Synthesis and Characterization of Novel Biodegradable Triblock Copolymers from L-Lactide, Glycolide, and PPG

S. M. F. FARNIA,¹ J. MOHAMMADI-ROVSHANDEH,¹ M. N. SARBOLOUKI²

¹ Department of Chemistry, Faculty of Sciences

² Institute of Biochemistry and Biophysics, University of Tehran, Tehran-Iran, Iran

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ABSTRACT: Copolymers with a PPG center block and two arms of random glycolide/ lactide copolymers have been synthesized and characterized. Compared to random glycolide/lactide copolymers, these new polymers have high toughness and low elastic modulus.¹ H-NMR spectral lines of glycolide CH_2 protons of the copolymers are essentially identical. These materials show no crystallization transition in DSC thermograms and their melting points with respect to PLLA appeared at lower temperatures, indicating the pivotal role of the PPG center block in the copolymer. Degradation in aqueous media (pH = 6.9, 70°C) with stirring, subjected the two end blocks to hydrolytic degradation. The glycolyl ester bond cleavage was faster than for the lactyl ester bond. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 73: 633–637, 1999

Key words: biodegradable polymers; lactic acid; glycolic acid; PPG

INTRODUCTION

Biodegradable polymers, particularly aliphatic polyesters of the poly(hydroxy acid)-type copolymers are being extensively used and studied for various biomedical and pharmaceutical applications.¹⁻³ Synthetic poly(hydroxy acids) derived from lactic acid (LA), glycolic acid (GA), ε-caprolactone and their various copolymers are the most promising bioresorbable materials in the field of surgery⁴ (sutures, implants, bone fixation, etc.) and pharmaceuticals⁵ (targeted and timely released drug delivery systems). Copolymerization of various monomers is among the best of suitable approaches towards achieving specific requirements in different applications. In this respect, we have investigated the synthesis and characterization of some novel triblock ABA polymers where B is a poly(propylene glycol) (PPG) block

and A is a random copolymer from lactide/gly-colide.

It is contended that PPG for its flexibility, hydrophilicity, and nontoxicity can impart the resultant copolymers with the much desired controllable properties.

EXPERIMENTAL

Materials

L-Lactide was prepared from 90% L-lactic acid solution (Merck Inc.) according to Gilding.⁶ Low molecular weight poly(L-lactide) was prepared by condensation polymerization, then heated to 250°C under high vacuum in the presence of Sb₂O₃. The crude L-lactide thus obtained was washed with ether and recrystallized $2\times$ from ethyl acetate. Glycolide was prepared likewise from glycolic acid (Merck Inc.) except that the low molecular-weight polyglycolide was heated to 300°C and the crude glycolide was washed with chloroform. Poly(propylene glycol) $\bar{M}_n = 2025$

Correspondence to: S. M. F. Farnia.

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Sample No.	mol % in Feed LA/GA/PO	mol % in Copolymers ^a LA/GA/PO	${ar M_n}^{ m b}$	
PLLA	100/0/0	100/0/0	$100,000^{\circ}$	
А	61/25/14	72/15/13	18,000	
В	68/22/10	76/10/14	20,000	

 $^{\rm a}$ Lactyl/Glycolyl/Propylene Oxide mol % as determined by $^1\mathrm{H}\text{-}\mathrm{NMR}$ spectra from an isolated copolymer.

^b Estimated from ¹H-NMR.

 $^{\rm c}$ Obtained by a GPC experiment using a Waters GPC system equipped with 500, 10³, 10⁴, 10⁵, Styragel column in series by THF as the solvent (flow rate 1.5 mL/min) at 40°C and refractive index detector.

(Hydroxyl Number 55 mg KOH/g; Merck Inc.) was used without any further purification. The polymerization catalyst was $Sn(Oct)_2$ (Sigma, St. Louis, MO) and purified by vacuum distillation. All chemicals or solvents were reagent grade (Merck Inc.) and dried or purified according to the established procedures.⁷

Polymerizations

Appropriate amounts of L-lactide, glycolide and poly(propylene glycol) were charged into a polymerization tube and kept under 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 tubes were then sealed under vacuum and polymerizations carried out at 95°C for 9 days. Subsequently, tubes were broken and contents dissolved in chloroform, filtered, and finally precipitated with methanol.

