

Modulating the Mechanical Properties of Poly(diols citrates) via the Incorporation of a Second Type of Crosslink Network

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ABSTRACT: Novel citric acid-based polyesters were synthesized by condensation of citric acid, 1,8-octanediol, and unsaturated monomers such as glycerol 1,3-diglycerolate diacrylate and bis(hydroxypropylfumarate). Under the synthesis conditions used, the crosslinked elastomeric network exhibited a wide range of mechanical properties. The mechanical properties of acrylated elastomers ranged from 7.4 to 75.9 MPa for Young's modulus, 2.8 to 15.7 MPa for ultimate tensile stress, and 86 to 133% for elongation at break. The mechanical properties of fumarate-containing elastomers ranged from 16.4 to 38.3 MPa for Young's modu-

lus, 5.5 to 10.2 MPa for ultimate tensile stress, and 218 to 260% for elongation at break, which depended on the content of 1-vinyl-2-pyrrolidinone. Addition of a secondary crosslink network is a viable method to increase the range of mechanical properties of citric acid-based biodegradable elastomers. The glass transition temperature (T_g) of the elastomers is between -12.7 and -1.6°C , confirming that all the elastomers are in a rubbery state at room temperature. © 2009 Wiley Periodicals, Inc. *J Appl Polym Sci* 114: 1464–1470, 2009

Key words: citric acid; biodegradable polyester; elastomer

INTRODUCTION

Aliphatic polyesters are of interest for medical and pharmaceutical applications because of their biocompatibility and biodegradation properties. Some of the most common aliphatic polyesters include poly(lactic acid), poly(glycolic acid), poly(ϵ -caprolactone), and copolymers thereof.^{1,2} Despite their utility in traditional medical devices such as sutures, pins, and screws, there is a need to develop biodegradable elastomeric polyesters to engineer the next generation of scaffolds that will be used to build soft tissues such as blood vessels, heart valves, cartilage, tendon, and bladder, all of which exhibit viscoelastic properties.³ There are two classes of elastomers, thermoplastic and thermoset elastomers. The semicrystalline properties of thermoplastic elastomers often lead to heterogeneous bulk degradation characteristics, and a nonlinear loss of mechanical properties during the degradation process.⁴ In contrast, thermoset elastomers can undergo a more linear loss of mechanical properties during degradation in aqueous media, a process that is desirable for tissue engineering

scaffolds. Several polyester-based biodegradable thermoset elastomers have been reported, which include poly(glycerol sebacate),^{5,6} polyesteramide,⁷ star-poly(ϵ -caprolactone-co-D,L-lactide),⁸ poly(trimethylene carbonate-co- ϵ -caprolactone),⁹ and crosslinked poly(ester-ether).¹⁰ Most of them require costly building blocks, catalyst, or harsh processing conditions that can translate into higher manufacturing costs and hinder the commercial and clinical implementation of their use in tissue engineering.

We have previously reported the synthesis and characterization of citric acid-based biodegradable and biocompatible elastomers, poly(diols citrates).^{11,12} These novel polyester elastomers were synthesized by the condensation of citric acid with one or several diols under mild conditions without a catalyst, a significant advantage over the existing elastomers. The mechanical properties and degradation rates of the elastomers can be modulated with the choice of diols, as well as by postpolymerization conditions used to create the polyester crosslink network.¹¹ However, the mechanical properties that can be obtained may not meet the demanding requirements of musculoskeletal tissues such as ligament or cartilage, which are often exposed to relatively large tensile or compressive loading forces. Furthermore, polycondensation-based elastomers cannot be rapidly "fixed" or set into shapes, a limitation that can negatively affect the ability of these materials to be processed into complex devices. Here, we describe a method to increase the

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range of mechanical properties via the incorporation of a second type of crosslink into the polyester network (Fig. 1). Acrylate or fumarate moieties were incorporated in order to provide a secondary crosslinkable network derived from free-radical polymerization. Radical polymerization also allows for the rapid curing or fixation of the elastomer if necessary. The mechanical, thermal, and degradation properties of the elastomers are evaluated.

