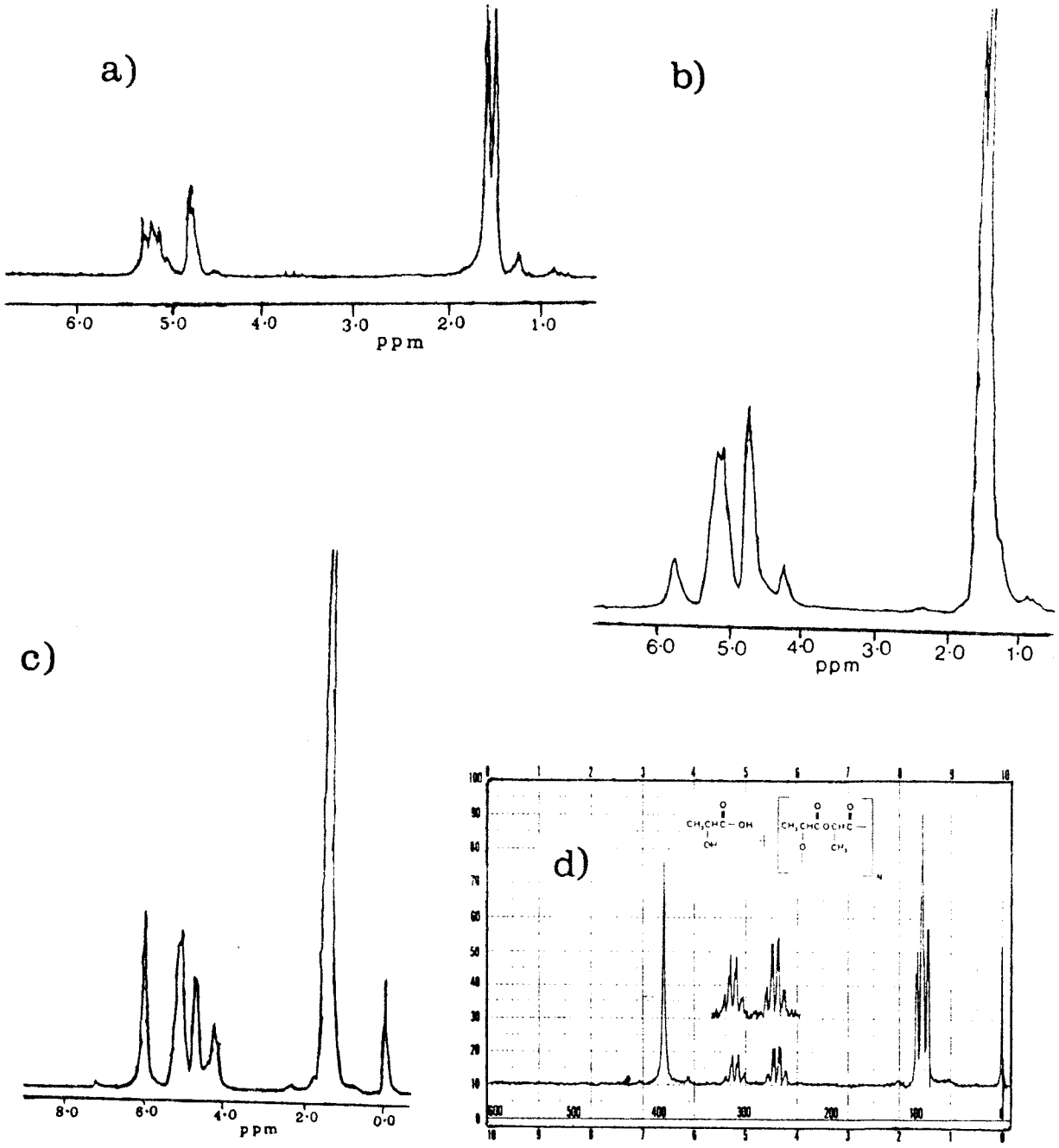

Figure 2 ^{1}H-NMR spectra of the copolymer (a) before degradation, (b) after 28 days, and (c) after 42 days of exposure to phosphate buffer (pH 7.35) at 37°C. (d) Standard ^{1}H-NMR spectra of lactic acid with some oligomeric products.

fragments were formed as evidenced from the ^{1}H-NMR spectra. The ^{1}H-NMR spectra show (in addition to those corresponding to CH_2 and CH peaks of glycolic and lactic units) two singlet peaks at 4.2 and 5.8 ppm. At day 42, these two singlet peaks became larger while the peak at 5.8 ppm shifts to 6.1 ppm [Fig. 2(a–c)]. In comparison to the ^{1}H-NMR spectra of lactic acid that show the presence of oligomeric products [Fig. 2(d)], these peaks show that the ester group is cleaved frequently and the percentage of low molecular weight OH- or COOH-terminated fragments are increased (Fig. 2).

Table I Changes in Composition of the Remaining Copolymer as a Function of Degradation Period

Time (Day)	Lactide/Glycolide Molar Ratio
0	70/30
11	70/30
15	71/29
20	72/28

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