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Synthesis of Poly(glycolide-caprolactone) Copolymers for Application as Bioabsorbable Suture Materials

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Abstract: A novel bioabsorbable suture, poly(glycolide caprolactone) (PGLCL) copolymer, was synthesized by second step polymerization. The effect of the reaction parameters on the inherent viscosity of the PGLCL prepolymer was examined. The chemical structure of the copolymer was characterized by ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectroscopy. The thermal properties of the copolymer were examined by differential scanning calorimetry and thermogravimetric analysis. Both the straight strength and knot strength of the PGLCL copolymer monofilament *in vivo* decreased significantly with increasing implant time. The organism resolvability tests confirmed that the PGLCL copolymer monofilament suture had been absorbed within 91 days with recovery from the inflammatory response. The biocompatibility tests indicated that all items had passed.

Keywords: poly(glycolide caprolactone), copolymer, suture materials, monofilament, bioabsorbable.

Introduction

Wounds are generally sutured with sutures, adhesive, tape, etc. Among them, sutures have been the most widely used method until recently. More than 2000 types of sutures with different materials, diameter, lengths, color, and needles are used. The suture can be absorptive or non-absorptive according to the absorption forms in an organism.[1-4]

Absorptive sutures can be divided into natural absorptive sutures, such as protein-composited catgut, which are extracted from the intestines of cows and sheep, and synthetic absorptive sutures, such as polyglycolic acid. When catgut is used as an absorptive suture, infection can occur and the diameter of the catgut is uneven, making it difficult to control the absorption rate properly. Synthetic absorptive sutures are more powerful and uniform than catgut, and absorption can be controlled easily. In 1970, linear polyglycolic acid was synthesized from one type of ingredient, and polyglycolide-lactide copolymer was prepared by the copolymerization of two ingredients.[5-8]

Outstanding sutures require the following characteristics: easily to make a knot, form a safety knot, excellent strength, no side effects during the treatment of wounds, and does not promote inflammation.

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In this study, poly(glycolide caprolactone) (PGLCL) copolymer, which has the advantage of polyglycolide and polycaprolactone, was synthesized by second step polymerization. The chemical structure of the copolymer was characterized by ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectroscopy. The straight strength and knot strength of the PGLCL copolymer monofilament were examined both in-vitro and *in vivo*. The organism resolvability of the PGLCL copolymer monofilament suture was measured after 2, 91, and 119 days. Biocompatibility tests of the suture were also carried out.

Experimental

Materials. The glycolide (GL) used in this study was purchased from Boehringer Ingelheim of Germany, and had a melting point and and molecular weight of 83-87 ºC and 116.06 g/mol, respectively. ε-Caprolactone (CL) was supplied by Union Carbide of Germany, and had a melting point and molecular weight of -1 ºC and 114.14 g/mol, respectively. 1,6-Hexanediol, diethylene glycol and lauryl alcohol were used as initiators. Stannous octanoate (Aldrich Chem.) was used as the catalyst.

First Step Polymerization. Glycolide (100 g, 0.862 mol) and ε-caprolactone (80.5 g, 0.706 mol) were added to a reactor. The initiator (0.416 g) and catalyst (3.34 mL) were then added. The solvent was removed at 60 ºC for 20 min

under reduced pressure. The mixtures were heated gradually to 200 °C and allowed to react for 5 h. Finally, the prepolymer was obtained after cooling.

Second Step Polymerization. Glycolide (100 g, 0.862 mol) and ε-caprolactone (80.5 g, 0.706 mol) were added to the reactor. Lauryl alcohol (0.416 g) and catalyst (3.34 mL) were then added to the reactor. The solvent was removed at 60 °C for 20 min under reduced pressure. The mixtures were heated gradually to 200 °C and allowed to react for 5 h. The mixtures were then re-heated to 220 °C, which was followed by the addition of glycolide (227.6 g, 1.962 mol). The mixture was reacted at this temperature for 1 h. Finally, the copolymer was obtained after cooling.