EXPERIMENTAL

Preparation of the liquid prepolymer

All the chemicals were purchased from Sigma-Aldrich (St Louis, MO). The acrylated prepolymers were synthesized by condensation of citric acid, 1,8-

octanediol, and glycerol 1,3-diglycerolate diacrylate with the molar ratio of 100 : 95 : 5 (A5), 100 : 90 : 10 (A10), and 100 : 85 : 15 (A15), respectively. Typically, citric acid (100 mmol, 19.12 g) and 1,8-octanediol (90 mmol, 13.41 g) were added to a 100-mL round-bottomed flask. The mixture was melted by vigorous stirring at 160–165°C, followed by addition of glycerol 1,3-diglycerolate diacrylate (10 mmol, 3.48 g). The mixture was polymerized at 130°C for 40 min in nitrogen atmosphere to get the prepolymer (A10).

Bis(hydroxypropylfumarate) was synthesized according to Wang et al.¹³ and was purified by precipitation in mixtures of hexane and ethyl acetate (4 : 1, v/v). The fumarate-containing prepolymer [the molar ratio of citric acid, 1,8-octanediol, and bis(hydroxypropylfumarate) was 100 : 75 : 25] was

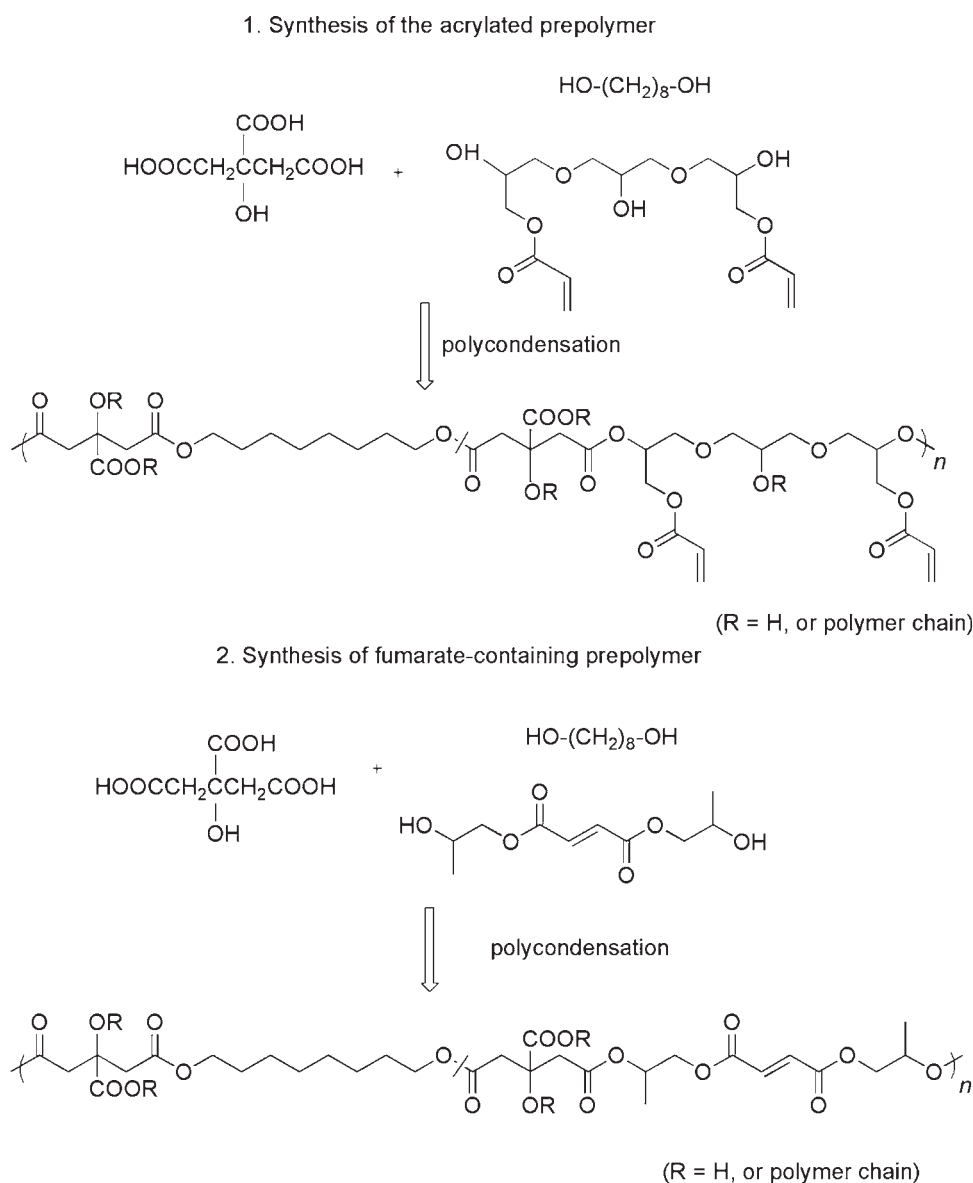


Figure 1 Scheme for the synthesis of the citric acid-based unsaturated prepolymers: (A) acrylated prepolymer; (B) fumarate-containing prepolymer. In this figure, R=H or polymer chain.

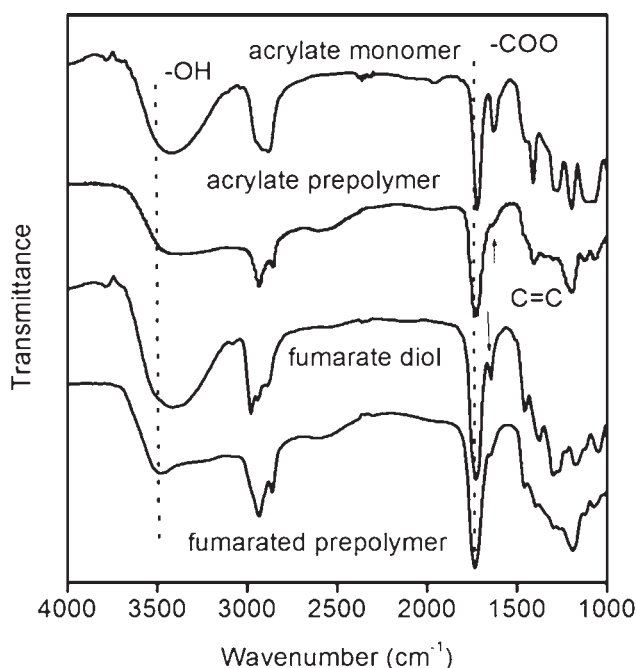


Figure 2 FTIR spectra of unsaturated monomers and prepolymers. In this figure, R = H or polymer chain.

prepared using a similar procedure to that of the acrylated prepolymer.

Poly(1,8-octanediol citrate) (POC) prepolymer (the molar ratio of citric acid and 1,8-octanediol = 1 : 1) was prepared according to methods previously described.⁹ All the prepolymers were purified via precipitation in water, followed by freeze-drying for 1 week prior to characterization.

