Synthesis and In Vitro Hydrolytic Degradation of Polyglycolide and Its *l*-Lactide Copolymer

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ABSTRACT

In this study homo- and copolymers of glycolide and *l*-lactide were synthesized and subjected to in vitro hydrolytic degradation. Glycolide and *l*-lactide were prepared from glycolic and *l*-lactic acid, respectively. Stannous octoate was used as polymerization catalyst. Poly(*l*-lactide) with M_w=9.4×10^5 and a polydispersity of 1.89 was synthesized and characterized. Also copolymers of *l*-lactide and glycolide were prepared. Polyglycolide and its lactide copolymers with high proportion of glycolide do not dissolve in organic solvents. Degradation studies were conducted at 37 °C and pH=7.35. The concentration of released glycolic acid was determined by chromotropic acid reagent. Purified polyglycolide powder shows a fast degradation profile in the first 10 days, after which it levels off. A copolymer obtained from 10 mol% *l*-lactide and 90 mol% glycolide shows different degradation pattern as polyglycolide, because of its amorphous nature it exhibits a higher degradation rate.

Key Words: polyglycolide, poly(*l*-lactide), in-vitro degradation, stannous octoate

INTRODUCTION

Aliphatic polyesters derived from lactic acid (LA) and glycolic acid (GA) were synthesized early in the 50's, when most of the commercial polymers were launched on the market. However, no attention was paid to these polyesters because of their poor hydrolytic and thermal stabilities. But, in the years later their hydrolytic instability turned into an exciting advantage and made these materials suitable for a wide variety of surgical and pharmaceutical applications. Lactic and glycolic acids are Kreb's cycle acids, and in body, they are oxidized completely to carbon dioxide and water.

Polymers derived from these α-hydroxy acids are biocompatible and biodegradable, and their degradation products are non-toxic. Since 1970, poly(glycolic acid) has been commercially available as the surgical suture, Dexon [1], and the copolymer made of 92 mol% GA/8 mol% LA has had a limited application as the competitive suture, Vicryl [2], since 1975.

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Poly(glycolic acid) (PGA) and poly(lactic acid) (PLA) can be prepared by simple polycondensation reaction of glycolic acid and lactic acid in the presence of antimony trioxide.

However, because of thermal instability of the polymer formed and the equilibrium nature of the reaction as well as difficulties associated in removing water from the viscous polymer mass, only low molecular weight polymers are obtainable which lack the optimum properties for most applications.

The preferred method for producing high molecular weight polymers is the ring-opening polymerization of the cyclic dilactons, glycolide and lactide, in the presence of tin catalysts.

In the work reported we prepared polyglycolide, polylactide and their copolymers and studied in vitro hydrolytic degradation of polyglycolide and a copolymer with 10 mol% *l*-lactide and 90 mol% glycolide (in the feed).

EXPERIMENTAL

Materials

Glycolide was prepared from glycolic acid (Merck, Darmstadt, Germany) and the crude extract was washed with chloroform and recrystallized twice from ethyl acetate [3]. *l*-Lactide was prepared from 90 % *l*-lactic acid solution (Merck Inc.) and recrystallized three times from ethyl acetate [4]. Due to instability of glycolide and lactide they are used fresh just after preparation. Tin-2-ethyl hexanoate, $Sn(Oct)_2$ (Sigma, St. Louis, USA) was purified by vacuum distillation. Chromotropic acid sodium salt (dihydrate, analytical grade) was purchased from Merck. All solvents (Merck) were purified, if necessary, by the standard procedures [5].

Polymerizations

Glycolide was charged into a polymerization tube together with 0.1 mL of the catalyst (3% solution in toluene) and 0.01 % lauryl alcohol as a catalyst activator. The tube was kept under high vacuum (<0.1 mmHg) at 80 °C for 2 h, and subsequently it was heat-sealed and kept at 120 °C for three days. After this period, the tube was broken and the crude polymer was crushed and refluxed in ethyl acetate and dried in vacuum. Poly(*l*-lactide) was prepared analogous to polyglycolide except that in the absence of lauryl alcohol. For copolymer synthesis appropriate amounts of *l*-lactide and glycolide were charged in a polymerization tube and kept under high vacuum at 70 °C for 2 h. Catalyst solution (0.1 mL, 3% $Sn(Oct)_2$ in toluene) was then added to the reaction mixture and kept under vacuum for 2 h to remove all volatiles. The tube was then sealed under vacuum and copolymerization carried out at 110 °C for three days. Subsequently tube was broken and the copolymer was cut to equal weight specimens for in vitro degradation studies.