Spinning of the Copolymer Filament. To distribute the pressure uniformly while spinning of copolymers, a nozzle pack composed of metal particles was used as a filter medium, and the spinning detention diameter was 1.8 mm. The temperature for the feeding, melting, and mixing parts of the barrel zone was 215-220, 220-225, and 225-230 °C, respectively. The temperature of the die head was 230-240 °C. The thread was prepared according to USP 2-0, and the diameter was 0.350-0.399 mm.

Characterization and Measurements. The specimens were dissolved in hexafluoroisopropyl alcohol. The concentration was measured using an Ubbelohde viscosimeter (Schott, 1C type) at 30 °C. The inherent viscosity (IV, $[\eta]$) was calculated using the Solomon-Ciuta equation.[9,10]

$$[\eta] = \frac{1}{c}[2(\eta_{sp} - \ln \eta_r)]^{\frac{1}{2}} \quad (1)$$

where η_{sp} is the specific viscosity, η_r is the relative viscosity and c is the concentration of the polymer solution.

The melting temperature (T_m) of the samples was measured by differential scanning calorimetry (DSC, Universal, V2.5H TA) at a heating rate of 10 °C/min from -50 to 250 °C under a nitrogen atmosphere. The thermal stability of the samples was examined using a du Pont TGA-2950 analyzer at a heating rate of 10 °C/min from 30 to 700 °C under a nitrogen atmosphere. The ^{1}H NMR and ^{13}C NMR spectra were taken on a BRUKER Co. DRX500 spectrometer operating at 500 MHz in $CDCl_3$ and hexafluoroisopropyl alcohol.

A buffer solution at pH 7.4 was prepared from a 0.5 M KH_2PO_4, 0.5 M K_2HPO_4, and salt solution. A pasteurized monofilament suture was added to a buffer solution-containing glass tube, which was then placed in a shaking water bath at 37±1 °C. The tensile strength after one, two, three and four weeks was measured.

The tensile strength of the PGLCL copolymer monofilament suture before and after implantation was measured using a universal tester (Instron Model 4014 mechanical tester) at a tensile rate of 200 mm/min. The tensile properties were obtained from the means of seven experiments.

The local effect of the tentative material on organism organization after implantation was evaluated by measuring the inflammation, encapsulation, hemorrhage, necrosis and discoloration.

The biocompatibility tests were performed by the North American Science Associates (NAMSA) of USA, which involved measuring the cytotoxicity, sensitization, intracutaneous, systemic toxicity, genotoxicity, implantation and pyrogen.

Results and Discussion

Synthesis of Poly(glycolide caprolactone) Copolymer. Figure 1 shows the synthesis route of the poly(glycolide caprolactone) (PGLCL) copolymer. The PGLCL prepolymer was synthesized by first step polymerization, and the copolymer was prepared by a reaction of glycolide with the prepolymer in the second step polymerization. The type of reactions in the first step could be divided into three types: a reaction of glycolide and glycolide (labeled as GLGL); a reaction of glycolide and ε-caprolactone (labeled as GLCL); and a reaction of ε-caprolactone and ε-caprolactone (labeled as CLCL).

Figure 2 shows the inherent viscosity (IV) of the PGLCL prepolymer as a function of the reaction time and temperature. From Figure 2(a), IV increased with increasing reaction time up to 2-3 h. After 3 h, IV was either constant or decreased. At various reaction temperatures, the prepolymer exhibited a maximum value at 200 °C after the same reaction time. The IV at 190 °C was similar to that at 200 °C when the reaction time was < 3 h. On the other hand, a difference in IV was observed at longer times. These results show that the glycolide first participates in the reaction, which is followed by the participation of ε-caprolactone. As shown in Figure 2(b), IV increased with increasing reaction time up to 2 h, and then decreased at longer times. This was attributed to an increase in the decomposition reaction of glycolide after 2 h, followed by a decrease in IV of the prepolymer.[9]

To determine the catalyst content, the reaction temperature and initiator content were fixed at 200 °C and 1,200 ppm, respectively, and the catalyst content was varied from 25 to