Preparation of the elastomers

For the acrylated prepolymers, 1 wt % of benzoyl peroxide was first dissolved in tetrahydrofuran, and then mixed with the prepolymer in acetone. The mixture was casted onto a glass plate and put in the fume hood for 1 h to evaporate most of the solvent in open air. The mixture was then placed in the oven at 80°C for 12 h and further crosslinked at 120°C for 24 h, followed by 120°C for another 24 h under vacuum (2 Pa) to obtain the polyester network. For fumarate-containing prepolymers, 2.5, 5, 10 wt % of 1-vinyl-2-pyrrolidinone were mixed with 1 wt % benzoyl peroxide and prepolymer, respectively. The crosslinking conditions were the same as those used for the acrylated prepolymers. The crosslinked film was referred to as F2.5, F5, and F10 according to the content of 1-vinyl-2-pyrrolidinone. POC elastomer was prepared using a similar procedure without addition of catalyst.

Characterization

Fourier transform infrared (FTIR) spectra were obtained at room temperature using a FTS40 Fourier

transform infrared spectrometer (BioRad, Hercules, CA). ¹H-NMR spectra were recorded in dimethylsulfoxide-*d*₆ using a GERMIN 300 NMR spectrometer. The number and weight-average molecular weights (M_n and M_w) of the prepolymer were determined by gel permeation chromatography on a JASCO Gulliver system (PU-980, CO-965, RI-930, and UV-1570) equipped with polystyrene gel columns (Shodex columns K804, K805, and J806) using THF as an eluent at a flow rate of 1.0 mL/min, calibrated by polystyrene standards at 40°C. Elastomer density was measured by a Mettler Toledo balance with a density determination kit (Greifensee, Switzerland). Absolute ethanol was used as auxiliary liquid.

