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Physical Properties and Biodegradation of Lactide-based Poly(ethylene glycol) Polymer Networks for Tissue Engineering

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Summary

New lactide-based poly(ethylene glycol) (PEG) polymer networks (GL-PEG) have been prepared by photopolymerization using two nontoxic macromers, triacrylated lactic acid oligomer emanating from a glycerol center (GL) and monoacrylated PEG. These materials may use as polymer scaffolds in tissue engineering because they provide biodegradable, cell-adhesion resistant, and ligand-immobilizable characteristics. The thermal and mechanical properties of the resulting GL-PEG networks were evaluated and their biodegradability was investigated in phosphate buffered saline (PBS) at 80℃. The glass transition temperature (Tg) of all networks after degradation relatively decreased and the trend was similar to those before biodegradation, whereas thermal decomposition temperature ($Td_{1/2}$) increased in all networks to a certain degree. The tensile strength decreased as PEG was incorporated and as the molecular weight and content of PEG increased due to the soft PEG chains. Degradation rate of GL-PEG networks was controlled by the ratio of GL to PEG, and generally the rate of GL-PEG networks was faster than that of GL homonetworks.

Introduction

Many biodegradable poly(α-hydroxy ester)s such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(D,L-lactic-co-glycolic acid) (PLGA) copolymers have been extensively studied as polymer scaffolds and barriers for tissue engineering applications [1]. These materials have also been used in drug delivery of bioactive molecules [1,2] and many surgical repair materials such as absorbable sutures [3], composite bone plates [4], and fracture pins [5]. PLA, PGA, and their copolymers are decomposed by biodegradation *in vitro* and *in vivo* [6] and lead to produce nontoxic degradation fragments. These polymers have relatively good biocompatibility and suitable biodegradability, but they lack the ability to interact biospecifically with cells [7]. To improve the cell adhesion, Langer and co-workers [8] have synthesized

functional PLA-lysine copolymer scaffolds with amino side groups from lactide and cyclic monomer. This biodegradable copolymer contained amino groups on the side chain of the lysyl residues and combined with ligand such as arginine-glycine-aspartic acid (RGD) [9] to induce cell adhesion. Hubbell group [10] prepared nondegradable and ligand-immobilizable semi-IPN using triacrylate and a poly(ethylene glycol) (PEG)-diacrylate copolymer. PEG in the network resisted protein adsorption and cell adhesion, but high cross-link density from the trimethylolpropyl triacrylate prevented swelling that would be induced by the high amount of hydrophilic PEG. Suitable biodegradation as well as biocompatibility and ligand-immobilization of polymer scaffolds are required. Because scaffold materials should be completely degraded *in vivo* within a desired period of time, transplanted cells should be well compatible with scaffold materials for tissue formation with the original function property.
In order to study biodegradation of various polymers, many investigations have been performed hydrolytic degradation study of polyester (PLA, PLGA) copolymers having hydrophilically segmented PEG. Sheth, *et al.* [11] prepared biodegradable polymer blend of PLA and PEG through melt-blending techniques to study the blend miscibility and its effect on the mechanical and thermal properties and hydrolytic degradation. Li and coworkers [12] preparaed poly-*dl*-lactide-PEG microspheres and reported their degradation properties. Hu and Liu [13] and Du, *et al.* [14] synthesized ABA type block copolymers of lactide and poly(ethylene oxide) (PEO) with various molar ratios. Li and Kissel [15] described novel type of star-block copolymers from multi-arm PEO and L-lactide or L-lactide/glycolide, and they were interested in the effects of the molecular architecture on the degradation properties of the polyesters.
We have prepared new biodegradable lactide-based PEG polymer network (GL-PEG) films which have biodegradable, biocompatible, and ligand-immobilizable properties by photocopolymerization. The networked polymers could be use as nonporous biodegradable polymer scaffold films in tissue engineering [16,17]. In this study, the thermal and mechanical properties as well as biodegradation of the resulting GL-PEG network films were examined and compared to GL ones without PEG.