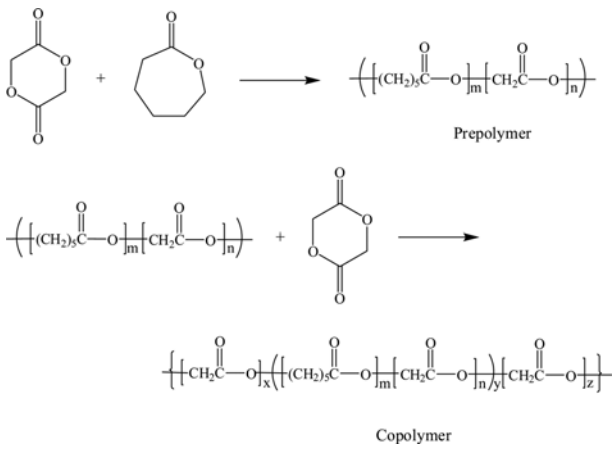

Figure 1. Schematic outline for the synthesis of PGLCL copolymer.

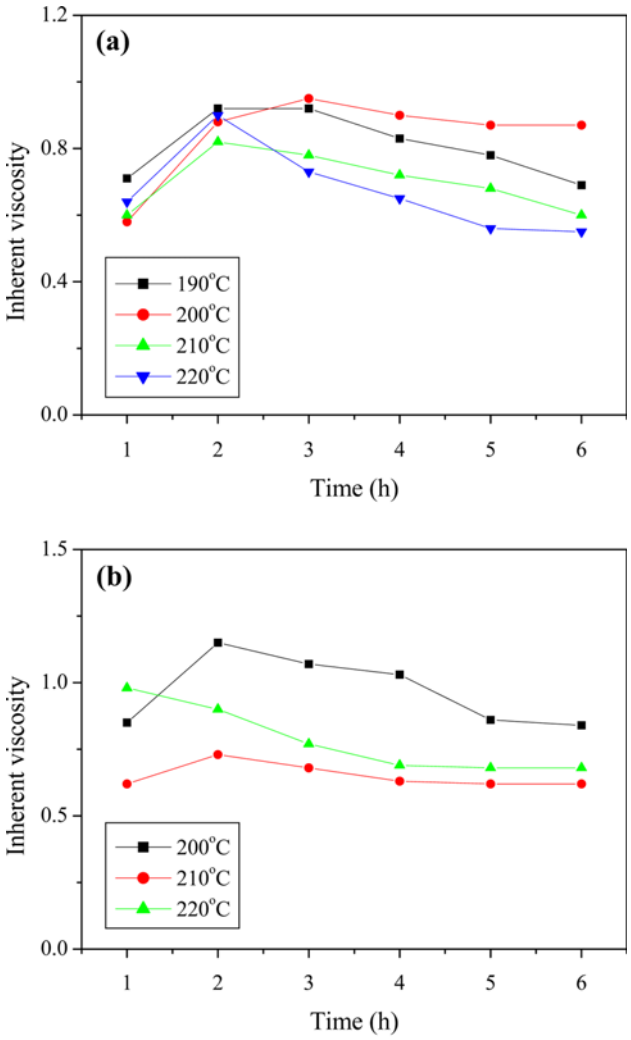

Figure 2. IV of PGLCL prepolymer with GL/CL molar ratio of 60/40 (a) and 70/30 (b) as functions of reaction time and temperature.

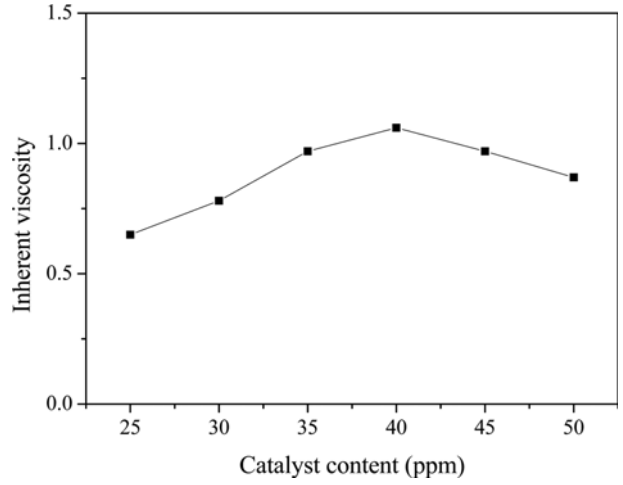

Figure 3. IV of PGLCL prepolymer as a function of catalyst content.