Tensile mechanical tests were conducted according to ASTM D 412a on an Instron 5544 mechanical tester equipped with a 500-N load cell (Instron, Canton, MA). Briefly, the dog-bone shaped sample (26 × 4 × 1.5 mm, length × width × thickness, prepared with a steel mold cutter) was pulled at a rate of 500 mm/min. Values were converted to stress-strain and a Young's modulus was calculated from the initial slope. At least 4 to 6 samples were measured and averaged. The density and Young's modulus of the samples were used to calculate the crosslink density and relative molecular mass between crosslinks (M_c).⁵

Thermal properties of the elastomers were characterized by using differential scanning calorimetry (DSC; Pyris 1; Perkin Elmer1, Waltham, MA). Samples were first scanned up to 150°C at a heating rate of 10°C/min under nitrogen purge (40 mL/min), and then cooled at a rate of -40 to -10°C/min. A second scan was performed and recorded up to 200°C. The glass transition temperature (T_g) was determined as the middle of the recorded step change in heat capacity from the second heating run. Thermogravimetric analysis (TGA) of the samples was conducted in nitrogen with a Perkin-Elmer TGA-2 thermogravimetric analyzer and the experiments were carried out with 5 mg samples at a heating rate of 10°C/min.

In vitro degradation of the elastomers (disk-shaped films, 6 mm in diameter, 1 mm thickness) was conducted in phosphate-buffered saline (PBS). The films were placed in a tube containing 10 mL PBS (pH 7.4) and incubated at 37°C for 1 or 2 months. After incubation, samples were washed with water and freeze-dried for 1 week. Mass loss was calculated by comparing the initial mass with the mass measured at a given time point. Five individual experiments were performed for the degradation test.

RESULTS AND DISCUSSION

Prepolymer characterization

Figure 1 illustrates the syntheses of citric acid-based unsaturated prepolymers by polycondensation of citric acid, 1,8-octanediol, and acrylated triol or

