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Synthesis, Characterization and in Vitro Degradation of Poly(DL-Lactide)/Poly(DL-Lactide-co-Glycolide) Films

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Poly(dl-lactide) (PLA) homopolymers and poly(dl-lactide-co-glycolide) (PLGA) copolymers were synthesized from their cyclic dimers, i.e. dl-lactide and glycolide, by ring-opening polymerization in the presence of catalyst stannous octoate and chain control agent lauryl alcohol. The effects of catalyst and chain control agent concentrations, reaction temperature, and reaction time on the molecular weight and yield of homopolymers were studied. The homopolymers were obtained in the intrinsic viscosity 0.1 to 1.0 dl/g range by changing the polymerization conditions. The copolymers in two different lactide/glycolide ratios, i.e. 90:10 and 70:30 and in 0.60 intrinsic viscosity were synthesized. The polymers were further characterized by IR, ¹H-NMR, ¹³C-NMR, and DSC. In vitro degradation studies were conducted at 37° C in pH 7.4 phosphate buffered saline. The results showed that the intrinsic viscosities of all polymers decrease continuously until 0.20 dl/g after exposure to phosphate buffered saline and then a very sharp mass loss occurs.

Key Words: Pol(dl-lactide), poly(dl-lactide-co-glycolide), biodegradable polymer, in vitro degradation.

Introduction

Recent developments in the biomaterial field have been focused on biodegradable polymers. Among these polymers much progress has been made in polylactic acid (PLA), polyglycolic acid (PGA) and their copolymers (PLGA). Because they degrade to body metabolites, i.e. lactic and glycolic acid, by hydrolysis of ester bonds, they have high biocompatibility, nontoxicity and easy processability in different forms. In addition, they have been accepted by the U.S. Food and Drug Administration for internal use in the human body. PLA, PGA and their copolymers can be synthesized in a wide range of molecular weights by following two processes: 1) direct polycondensation reaction of lactic and/or glycolic acid which leads to low molecular weight products^{1,2} 2) ring-opening polymerization of cyclic dimers, i.e. lactide and glycolide, in the presence of metal catalysts to synthesize high molecular weight polymers^{3,4}. Studies have been carried out to modify these group of polymers, especially by copolymerization with other proper monomers^{5,6}. However, details of the polymerization/copolymerization procedure and characterization are not given in the literature.

PLA, PGA and their copolymers are suitable for the design of controlled drug delivery systems including anticancer and antimalarial agents, contraceptive steroids, local anesthetics and narcotic antagonists⁷⁻⁹. Recently, we developed a PLA/PLGA based sustained drug release system which delivers mitomycin-C (MMC), and anticancer drug, to malignant tumours¹⁰. In this paper, we describe the synthesis of those polymers/copolymers together with their detailed characterization and in vitro degradation.

Experimental

Chemicals

Cyclic diesters of dl-lactic acid and glycolic acid, i.e. dl-lactide and glycolide, respectively were obtained from Polysciences (Warrington, PA). They were purified by the method described in the literature⁴ and dried at 40° C before use. Catalyst stannous octoate, chain control agent lauryl alcohol and other chemicals and solvents, such as methylene chloride, methanol, hexane, and Sigmacote were purchased from the Sigma Chemical Company (St. Louis, MO). Phosphate buffer solution (PBS, pH 7.4) was prepared by dissolving the mixture of KH_2PO_4 (4.710 g) and Na_2HPO_4 (19.778 g) in 1 liter deionized water.

Synthesis of Poly(dl-lactide) Homopolymers

Homopolymers of dl-lactide were synthesized using method similar to that described by Gilding and Reed³. Two grams dl-lactide was placed in a polymerization tube together with solutions of stannous octoate and lauryl alcohol in hexane, i.e. 8 % (v/v) stannous octoate and 13 % (v/v) lauryl alcohol in hexane. Stannous octoate and lauryl alcohol concentrations were varied between 0.01-0.06 % and 0.0025-0.01% (w/w), respectively. The polymerizations were carried out in a silicone oil bath in the temperature range of 165-200° C for time periods ranging from 10 min to 6h. The reaction mixture was stirred magnetically at 750 rpm during the polymerization process. Hexane and liberated water were removed by vacuum pump under 25 mm Hg pressure with a liquid nitrogen trap connected to the polymerization tube. The reaction was quenched by immersing the tube in ice water. The solidified product was dissolved in 10 ml of methylene chloride and residual monomer was removed by adding excess methanol. This procedure was repeated to improve the yield of purification. The precipitated polymer was then dried in a vacuum oven at 60° C for 48 h. The yield of the polymerization reaction was determined by weighing the insoluble polymer fraction.