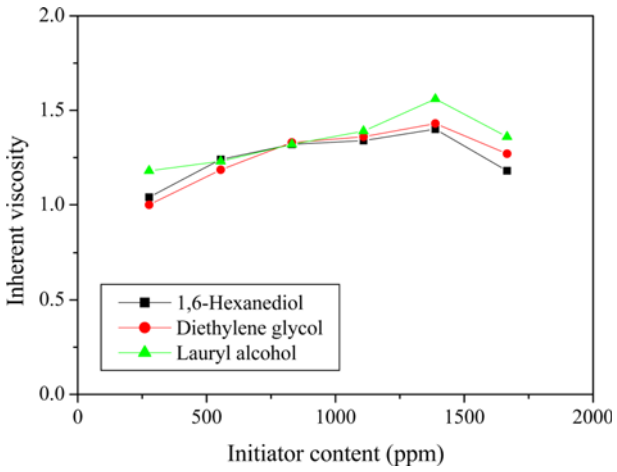

Figure 4. IV of PGLCL prepolymer as a function of initiator content.

50 ppm. Figure 3 shows the IV of the prepolymer as a function of the catalyst content. The IV increased with increasing catalyst content up to 40 ppm, but decreased with further increases in concentration.[11]

In this study, 1,6-hexanediol, diethylene glycol and lauryl alcohol were used as initiators. Figure 4 shows the IV of the prepolymer as a function of the initiator content. The IV increased with increasing initiator content, exhibiting a maximum at 1,388 ppm. The order of IV at 1,388 ppm was lauryl alcohol > diethylene glycol > 1,6-hexanediol.

The effect of the reaction time on the IV of the prepolymer was examined using lauryl alcohol (1,388 ppm) as the initiator and a catalyst content of 40 ppm. Figure 5 shows the IV of the prepolymer as a function of the reaction time. As a result, IV increased significantly with increasing reaction time up to 5 h, but decreased gradually above this time.[12]

At the first step polymerization, the prepolymer with a GL content >70% was too hard. The prepolymer with a CL content >80% became too soft and transparent. Therefore, the soft

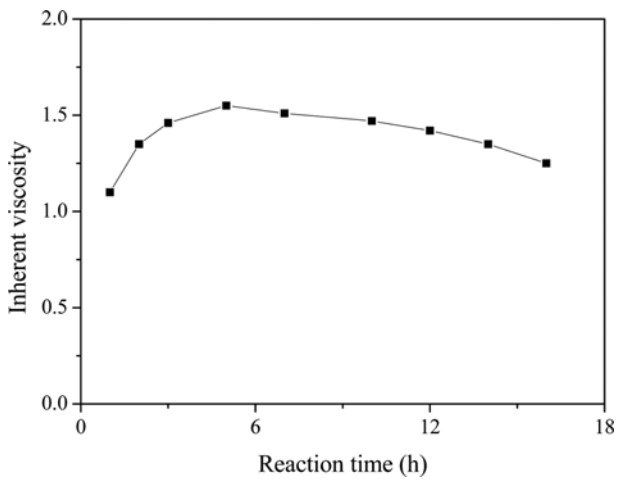

Figure 5. IV of PGLCL prepolymer as a function of reaction time.

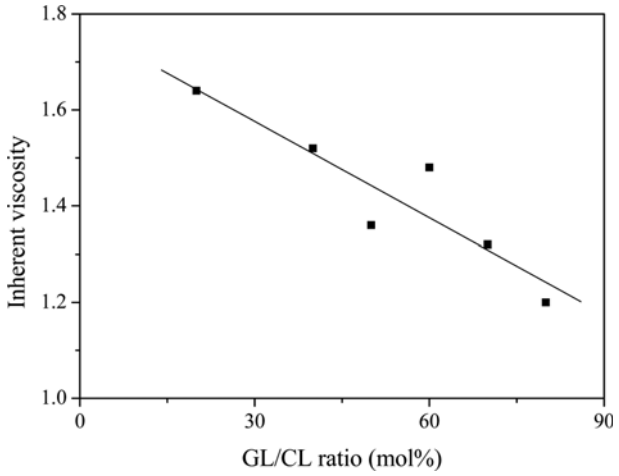

Figure 6. IV of PGLCL prepolymer as a function of GL/CL molar ratio.