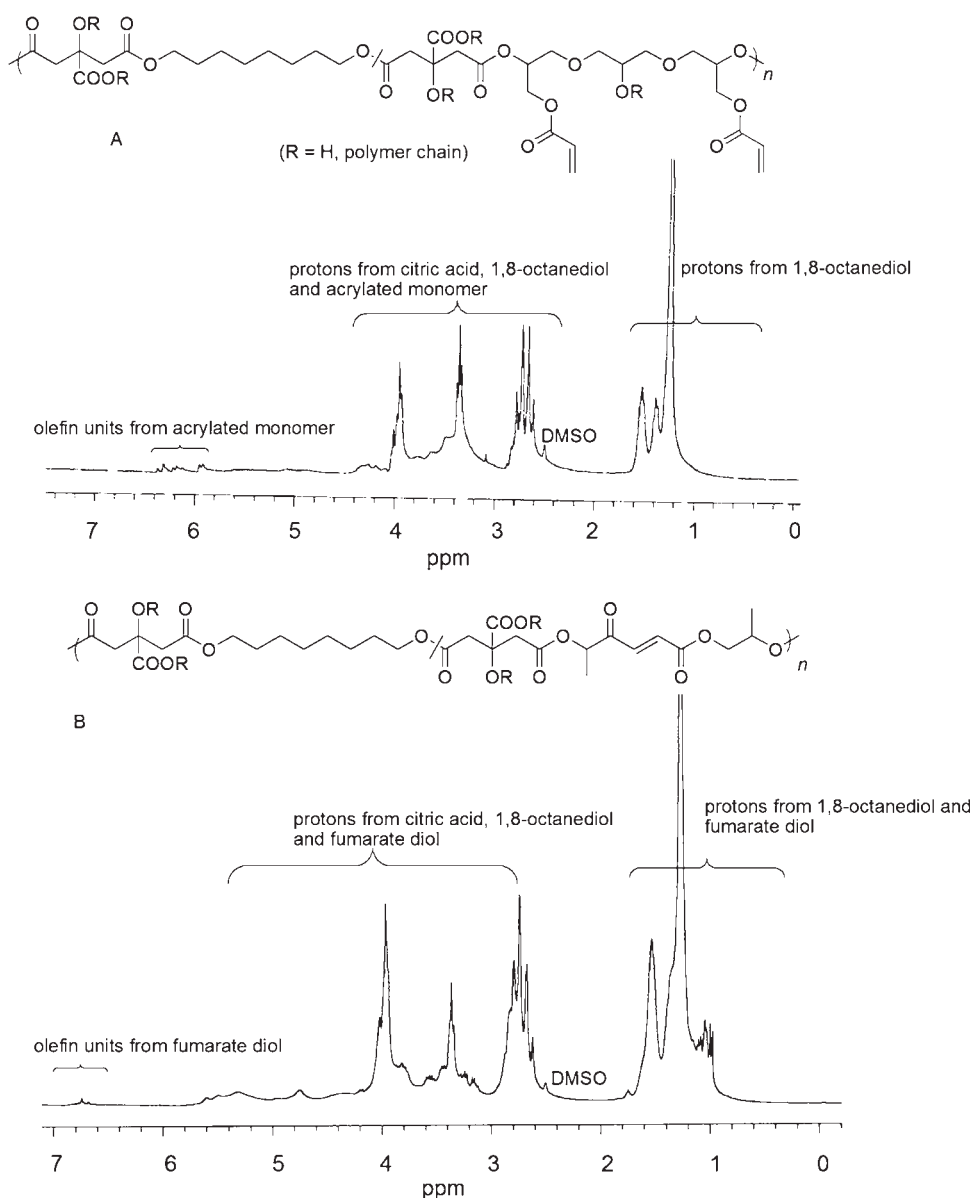


Figure 3 $^1\text{H-NMR}$ spectra of prepolymer of (A) acrylated prepolymers and (B) fumarate-containing polymers.

fumarate diols. All the prepolymers are liquid. The M_n and M_w/M_n of acrylated prepolymer (A10) are 1700 and 2.08, respectively. The molecular weight of fumarate-containing prepolymer is bimodal with $M_n = 3800$ (77.4%, $M_w/M_n = 1.27$) and 600 (22.6%, $M_w/M_n = 1.06$), possibly due to the different reactivity of 1,8-octanediol and fumarate diol (primary vs. secondary hydroxyl groups). The potential of having two different polyester prepolymers is not of significant consequence because upon subsequent polymerization via radical polymerization or polycondensation a crosslinked network with controllable mechanical and degradation properties is formed.

The incorporation of unsaturated monomers into the prepolymers was confirmed by FTIR and $^1\text{H-NMR}$ (Figs. 2 and 3). The peaks at around 3450

cm^{-1} are attributed to hydroxyl groups and the peaks at 1730 cm^{-1} are esters groups. The bands at around 1635 cm^{-1} are due to the $\text{C}=\text{C}$ stretching absorption. The chemical shifts with the peak position at about 5.9, 6.1, and 6.4 ppm are attributed to the protons from acrylate groups [Fig. 3(A)]. The chemical shift at ~ 6.8 ppm is assigned olefinic protons from fumarate [Fig. 3(B)].

Mechanical properties of the elastomers

Biodegradable poly(diols citrate) elastomers had been previously synthesized by reacting carboxyl and hydroxyl groups to form a crosslinked network.^{11,12} The citric acid provides three carboxylic acids to enable the polyester crosslinks. In this study, poly(diols citrate) elastomers were prepared from the

TABLE I
Properties of the Elastomers^a

Samples	Density (g/cm ³)	Tensile stress (MPa)	Young's modulus (MPa)	Elongation (%)	Relative molecular mass between crosslinks (g/mol)	Crosslink density (mol/m ³)
POC	1.22	1.8 ± 0.2	5.3 ± 1.4	164.4 ± 13.0	1711 ± 354	713 ± 122
A5	1.23	2.8 ± 0.1	7.4 ± 0.7	86.1 ± 2.1	1232 ± 92	998 ± 69
A10	1.24	11.8 ± 0.6	24.8 ± 3.9	133.1 ± 7.4	372 ± 61	3333 ± 469
A15	1.25	15.7 ± 2.4	75.9 ± 12.3	100.6 ± 9.2	122 ± 17	10,245 ± 546
F2.5	1.24	5.5 ± 0.6	16.4 ± 1.8	217.7 ± 14.0	576 ± 70	2152 ± 232
F5	1.24	7.9 ± 0.8	24.0 ± 1.9	248.2 ± 9.9	384 ± 27	3229 ± 212
F10	1.25	10.2 ± 1.0	38.3 ± 2.9	260.0 ± 16.0	242 ± 17	5165 ± 339