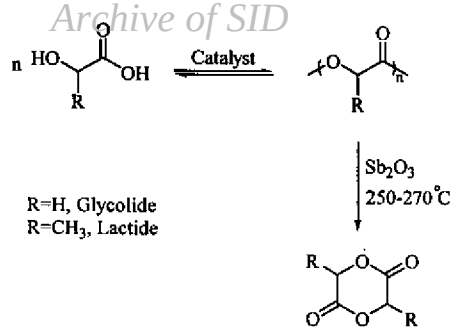
In Vitro Degradation

For preparation of a calibration curve, one mL of each of the 5 different concentrations of pure glycolic acid (0.2, 0.05, 0.005, 0.0005, 0.0001 M) was mixed with 3 mL of analytical-grade chromotropic acid solution (to prepare chromotropic acid solution, 1.0 g of the acid disodium salt was dissolved in 250 mL concentrated sulphuric acid).

The resulting absorbance of the most concentrated solution (0.2 M) was determined by scanning the solution through the wavelength ranging from 200 to 900 nm in a Shimadzu-240A UV-visible spectrophotometer. The wavelength at which the maximum absorbance was observed was taken for the determination of the subsequent absorbance of the rest of the sample solutions. The calibration curve was constructed by plotting the observed maximal absorbance (578 nm) vs. the corresponding glycolic acid solution concentration.

Ten samples of polyglycolide powder with equal weights were immersed in 7 mL of phosphate buffer solution (PH=7.35) separately. The solutions were kept at 37 °C for a predetermined period of time. One mL of each of the immersion solutions was withdrawn after the predetermined immersion period and immediately mixed with 3 mL of the chromotropic acid solution.

The absorbance maximum of each solution was determined in the manner described above. The corresponding glycolic acid concentration at the absorbance maximum was determined by the use of the previously constructed calibration curve [6].



Scheme I

Instruments and Measurements

The concentration of glycolic acid released at different intervals was determined by a Shimadzu-240A UV-vis spectrophotometer, measuring the UV absorbance in the presence of chromotropic acid at 578 nm and extrapolation through a calibration curve. Infra-red spectra were recorded by a Shimadzu-4300 FT-IR spectrophotometer. Differential scanning calorimetry (DSC) themograms were obtained with a Mettler Instrument DSC series PC11. Thermogravimetric analysis was carried out on a Dupont 2000 V5.1 A.

Molecular weight and molecular weight distribution of poly(*l*-lactide) was determined by a Shimadzu-LC9A, Tokyo, Japan gel permeation chromatography on a 10^4 Styragel column, (refractive index detector), using tetrahydrofuran as solvent, flow rate 1 mL/min at 40 °C, and polystyrene of low polydispersity as standards.

RESULTS AND DISCUSSION

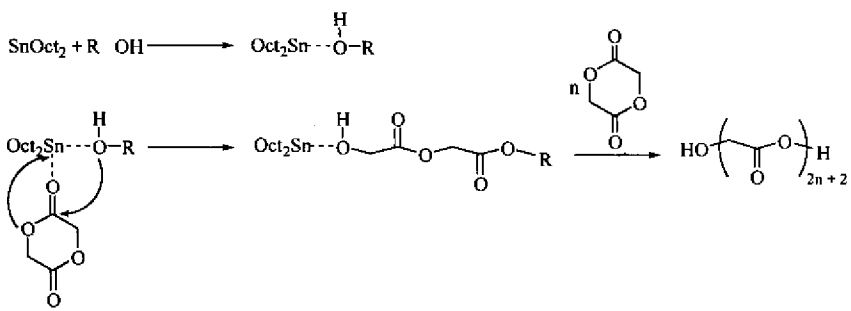
Glycolide and *l*-lactide were prepared from corresponding α-hydroxy acids, glycolic acid and *l*-lactic acid as shown in Scheme I.

Polyglycolide was obtained by ring-opening polymerization of glycolide in the presence of lauryl alcohol as coinitiator and $Sn(Oct)_2$ as catalyst. On the basis of the mechanism suggested by Kricheldorf [7–8] and Duda [9] for polymerization of lactones in presence of $Sn(Oct)_2$ catalyst and alcoholic coinitiators, the steps in Scheme II are proposed for the formation of polyglycolide.

According to Duda's recent works, polymerization proceeds via "active chain end" mechanism, i.e., on the Sn-alkoxide bonds present at the chain ends.