Table I. Results of Second Step Polymerization Different with GL/CL Molar Ratio

Mole Ratio of GL/CL	IV at First Step	IV at Second Step	T_m (°C)
80/20	1.86	2.04	206.5
78/22	1.70	1.93	203.4
75/25	1.74	1.99	203.0
60/40	1.55	1.61	119.0/164.9

degree with a GL content of 55%~60% was considered suitable as a suture material. Figure 6 shows the IV of the prepolymer as a function of the GL/CL molar ratio. The IV decreased with increasing GL content, which was attributed to the highly reactive GL decomposing at high reaction temperatures over long reaction times.

When the GL content was >80% at the second step polymerization, the resulting thread became too hard, making it unsuitable as a monofilament material. On the other hand, the thread exhibited low rigidity and broke easily when the GL content was <60%, also making it unsuitable as a monofilament material. Therefore, a GL content in the resulting thread ranging from 75% to 80% was considered suitable as a monofilament material. Table I lists the results of second step polymerization with different GL/CL molar ratios. The IV and T_m of the second step increased with increasing IV of the first step. Therefore, to obtain copolymers with a high IV, first step polymerization must be carried out under conditions that result in prepolymers with a high IV.

Characterization of the Copolymer. The chemical structure of the PGLCL copolymer was characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. Figure 7(a) shows the ^{1}H NMR spectrum of the copolymer. The chemical shift at 2.51 ppm (number 1) was assigned to the protons of GLCL, which results from a reaction of GL and CL. The chemical shifts for methylene in GLCL (number 2 and 4) overlapped and exhibited a multi peak at 1.71 ppm. The peak at 1.43 ppm (number 3) was assigned to the methylene peak of GLCL. The chemical shifts of GLGL (number 6) appeared at 4.79 and 4.76 ppm.[13,14]

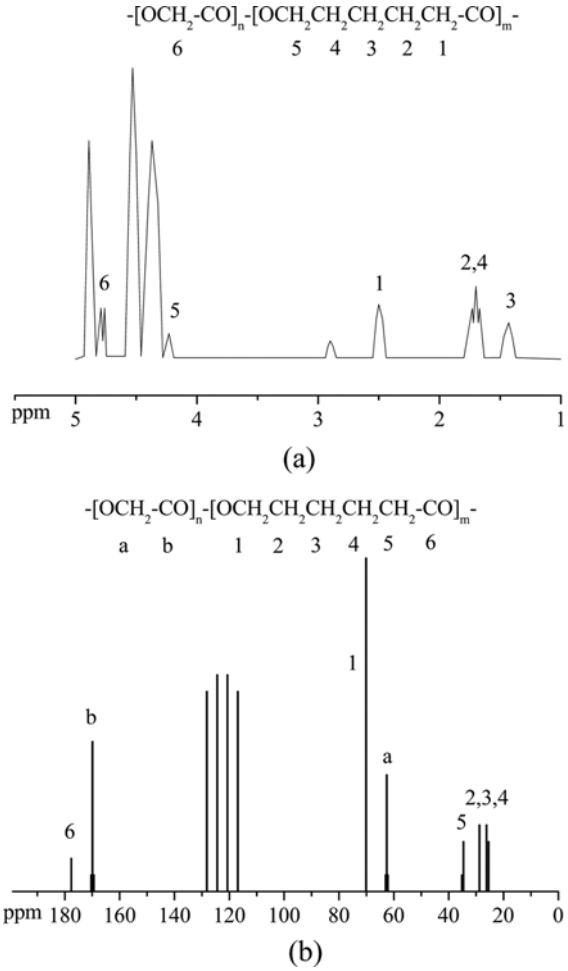

Figure 7. ^{1}H NMR (a) and ^{13}C NMR (b) spectra of PGLCL copolymer.