Synthesis of Poly(dl-lactide-co-glycolide) Copolymers

The same procedure described for homopolymers was applied to the synthesis of copolymers. However, the reaction temperature, reaction period, lauryl alcohol and catalyst concentrations were kept constant at 200° C, 2h, 0.01% (w/w) and 0.02 % (w/w), respectively. The dl-lactide/glycolide ratio was varied as 90:10 and 70:30.

Characterization

The samples used in the characterization studies were in the form of films cast by pouring solution of homo/copolymer in methylene chloride (75% v/v) into petri dishes precoated with silicone (Sigmacote), and allowing them to dry initially at room temperature for 24 h, then in a vacuum oven for a further 48 h.

Intrinsic viscosities of the homo and copolymers were determined by the single point method described by Solomon and Ciuta ¹¹. The equation of intrinsic viscosity $[\eta]$ is

$$[\eta] = [2(\eta_{sp} - \ln \eta_{rel})^{0.5}]/C$$

Here, η_{sp} and $\ln \eta_{rel}$ are the specific and the relative viscosity, respectively, and C is the concentration of the polymer solution. The flow time of 0.2 % (w/w) polymer solution in chloroform was measured at 25 °C with an Ubbelohde viscometer.

A Shimadzu DR 8001 Model Fourier transform infrared spectrophotometer (FTIR) was used to record the IR spectra of the polymeric films.

The glass transition temperatures of homo and copolymers were determined using a Mettler TC 10A Model differential scanning calorimeter (DSC). Six milligram samples were placed in covered aluminium sample pans, then placed into the DSC sample holder. The sample was then heated at 10 °C/min, in the 25-225 °C temperature range and nitrogen atmosphere. An average of three determinations were made for each sample.

¹³C NMR spectra of monomers and polymers were recorded on a AC-80 pulsed FT-NMR spectrometer at room temperature in CDCl₃ with TMS as the internal standard.

In vitro Degradation Studies

The in vitro degradation characteristics of pure homopolymers and copolymers were evaluated by measuring weight loss and decrease of intrinsic viscosity. For this purpose, preweighed polymer films, 150 μm in thickness, were placed in 25 ml of PBS, pH 7.4 at 37 °C. Samples were recovered periodically, dried in a vacuum desiccator for several days and then weighed to determine the weight loss. In addition, the intrinsic viscosity of the sample was determined at the same time intervals.

Results and Discussion

Synthesis of Homo and copolymers

Homopolymers of dl-lactide were synthesized by ring opening polymerization in the presence of catalyst, stannous octoate, and a chain control agent, lauryl alcohol. Stannous octoate is preferred for biomedical applications because of its low toxicity⁴. The polymerization reaction was carried out in different conditions by changing the reaction temperature, time, and concentration of catalyst and chain control agent in order to determine the optimum polymerization conditions. The effect of these parameters on yield and intrinsic viscosity of homopolymers are shown in Figure 1-4. As can be clearly seen in Figure 1, the polymerization yield is not affected by the variation of temperature between 165 °C and 200 °C. By increasing temperature above the optimal level, the yield of polymerization decreases because the formation of residual monomer increases. However, intrinsic viscosity, in other words, molecular weight of polymers reaches a maximum, $[\eta] = 1.01 \text{ dl/g}$, at 175 °C and after that point it decreases linearly with increasing temperature. At 200 °C, the intrinsic viscosity of polymer is 0.32 dl/g. According to the curves in Figure 2, the polymerization reaction occurs rapidly, and the yield is 85 % at the end of 1 hour, then it increases very slowly up to 90 % during the 6 hour period. Intrinsic viscosity also shows a similar pattern, but the increase between 1 and 2 hours is more noticeable. Figure 3 shows the dependency of yield and intrinsic viscosity to catalyst concentration. It is clear that the polymerization reaction does not occur in the absence of catalyst and increasing catalyst

concentration above 0.02 % leads to some decrease in intrinsic viscosity which could reflect a molecular weight decrease. As shown in Figure 4, homopolymer intrinsic viscosity and yield reach maxima at the 0.005% lauryl alcohol concentration.