Polyglycolide is usually insoluble in all organic solvents but dissolves in hexafluoroisopropanol to a small extent. The TGA thermogram of polyglycolide (Figure 1) shows that the polymer begins to degrade at 272 °C and the DSC studies show that the crystalline melting point of the polymer is 224 °C (Figure 2). Thus, the processing temperature range of polyglycolide is about 45 °C reflecting its extreme sensitivity to the processing temperature, which calls for accurately controlled process equipment. Figure 3 shows the FT-IR spectrum of polyglycolide.

Lactic acid exists in two stereoisomeric forms: *d* and *l*-lactic acid. In this study *l*-and *dl*- lactide were prepared from *l*- and *dl*-lactic acid in a manner analogous to glycolide. The melting points of *l*- and *dl*-lactide crystals were 98 °C and 126 °C, respectively.



Scheme II

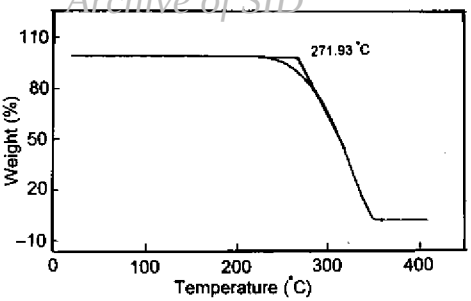


Figure 1. TGA Thermogram of polyglycolide.

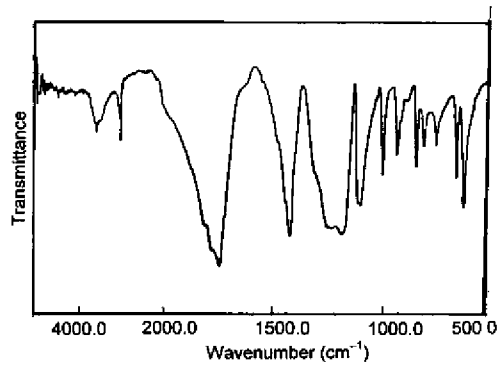


Figure 3. FT-IR Spectrum of polyglycolide.

Poly(*l*-lactide) and poly (*dl*-lactide) were prepared by ring-opening polymerization of the respective monomers in the presence of stannous octoate at temperatures slightly above their melting points.

Films prepared by solution casting of poly(*dl*-lactide) were transparent and this shows the amorphous nature of the polymer, while the films prepared from poly (*l*-lactide) were opaque because of semicrystalline nature of the polymer. In contrast to polyglycolide, polylactides are soluble in some organic solvents, like chloroform and solubility-dependent characterization were achieved readily. Poly(*l*-lactide) with $\bar{M}_w$=9.4×10^5 and a polydispersity of 1.89 was synthesized with crystalline mp=172 °C.

Various ratios of glycolide/lactide can be copolymerized in melt, in the presence of $Sn(Oct)_2$. Figure 4 shows the FT-IR spectrum of poly(*l*-lactide).

It has been shown that the reactivity of glycolide is higher than lactide in copolymerization and this causes the copolymer to have microblock structures [10]. A copolymer was made from a monomer mix of 90 mol % glycolide and 10 mol % *l*-lactide according to the above procedure.

According to Vert's acronyms [11], this copolymer was designated as PLA_{10}/GA_{90}. Because of the copolymerization, the crystallinity of this copolymer is lower than polyglycolide or poly(*l*-lactide) homopolymers, but it does not dissolve in most of the common organic solvents. As mentioned, polyglycolide and its lactide copolymers with high proportion of glycolide do not dissolve in organic solvents. Due to this insolubility, the as-polymerized copolymer was used for in vitro degradation studies.

For degradation studies the released glycolic

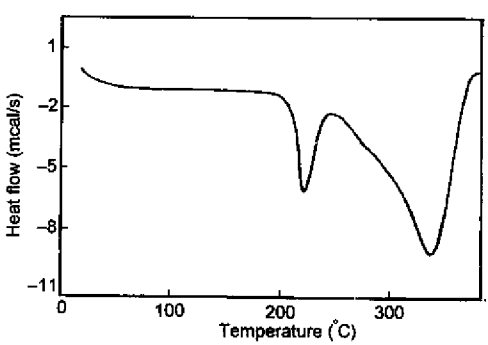


Figure 2. DSC Thermogram of polyglycolide.