^a The elastomers were synthesized at 80°C for 12 h, followed by 120°C for 1 day and 120°C under vacuum for the second day.

reaction of the prepolymer bearing crosslinkable —COOH/—OH and olefinic units polymerizable by free-radical polymerization. Inclusion of the second type of crosslinked network was expected to result in improved mechanical performance. Typically, for a fixed monomer molar ratio of diol to carboxyl group, there is a limit to the crosslink density and hence the mechanical properties that can be achieved for the resulting elastomer. For example, for a highly crosslinked poly(1,8-octanediol citrate), the lowest molecular weight between crosslinks is within the range of 1457 g/mol. The corresponding Young's modulus, ultimate tensile stress, and the elongation at break are 5.8 MPa, 6.4 MPa, and 164%, respectively.¹² By incorporating the secondary aliphatic crosslinks within the polyester network, the molecular weight between crosslinks can be reduced to 242 g/mol and the Young's modulus, ultimate tensile stress, and elongation at break increased to 38 MPa, 10 MPa, and 260%, respectively (Table I). Hence, significant design flexibility in the range of mechanical properties is achieved without significantly compromising the degradability of the elastomer, an important criterion for biomedical applications.

Approaches to adjust the mechanical properties of elastomers include varying the type and content of the chemical crosslinker, varying the crosslinking temperature, and varying the crosslinking time. In this study, the influence of the contents of acrylated monomer on the mechanical properties of poly(diols citrate) elastomers and the influence of the content of 1-vinyl-2-pyrrolidinone crosslinker on the mechanical properties fumarate-containing poly(diols citrate) elastomers were investigated.

Table I summarizes the density and mechanical properties of elastomers at specific crosslinking conditions. The density of the elastomers from unsaturated prepolymers was slightly increased compared to that of POC. The acrylated POC networks had a Young's modulus that ranged from 7.4 to 75.9 MPa, an ultimate tensile stress that ranged from 2.8 to 15.7 MPa, and elongation at break between 86 and 133% strain

under the synthesis conditions depending on degree of acrylated monomer. The Young's modulus of fumarate-containing elastomers ranged from 16.4 to 38.3 MPa, the ultimate tensile stress ranged from 5.5 to 10.2 MPa, and the elongation ranged from 218 to 260% strain under the synthetic conditions depending on the content of 1-vinyl-2-pyrrolidinone. POC synthesized with the same crosslink conditions had a Young's modulus of 5.30 MPa, ultimate tensile stress of 1.8 MPa, and elongation at break of 164%. The crosslink density and relative molecular mass between crosslink (M_c) were calculated using the density and Young's modulus of the elastomers.³ By increasing the content of acrylated monomer or the content of 1-vinyl-2-pyrrolidinone of fumarate-containing prepolymer, the crosslink density increased and the relative molecular mass between crosslink decreased as expected. The high crosslink density of the elastomeric polyester network leads to significantly increased tensile strength and Young's modulus. The mechanical properties of the polyesters can be controlled by varying the content of acrylated monomer or the content of crosslinker in fumarate-containing elastomers. The mechanical properties of elastomers can also be tuned by addition of chemical crosslinker to the acrylated prepolymers during the crosslinking or changing fumarate diol content for fumarate-containing elastomers. Representative stress-strain curves of elastomers are shown in Figure 4. Although it is possible to increase the mechanical properties of POC by increasing the extent of reaction (i.e., crosslink density), addition of aliphatic crosslinks via radical polymerization allows for the rapid curing or fixation of the prepolymer into a desired shape. Also, photopolymerization can potentially be used to spatially control or vary the crosslink density if necessary. No permanent or plastic deformation of the elastomers occurred after break during the tensile tests.