Experimental

Materials

L-Lactide (L) was obtained from Aldrich and was recrystallized from ethyl acetate. α-Monoacrylate-ω -monohydroxy poly(ethylene glycol)s (PEG-Ac) with molecular weights of 1000 (PEG1K), 4000 (PEG4K), and 8000 (PEG8K) were purchased from Monomer-Polymer and Dajac Lab. and dried by azeotropic distillation with benzene. Acryloyl chloride (AcCl) was obtained from Aldrich and distilled before use. Glycerol (G, spectrophotometric grade, Aldrich), stannous octoate (St-oct, Sigma), triethylamine (TEA, Aldrich), and benzil dimethyl ketal (BDMK; 2,2-dimethoxy-2-phenyl-acetophenone, Aldrich) were used as received. All other chemicals were of reagent grade and used without further purification.

Synthesis of GL-PEG networks

The synthetic methods of GL triols, GL triacrylates, and GL-PEG polymer networks have been previously described in detail elsewhere [16,17]. Three types of glycerol-

lactide (GL) triols (GL3, GL9, and GL15) have been synthesized with controlling each molar ratio and then reacted the GL triols with acryloyl chloride to get GL triacrylates (GL-Ac). The photo-crosslinked network films having the GL-Ac and various PEG-Ac (molecular weights of 1,000, 4,000, 8,000, and contents of 10, 20, 30 wt%) were prepared by simple UV exposure. The synthesized networks were denoted as follows: GLm-PEGnK-p, where, m (3, 9, and 15) is the number of repeats of lactide or dimeric repeats of lactic acid, n (1, 4, and 8) is the molecular weight (K=1000) of PEG-Ac, and p (10, 20, and 30) is the weight percent of PEG-Ac per GL-Ac. In addition, GL homonetworks were prepared using only GL-Ac in the absence of PEG-Ac for control.

Thermal analysis

The thermal properties of GL and GL-PEG network films were examined by using differential scanning calorimeter (DSC, Perkin-Elmer model DSC 7) and thermogravimetric analysis (TGA, Du Pont TA 2000). DSC was performed with a heating rate of 10 ℃/min under constant nitrogen purge and an empty aluminum pan was used as reference. Samples were dried *in vacuo* prior to sealing in aluminum pan. The glass transition temperature (Tg) was determined as the middle of the recorded step change in heat capacity. The TGA measurement of the GL-PEG network films was expressed in terms of half thermal decomposition temperature ($Td_{1/2}$).

Mechanical testing

Mechanical property of GL and GL-PEG networks was measured using an Instron tensile testing machine with a 50-Kgf load cell at a crosshead speed of 5 mm/min.

Biodegradation

Biodegradation of the network films was analyzed in a phosphate buffered saline (PBS, pH 7.4) solution at 80 ℃ in a shaker bath at 100 rpm for various time periods up to 5 days. And then the biodegraded film surfaces were gold-deposited in vacuum and observed by scanning electron microscopy (SEM, Hitachi S-510). The biodegradability of network films was examined by measuring the weight change. The obtained GL and GL-PEG network films were dried under vacuum at 60℃ for 1 day, weighed (W_1), and then the samples taken out each 1, 3, 5 days and dried in vacuum oven at room temperature for 24 h. The dried samples were weighed (W_2) and the weight change was determined as follows:

$$\text{Weight change (\%)} = W_2 / W_1 \times 100.$$

Results and Discussion

The obtained nonporous network films were glassy and transparent irrespective of PEG incorporation. Table 1 summarizes the thermal properties of GL9 and GL9-PEG networks before and after biodegradation.

Table 1. Thermal properties of GL9 and GL9-PEG network films.

Material	Before degradation (℃)		After 1D degradation (℃)	
	Tg	$Td_{1/2}$	Tg	$Td_{1/2}$
GL9 network	67	289	49	323
GL9-PEG1K-20	49	285	44	306
GL9-PEG4K-10	48	283	43	308
GL9-PEG4K-20	44	286	41	306
GL9-PEG4K-30	40	290	38	293
GL9-PEG8K-20	40	286	37	304

There were no melting endotherms (Tm) in all networks because the GL and PEG macromers were completely polymerized to form the cross-linked networks. GL9-PEG had lower Tg than GL9 homonetwork did owing to the flexible PEG groups. As the molecular weight and content of PEG increase, Tg decreased by means of incorporation of soft PEG. However, no significant difference was observed in half thermal decomposition temperature ($Td_{1/2}$), regardless of the incorporation of PEG. The $Td_{1/2}$ is defined as the temperature at which the loss of weight of a polymer during thermal decomposition reaches 50% of its final value [18]. The TGA thermograms of some network films were shown in Fig. 1. At first, the lactide part was thermally degraded and then the PEG part followed. Among all networks, GL9-PEG4K-30