Copolymers of lactide and glycolide monomers were synthesized to contain lactide-to-glycolide ratios of 90:10 and 70:30 while all other polymerization parameters were kept constant (temperature= 200°C, time=2h, lauryl alcohol concentration=0.01 % (w/w), and catalyst concentration=0.02% (w/w)). They are random copolymers obtained by a ring-opening reaction of cyclic dimers, lactide and glycolide, as illustrated in Figure 5. Their intrinsic viscosities were calculated to be 0.61 and 0.60 dl/g, respectively. Lactide-to-glycolide ratios were determined from ¹H NMR spectra (Table 1).

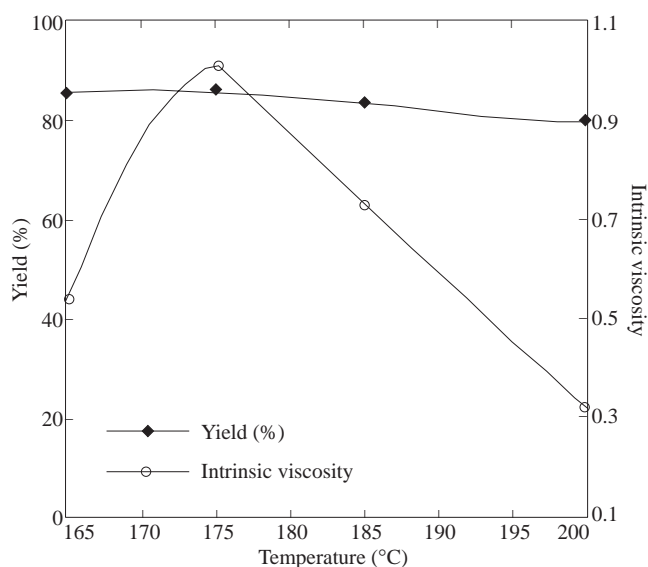


Figure 1. Effect of polymerization temperature on yield and intrinsic viscosity of PLA homopolymers (catalyst 0.02 wt %; lauryl alcohol 0.01 wt %; reaction period 2h)

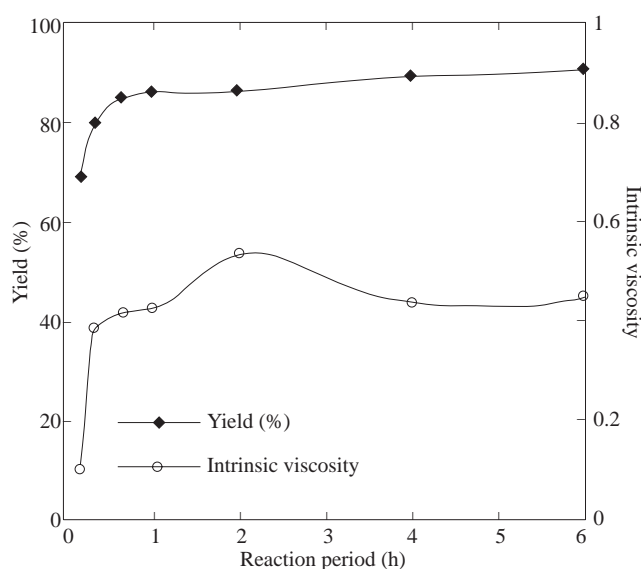


Figure 2. Effect of reaction period on yield and intrinsic viscosity of PLA homopolymers (catalyst 0.02 wt %; lauryl alcohol 0.01 wt %; temperature 165°C)