Measurements

¹H- and ¹³C-NMR spectra of copolymers were recorded on a Varian VXR-300 spectrophotometer. Chloroform-d₁ and TMS were used as solvent and internal standard, respectively. Stress–strain behavior of copolymer films was studied with an Instron Universal Testing Machine model 4204 with a 100 mm/min crosshead speed. Film specimens (70 × 20 × 0.1 mm) were prepared by solvent casting from a 20% chloroform solution. Differential Scanning Calorimetry (DSC) thermograms were obtained with a Mettler Instrument DSC series PC11. \bar{M}_n was estimated from ¹H-NMR data by considering relative intensities of CH–CH₂ moiety of propylene oxide designated as I_p (34.9 repeating units); CH and CH₂ moieties of lactyl and glycolide units designated as I_l and I_g according to the following equations:

$$\bar{M}_n(\text{Total}) = \bar{M}_n(\text{PPG}) + \bar{M}_n(\text{Polylactide}) + \bar{M}_n(\text{Polyglycolide})$$

$$ar{M}_n({
m Polylactide}) = 2 imes rac{I_l imes 34.9}{I_p} M_w({
m Lactyl})$$

$$\bar{M}_n(\text{Polyglycolide}) \times \frac{1}{2} \times \frac{I_g \times 34.9}{I_n} \, M_w(\text{Glycolyl})$$

In Vitro Degradation

For degradation studies film specimens with 1 cm² surface area and approximate identical weights (70 mg) were prepared by solvent casting from 20% chloroform solution. Films were cut to obtain the desired surface area. Copolymer B was selected for degradation. The specimens were incubated in 50 mL phosphate buffer of pH = 6.9 at 70°C with continuous stirring. Specimens were periodically removed, vacuum dried, and subjected to weight measurement and ¹H-NMR analysis. Percent weight loss was calculated as follows: $W_0 - W/W_0 \times 100$ (W_0 is the initial weight before degradation and W is the final weight after degradation).

RESULTS AND DISCUSSIONS

When PPG, glycolide, and L-lactide in varying ratios reacted in the presence of catalytic amounts of tin octoate at 95°C, copolymers with interesting characteristics are obtained according



Figure 1 ¹H-NMR spectrum of the copolymer B.

to the following reaction.



PPG acts as a macroinitiator, and with its two end terminal hydroxyl groups forms the center block of the copolymer. The other two blocks are constituted from random glycolide/L-lactide copolymers. Table I shows compositions of the monomer feed and resultant molar ratio of the triblock copolymers as determined by ¹H-NMR analysis. Because of the preparative methods and workup procedures, the feed molar ratio was not identical with the ¹H-NMR-determined molar ratio of isolated copolymers. The ¹H-NMR spectrum of a typical copolymer B shows lines related to each monomer that are well separated. Characteristics of the proton spectra include a multiplet at δ 5.05–5.3 for lactyl methinic protons. Methylenic protons of glycolyl units appear at δ 4.6–4.9 as a nine line multiplet, attributed to various pentads at end blocks of the copolymer. These signals are sensitive to microstructure sequences of lactide/glycolide copolymer. Spectral analysis⁸ shows that pentads with LGL and GLG sequences have low intensity, implicating a low extent of transesterification in the mild polymerization



Figure 2 ¹³C-NMR spectrum of the copolymer B.

conditions employed (G and L denote to glycolyl and lactyl units, respectively).

¹³C-NMR spectra of a typical copolymer B shows signals at δ 55 and 75 related to propylene oxide units. The signals at δ 61 and 69 are assigned to methylenic and methinic carbons of glycolide and lactide units, respectively. The expanded ¹³C-NMR spectrum of these regions are shown in Figure 3. As shown, the lines due to various pentads appears as multiplets similar to proton spectra.