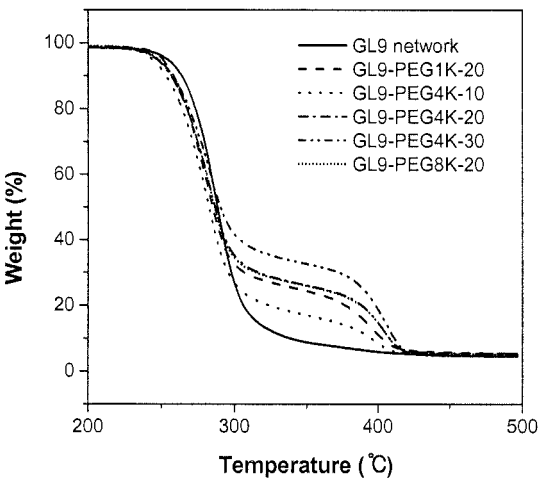

Fig. 1. TGA thermograms of GL9 and GL9-PEG network films before biodegradation.

showed the highest thermal stability. The enhanced thermal stability of the incorporated PEG was related closely with its content rather than its molecular weight. The $Td_{1/2}$ of the GL homonetwork was similar to the results that reported in previous study on the novel star-shaped poylactide having glycerol [18]. After biodegradation, the Tg of networks slightly decreased as compared to the same samples before biodegradation. These phenomena may be attributed to the reduction of molecular weights by degradation of the long chain PLA. The $Td_{1/2}$ of networks considerably increased to a certain degree due to extraction of the low molecular weight parts in film.

The tensile strengths of the GL and GL-PEG networks were shown in Fig. 2. The tensile strengths of GL homonetworks increased with increasing the lactide content. In addition, in the case of GL9 series, the tensile strengths decreased as the PEG molecular weight and content increased due to the soft PEG. It seems that the PEO chain acts as a kind of plasticizer in GL-PEG network films. Similar mechanical property was demonstrated in Sheth's study using the biodegradable PLA/PEG blends that the tensile strength decreases with increasing the PEG content [11]. It is expected that the soft segment PEG imparts flexibility to the blend system.

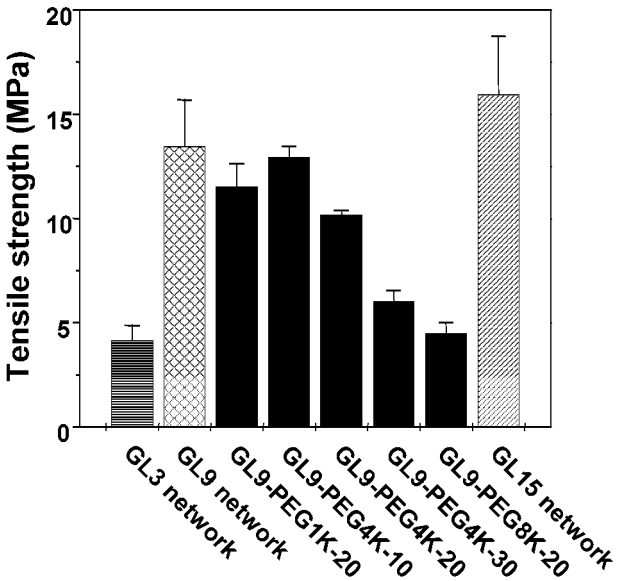

Fig. 2. Tensile strengths of GL and GL-PEG network films.

Fig. 3 shows the remaining weights after biodegradation of the networks for 1 day. As expected, GL-PEG networks degraded faster than GL homonetworks. Weight loss in GL-PEG networks significantly increased with increasing the PEG content at the same molecular weight. However, the lactide content of the GL homonetworks and the PEG molecular weight of GL-PEG networks did not greatly affect the biodegradability.