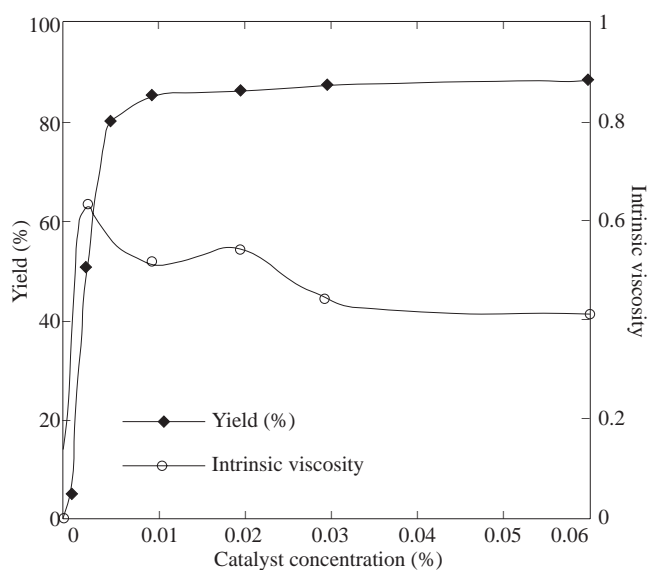


Figure 3. Effect of catalyst concentration on yield and intrinsic viscosity of PLA homopolymers (lauryl alcohol 0.01 wt%; temperature 165 °C; reaction period 2h).

Table 1. Polymerization conditions and some structural properties of selected PLA, PLGA samples synthesized here

Sample	Monomer composition (LA:GA)	Polymer* composition (LA:GA)	Temperature** (°C)	$[\eta]$ (dl/g)	Tg (°C)
D-1	100:0	100:0	165	0.50	50
D-2	100:0	100:0	185	0.60	51
D-3	100:0	100:0	175	1.01	55
B-2	95:5	90:10	200	0.61	48
A-2	80:20	70:30	200	0.60	45

* Determined by ^1H NMR, as mole percentage

** Catalyst conc.: 0.02 % (w/w); Lauryl alcohol: 0.01 % (w/w)

Reaction time: 2 hours.

Characterization Studies

IR spectra of lactide, glycolide monomers, PLA homopolymers, and PLGA copolymers were recorded. The IR spectrum of the dl-lactide exhibited absorbance peaks at 2850 (CH-stretch), 1760 (C=O anhydride), 1275, 1100 (C-O stretch), 940 (CH-bend) cm^{-1} . In the case of glycolide monomer, absorbance peaks at 1750 (C=O anhydride), 1540, 1430 (CH-bend), 1265, 1050 (C-O stretch) cm^{-1} were observed. The IR spectra of PLA homopolymers showed absorbance peaks at 3650 (OH-stretch), 1750 (C=O ester), 1450, 1360 (CH-bend), 1130, 1090 (C-O stretch), 750 (CH-bend) cm^{-1} . The IR spectra of copolymeric samples were found to be similar to the IR spectra of homopolymers.

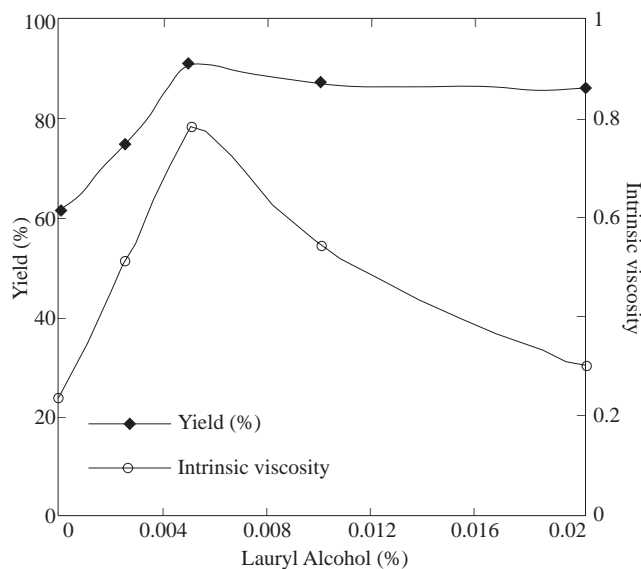


Figure 4. Effect of lauryl alcohol concentration on yield and intrinsic viscosity of PLA homopolymers (catalyst 0.02 wt %; temperature 165 °C; reaction period 2h).

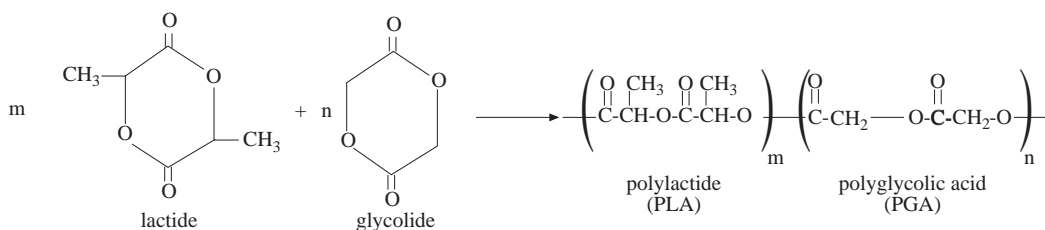


Figure 5. Chemical structure of dimers, polymers, and copolymerization reaction.