Thermal analysis of the elastomers

Thermo properties of the elastomers were characterized by DSC and TGA. The DSC curves show an

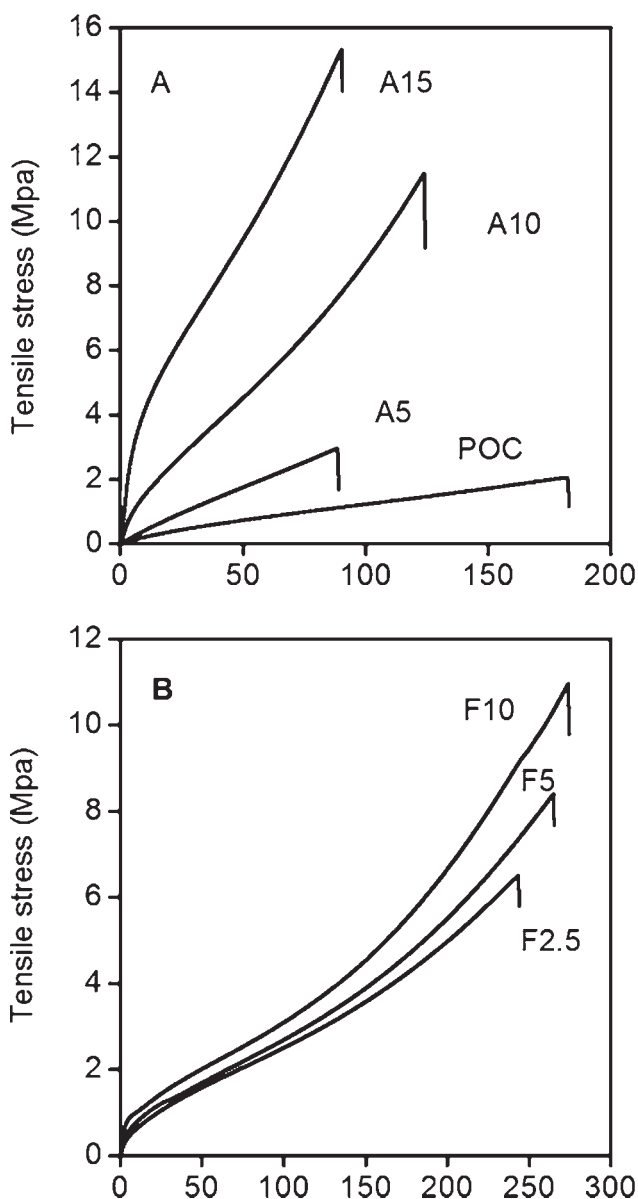


Figure 4 Stress-strain curves of elastomers from POC: (A) acrylated prepolymers; (B) fumarate-containing prepolymers.

apparent glass transition (T_g) for each elastomer (Fig. 5). The T_g values of elastomers from acrylated prepolymer are -12.7°C (A5), -12.3°C (A10), and -2.8°C (A15), respectively. The influence of T_g on the elastomers depends on many factors such as composition, the content of unsaturated groups, and crosslink density. The T_g of A15 is much higher than that of A5 and A10, possibly because of the higher crosslink density. The T_g values of the elastomers from fumarate-containing prepolymers with various contents of 1-vinyl-2-pyrrolidinone are -4.4 , -1.6 , and -4.1°C . No melting or crystallization peaks were observed. These results confirmed that all the monomers were fully reacted and copolymers are amorphous and in a rubbery state at 37°C . TGA curves showed