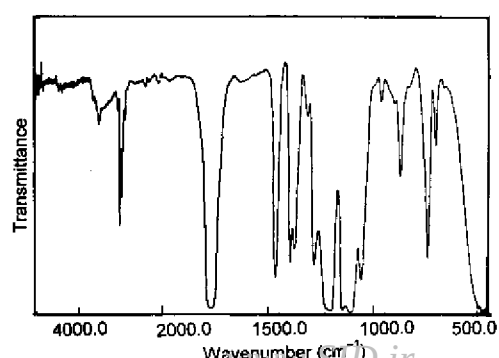
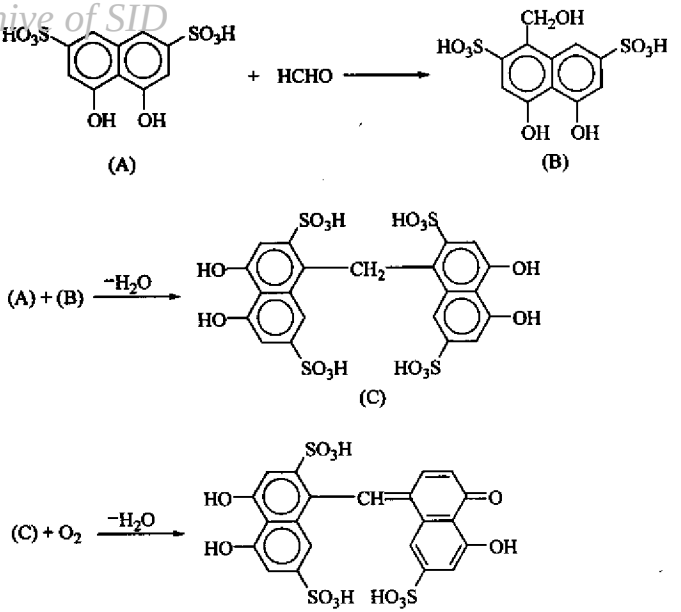


Figure 4. FT-IR Spectrum of poly(*l*-lactide).



Scheme III

acid, by the action of the concentrated sulphuric acid, is converted to formaldehyde.

The resulting formaldehyde then reacts with chromotropic acid through a condensation followed by oxidation, and forms a *p*-quinoidal compound as shown Scheme III.

The conjugated double bonds in *p*-quinoidal compound are responsible for the formation of colour [12].

The concentration of released glycolic acid during degradation can be determined from the corresponding calibration curve. Figure 5 shows the molarity of the released glycolic acid versus degradation time at 37 °C. This figure is analogous to the degradation pattern of polyglycolide suture (Dexon®) [12]. However, since the polymer sample used is in a powder form, its degradation is faster. The concentration-time profile obtained in this study shows that in the initial 10 days there is a sharp increase in the concentration of released glycolic acid, pointing to the degradation of amorphous regions of polymer sample. This is followed in the subsequent stage by the slow degradation of the crystalline regions.

The as-polymerized copolymer, PLA_{10}/GA_{90}, was subjected to in vitro degradation in a manner analogous to polyglycolide and the concentration-time profile is shown in Figure 6. As seen, the degradation

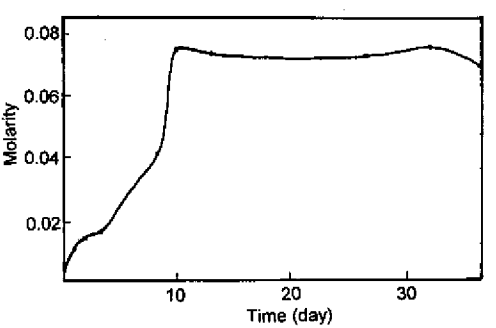


Figure 5. Molarity of released glycolic acid vs. time for polyglycolide powder.

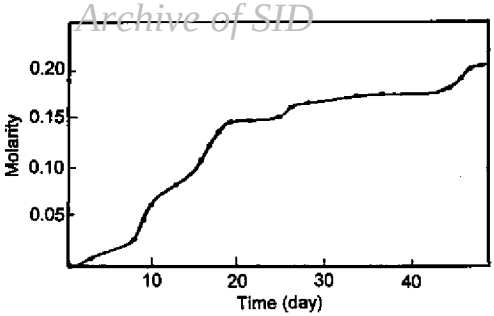


Figure 6. Molarity of released glycolic acid vs. time for copolymer PLA_{10}/GA_{90}.

pattern is different from polyglycolide and the degradation rate is faster than that of the polyglycolide. In this case the copolymer is mostly amorphous and as expected the degradation occurs at a constant rate.

CONCLUSION

High molecular weight poly(α-hydroxy acid)s, suitable for biomedical applications can be prepared by ring opening polymerization of dilactones. Degradation characteristics of these polymers are affected by the physical form of the specimens. As expected, their powder form degrades faster than their fiber form. Due to its amorphous nature, the as-polymerized copolymer PLA_{10}/GA_{90} has a different degradation pattern with a faster kinetics.

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