The structures of the lactide, glycolide monomers and their copolymers were elucidated from the ^{13}C NMR spectra. Figures 6a and b show the ^{13}C NMR spectra of PLA and PLGA (70:30), respectively. The ^{13}C NMR signals were at 167.6 ppm (C=O), 72.3 ppm (C-H) and 15.5 ppm (CH_3) for dl-lactide monomer; 163.5 ppm (C=O) and 64.9 ppm (C- H_2) for glycolide monomer; 169.6 ppm (C=O), 69.0 ppm (C-H) and 16.7 ppm (CH_3) for dl-lactide homopolymers. All signals of C=O (169.2 ppm), C-H (69.9 ppm), CH_2 (60.7 ppm) and CH_3 (16.6 ppm) were observed in the spectra of copolymers.

^1H NMR spectra of homopolymers exhibited signals at 1.57 ppm (d- CH_3) and 5.20 ppm (m C-H). In the ^1H NMR spectra of copolymers an additional signal at 4.77 ppm (CH_2) was also observed. The lactide/glycolide ratios of copolymers were calculated from the peak intensities at 5.20 ppm and 4.77 ppm.

Differential scanning calorimetry showed no melting endotherms, suggesting the amorphous nature of the homo and copolymers. T_g values were obtained from the thermograms, using the midpoint between the intersections of the two parallel baselines, before and after T_g . The T_g increased from 42 °C for the lowest molecular weight PLA ($[\eta] = 0.1$ dl/g) to 55 °C for the highest molecular weight PLA ($[\eta] = 1.01$ dl/g). This was expected, since the glass transition is dependent on the free volume of polymer. It should be noted that T_g values decreased due to the increasing ratio of glycolide monomer in the copolymer (Table 1). This was attributed to the relatively high hydrophilicity of glycolide monomer.