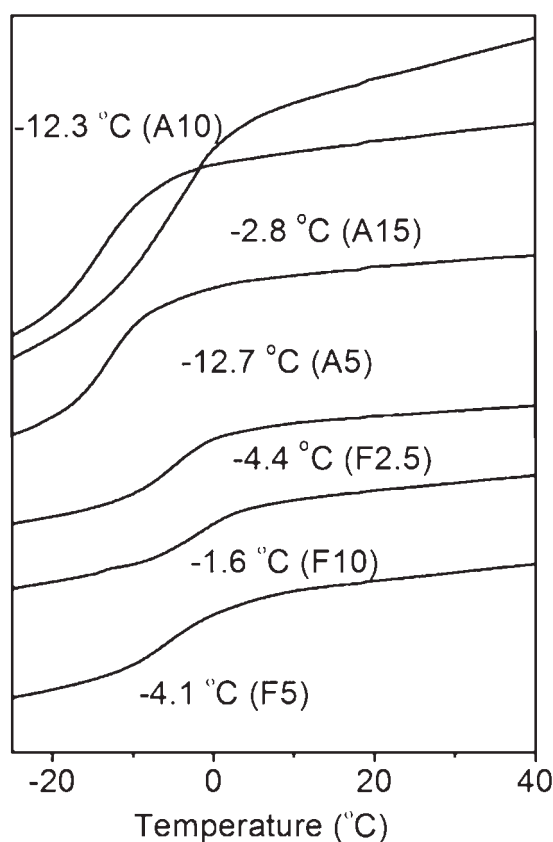


Figure 5 DSC thermograms of elastomers prepared from acrylated prepolymer and fumarate-containing prepolymer.

that all the elastomers are thermally stable below 220°C , and the elastomers were quickly decomposed when temperature is above 300°C (Fig. 6).

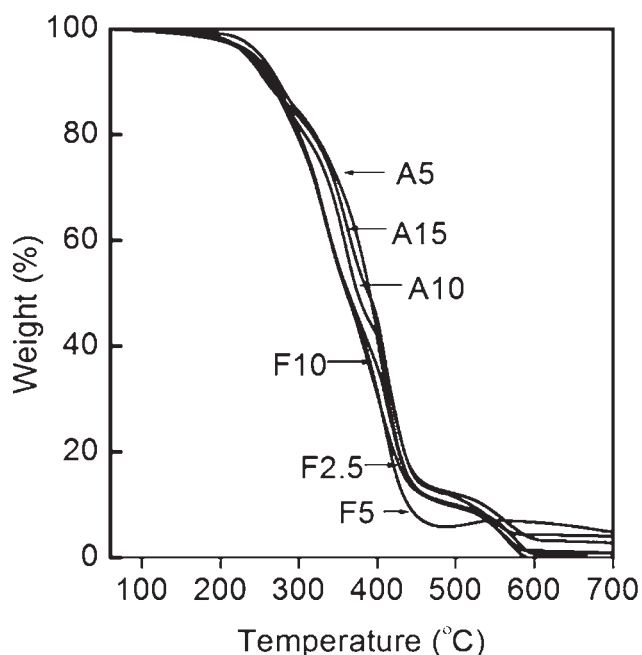


Figure 6 TGA curves of the elastomers.

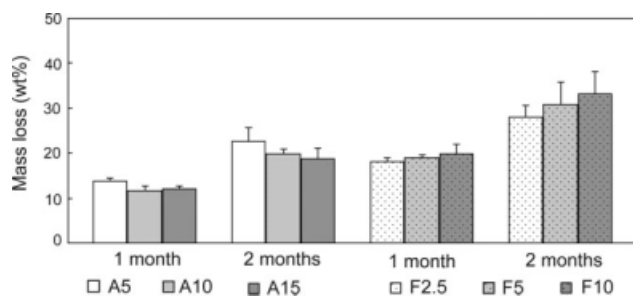


Figure 7 Mass loss of the elastomers after incubation in PBS at 37°C for 1 or 2 months.

In vitro degradation studies

The degradation properties of the elastomers were evaluated in PBS. The elastomers prepared from acrylated prepolymer degraded by 11–14% after 1 month and about 20% after 2 months. The elastomers prepared from fumarate-containing prepolymer degraded by 18–20% after 1 month and about 30% after 2 months (Fig. 7). The degradation rate of fumarate-based elastomers was faster than that of acrylated elastomer. Even though the aliphatic crosslinks created during the radical polymerization are not readily degradable, the ester bonds that connect the aliphatic crosslinks to the rest of the polyester network are hydrolyzable. The olefin groups are also a small percentage relative to the degradable polyester bonds.

CONCLUSIONS

Biodegradable citric acid-based elastomeric polyesters containing additional crosslinked networks were prepared via thermal polymerization. The mechanical properties of the elastomers can be easily controlled by altering the content of acrylate and the

content of crosslinker for the fumarate-containing polymer. These novel citric acid-based elastomeric polyesters are expected to have applications as coating, films, or a variety of biomedical devices used for drug delivery and tissue engineering.

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