Figure 7(b) shows the ^{13}C NMR spectra of the copolymer. The chemical shifts, a and b at 62.6 and 169.9 ppm, respectively, were assigned to methylene and carbonyl groups in GL, respectively. These peaks also showed a variety of random peaks due to the different environments. The chemical shifts of CL were observed more down field than that of the carbonyl carbon in GL. This is because CL contains more methylene groups and the electrons are distributed uniformly in the carbonyl group. The chemical shifts at 35.2 and 34.6 ppm (number 5) were assigned to the methylene carbon atoms in CLCL and GLCL, respectively. The chemical shifts of the methylene carbon atoms for numbers 2, 4, and 3 appear at 28.8, 26.2, and 25.4 ppm, respectively.[13,14]

Figure 8(a) shows the DSC thermograms of the PGLCL copolymer as a function of the GL/CL ratio. The T_m of polyglycolide and polycaprolactone was 225 and 65 °C, respectively.

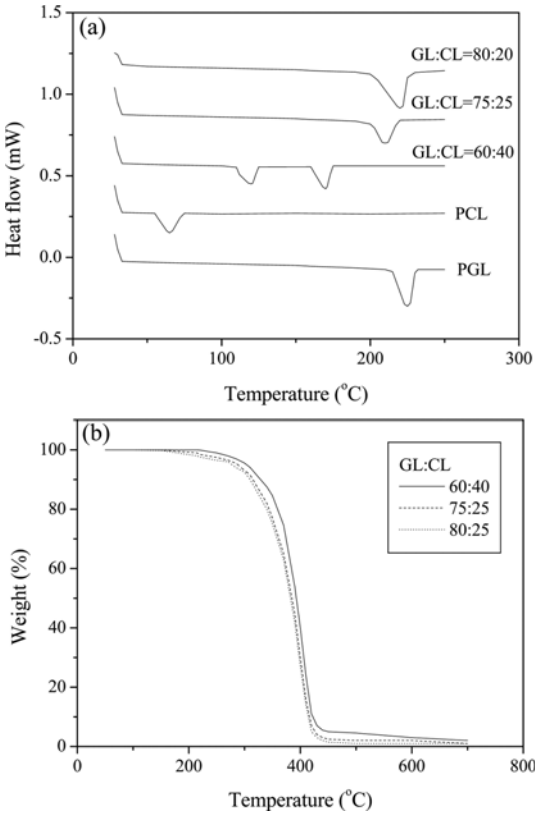

Figure 8. DSC (a) and TGA (b) thermograms of PGLCL copolymer as a function of GL/CL molar ratio.

The T_m of the coplymer decreased with increasing CL content. Specifically. the T_m of the copolymer with a GL/CL ratio of 75/25 and 80/20 was 210, and 220 °C, respectively.

Figure 8(b) shows the thermogravimetric analysis (TGA) thermograms of the PGLCL copolymer as a function of the GL/CL ratio. The initial decomposing temperature (IDT, the temperature of 5% weight loss) was determined from the TGA thermograms.[15,16] The IDT of the copolymer with a GL/CL molar ratio of 64:40, 75:25 and 80:20 was 305, 288 and 280 °C, respectively. This suggests that the thermal stability decreases with increasing GL content.

Application as Bioabsorbable Suture Materials. Figure 9 shows the *in vitro* straight strength rate and knot strength rate of the PGLCL copolymer monofilament as a function of the immersion time. The straight strength rate and knot strength rate decreased significantly with increasing immersion time. The straight strength after immersion for one, two, three, and four weeks was 62%, 20%, 6%, and 0%, respectively.[17]

Figure 10 shows the *in vivo* tensile strength of the PGLCL copolymer monofilament as a function of the implant time. The tensile strength was 74.1 N before implantation. After one, two, and three weeks implantation, the tensile strength was 47.1, 16.6, and 5.4 N, respectively. After four weeks, the absorption of the suture was completely advanced and the

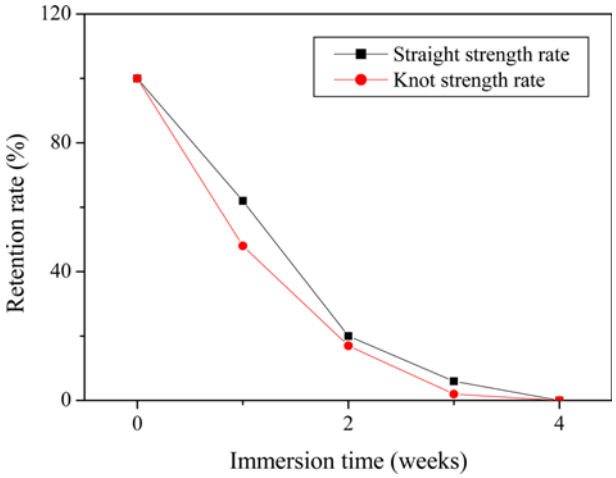

Figure 9. Strength retention rate of PGLCL copolymer monofilament under *in vitro*.