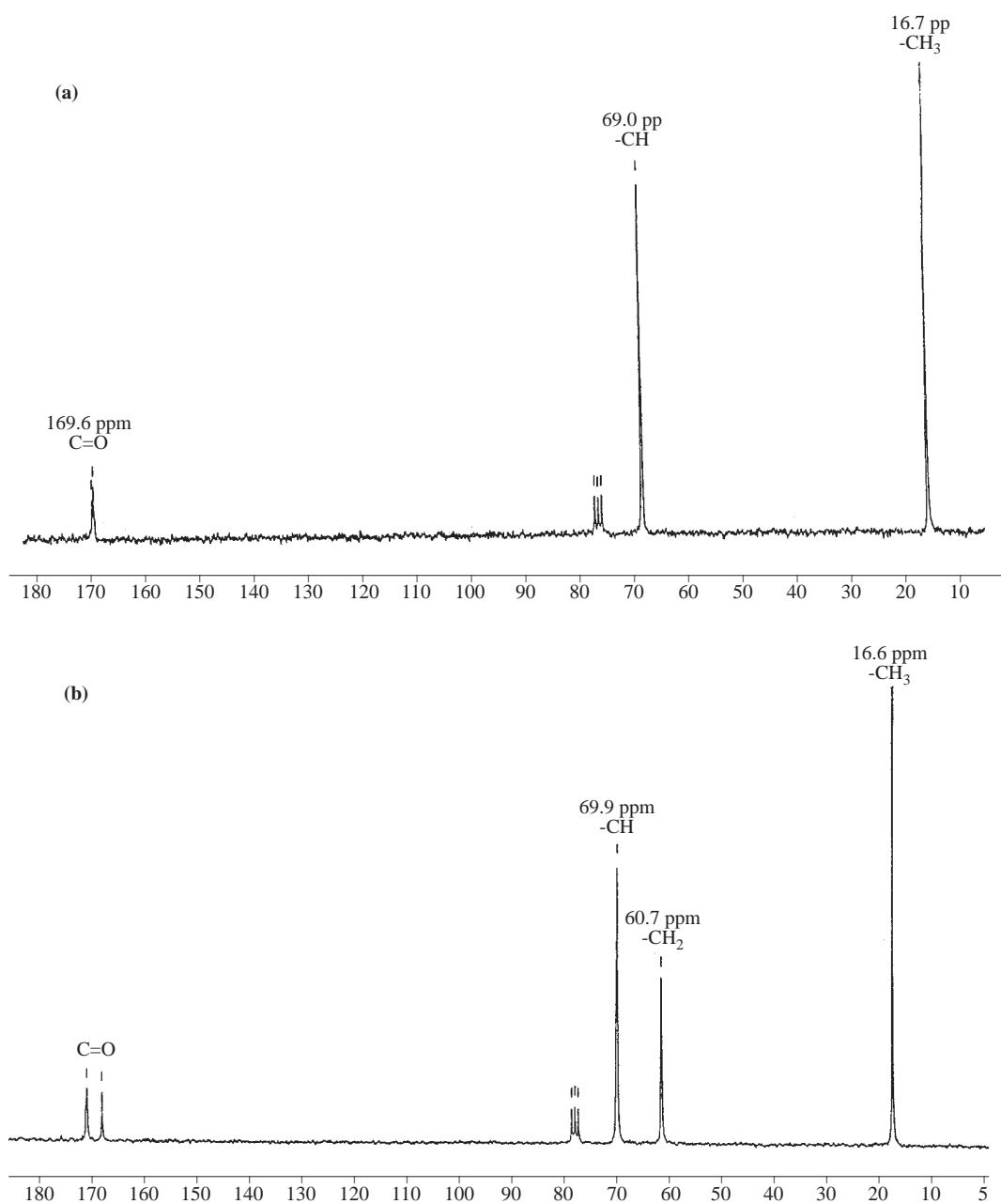


Figure 6. ^{13}C NMR spectra of a) PLA homopolymer b) PLGA (70/30) copolymer

In vitro Degradation Kinetics

The presence of ester linkages in the polymer/copolymer backbone allows gradual hydrolytic degradation. The in vitro degradation mechanism of homo and copolymers synthesized in this study was clarified by intrinsic viscosity and mass loss measurements. Figure 7a and b show the decrease in intrinsic viscosities with time for the PLA homopolymers and PLGA copolymers, respectively. These figures clearly indicate that the intrinsic viscosities of all polymers decreased continuously after being exposed to the PBS at 37° C. PLA homopolymers showed approximately the same rate, whereas copolymer degraded at a slightly faster rate depending on the glycolide ratio. The result of the mass loss experiments suggest that all polymers

give a sigmoidal curve characteristic of bulk hydrolysis Figures 8a and b. This observation is consistent the results of other degradation studies^{12,13}. It means there is no significant mass loss in the matrix during the initial time lag then rapid degradation occurs with time. This time lag depends on the molecular weight of polymer, e.g. 100 days for PLA $[\eta] = 0.50$ dl/g; 130 days for PLA $[\eta] = 0.61$ dl/g. Comparison of mass loss curves with intrinsic viscosity curves indicates that rapid mass loss occurs after the intrinsic viscosity has reached a threshold level, i.e. $[\eta] = 0.2$ dl/g.