Figure 4 shows the DSC thermograms of copolymers A and B. The endotherm of poly(L-lactide) homopolymer appears at about 170° C, whereas melting points, ranging from $60-90^{\circ}$ C, are recorded for copolymers A and B. PPG is liquid at room temperature, and, when copolymerized with glycolide and lactide, lowers the melting point of the resultant copolymers. No exo-



Figure 3 Expanded regions of glycolyl and lactyl methylenic and methinic units respectively: (a) ¹H-NMR spectrum; (b) ¹³C-NMR spectrum.



Figure 4 DSC thermograms of the copolymers A and B. Temperature increment: 10°C/min.

therm transition was detected in DSC thermograms, indicative of the amorphous nature of these copolymers. In general, polylactide, polyglycolide and their copolymers are materials with low toughness and high elastic moduli. Copolymerization with PPG lowers elastic modulus and increases toughness of the resulting materials. In Table II and Figure 5 mechanical properties of copolymers A and B are compared with a PLLA homopolymer. Interestingly, these copolymers have low elastic modulus and high toughness, contrary to PLLA alone. These polymers might have applications where biodegradable flexible properties are needed.

To obtain test results for *in vitro* degradation quickly, the polymers were subjected to accelerated hydrolysis at elevated temperatures. The specimens were immersed in a phosphate buffer at pH = 6.9 and 70°C with stirring. The evaluation of changes in composition of each sample were performed by analysis of ¹H-NMR spectral line intensities. The transparent films changed to opaque after 3 h, indicative of water diffusion into the bulk of the copolymers and the beginning of hydrolytic degradation of amorphous regions. After 7 h, weight gradually begins to decrease, and after 34 h total masses were disintegrated (Fig.



Figure 5 Stress-strain diagrams of PLLA homopolymer and copolymers A and B.

6). The samples taken at 10 h show an elastic nature, but after this time they become brittle. The ¹H-NMR intensity ratio of CH signal of lactyl unit to CH signal of propylene oxide was 8.4 before degradation. After 30 h this ratio decreased to 5.1, indicating the occurrence of degradation at the two end blocks. The ¹H-NMR intensity ratio of the CH signal of the lactyl unit to the CH₂ signal of the glycolyl unit at the beginning was 1.25, but after 30 h it reached 1.75. This implies a faster rate of hydrolysis for glycolyl ester relative to the lactyl ester bond in the copolymer. Apparently the enhanced hydrophobicity of the lactyl unit plays a significant role in the differing hydrolysis rates observed.

CONCLUSION

The studies clearly demonstrate that the block copolymers synthesized by ring-opening copolymerization of PPG, L-lactide, and glycolide, degrade under *in vitro* conditions and exhibit very

Sample No.	Stress at Break in Mpa	Stress at Yield in Mpa	Elongation at Yield in %	Elongation at Break in %
PLLA	38	_	_	3.6
Α	29.5	_		4.0
В	13.5	25.3	6.8	167

Table II Mechanical Properties of the Copolymers



Figure 6 Weight loss vs. time for the degradation of copolymer B in phosphate buffer (pH = 6.9) at 70°C.

good elasticity compared to homo- and copolymers of L-lactide and glycolide. The PPG moieties show

considerable stability, whereas L-lactide and glycolide blocks degrade at faster rates. It is predicted that these copolymers may be applied in drug delivery systems in soft tissues.

REFERENCES

- 1. Frazza, E. J.; Schmitt, E. E. J Biomed Mater Res 1971, 1, 43.
- 2. Glick, A., U.S. Pat. 3,626,948 1971.
- Holland, S. J.; Tighe, B. J.; Gould, P. L. J Controlled Release 1986, 4, 155.
- Schmit, E. E.; Polistina, R. A., U.S. Pat. 3,297,033 1976.
- Kwong, A. K.; Chou, S.; Sun, A. M.; Sefton, M. V.; Goosen, M. F. A.; J. Controlled Release 1986, 4, 27.
- 6. Gilding, D. K.; Reed, A. M. Polymer 1979, 20, 1459.
- Keese, R.; Muller, R. K.; Toube, T. P. Fundamentals of Preparative Organic Chemistry, John Wiley & Sons, New York, 1982.
- 8. Kasperczyk, J. Polymer 1996, 37, 201.