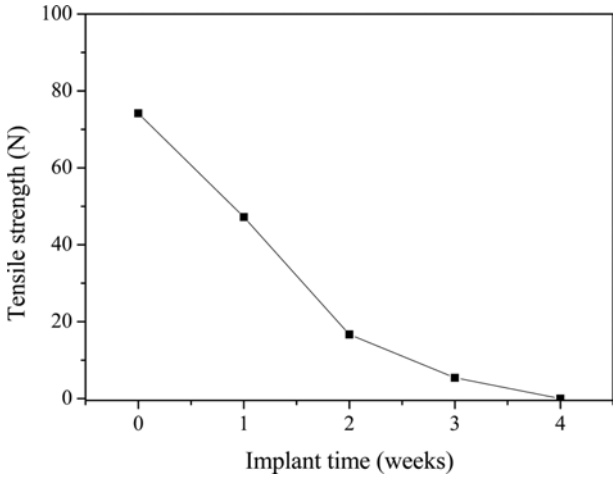

Figure 10. Tensile strength of PGLCL copolymer monofilament under *in vivo*.

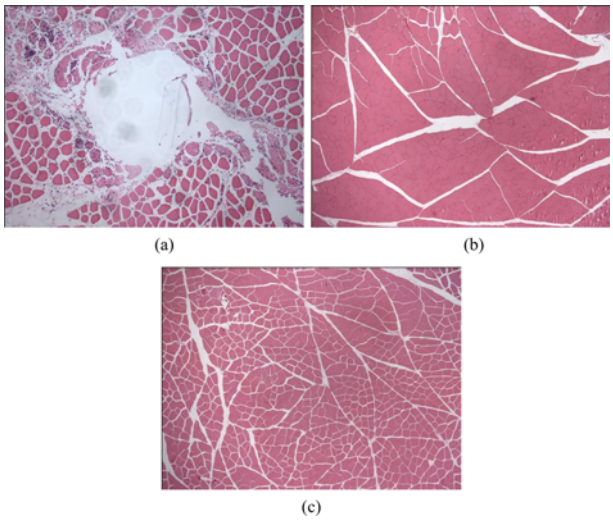

Figure 11. Optical micrographs after implantation: (a) after 2 days, ○ : test article (100×); (b) after 91 days (50×); (c) after 119 days (50×).

tensile strength was effectively zero.[18]

To examine the organism resolvability, a PGLCL copolymer monofilament suture was implanted in the internal muscle, and the internal absorbability was measured at 2, 91, and 119 days. Figure 11 shows optical microscopy images. An initial inflammatory response after implantation and muscle fiber necrosis were observed in some individuals at 2 days after implantation. Neverthless, these were no observed at 91 days. This suggests that the PGLCL copolymer monofilament suture had been absorbed within 91 days with recovery from the inflammatory response.[19]

The cytotoxicity, sensitization, intracutaneous, systemic toxicity, genotoxicity, implantation and pyrogen were assessed using biocompatibility tests; and all items passed.

Conclusions

A new PGLCL copolymer was synthesized for applications as a bioabsorbable suture material. The effect of the reaction parameters on the IV of the PGLCL prepolymer was examined. The chemical structure of the copolymer was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy. TGA indicated that the thermal stability of the copolymer decreased with increasing GL content. The straight strength and knot strength of the PGLCL copolymer monofilament under *in vitro* and *in vivo* conditions decreased significantly with increasing immersion time or implantation time. The organism resolvability tests showed that the PGLCL copolymer monofilament suture had been absorbed within 91 days with complete recovery from the inflammatory response. The biocompatibility tests indicated that all items had passed. The data reported in this paper suggests that the PGLCL copolymer is a promising candidate for bioabsorbable suture applications.

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