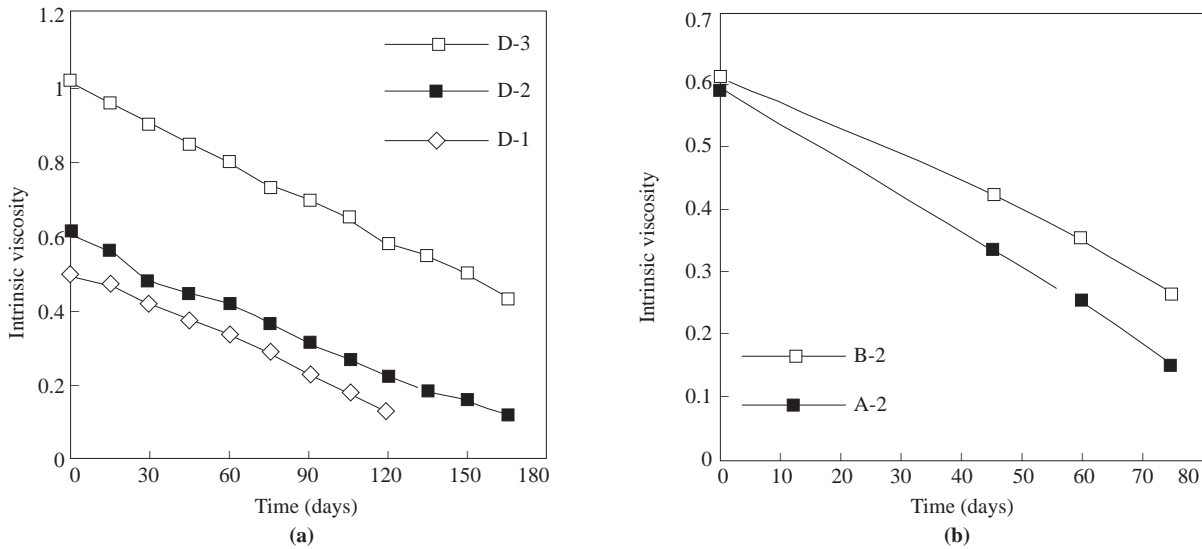


Figure 7. Changes in intrinsic viscosity of a) homopolymers (D-1, $[\eta]=0.5$ dl/g; D-2, $[\eta]=0.6$ dl/g; D-3, $[\eta]=1.01$ dl/g). b) copolymers (B-2, PLA/PGA: 90/10, $[\eta]=0.61$ dl/g; A-2, PLA/PGA: 70/30, $[\eta]=0.60$ dl/g) during the in vitro degradation

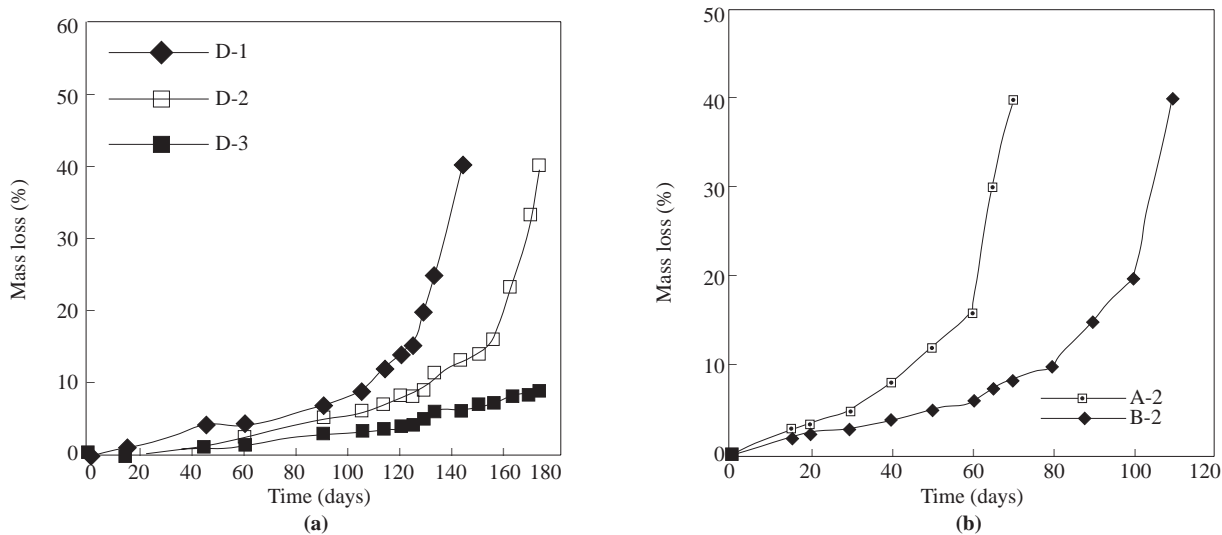


Figure 8. Changes in weight of a) homopolymers (D-1, $[\eta]=0.5$ dl/g; D-2, $[\eta]=0.6$ dl/g; D-3, $[\eta]=1.01$ dl/g). b) copolymers (B-2, PLA/PGA: 90/10, $[\eta]=0.61$ dl/g; A-2, PLA/PGA: 70/30, $[\eta]=0.60$ dl/g) during the in vitro degradation

In conclusion, by varying polymerization conditions, i.e. temperature, reaction period, catalyst, and chain control agent concentrations, and copolymer ratio, it is possible to produce a family of PLA and PLGA polymers with different degradation periods.

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