The morphological changes of GL9 and GL9-PEG4K-20 network surfaces before and after biodegradation in PBS at 80 ℃ for 1 day were shown in Fig. 4. After biodegradation, GL9 surface displayed some small cracks, however there were many large cracks and debris on all GL9-PEG surfaces. Therefore, this result means that the

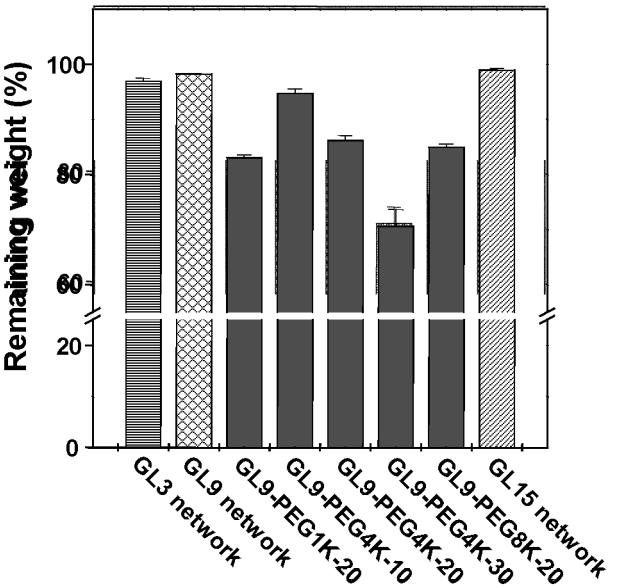

Fig. 3. Weight changes of GL9 and GL9-PEG networks after biodegradation for 1 day.

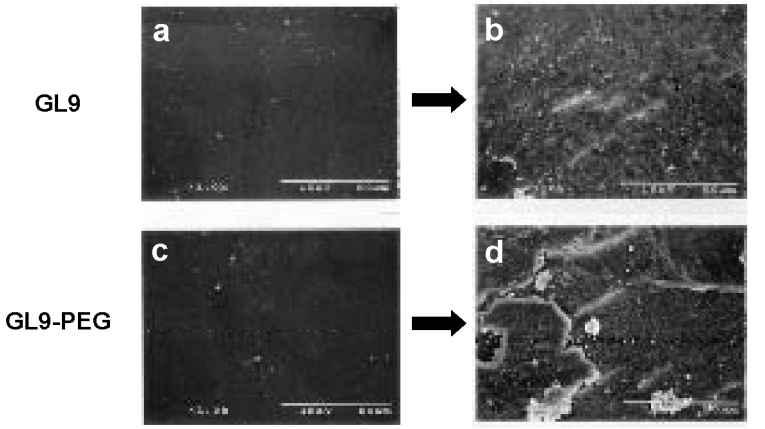

Fig. 4. SEM pictures before/after biodegradation in PBS at 80 ℃ for 1 day; a) GL9 network (before biodegradation), b) GL9 network (after biodegradation), c) GL9-PEG4K-20 network (before biodegradation), and d) GL9-PEG4K-20 network (after biodegradation).

GL-PEG networks are more apt to biodegrade than the GL homonetworks. Fig. 5 shows the degradation kinetics of GL9 and GL9-PEG networks. Appreciable weight loss was observed as incubation time increased from 1 to 5 days and the PEG content increased. But the PEG molecular weight hardly influenced the biodegradability. From these results, it is suggested that the main factor affecting biodegradation in the GL-PEG networks could be the hydrophilic PEG content rather than the PEG molecular weight. Li and Kissel [15] reported that the introduction of a

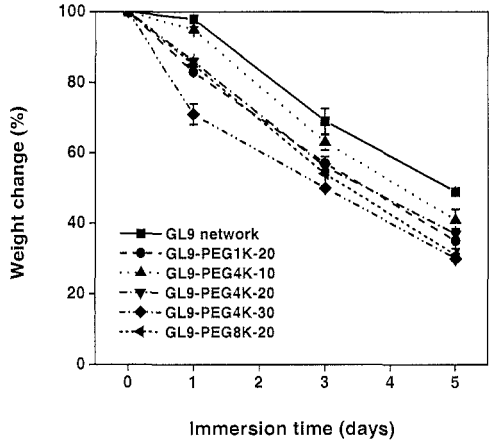

Fig. 5. Degradation kinetics of GL9 and GL9-PEG networks.

hydrophilic PEO block in linear ABA type block copolymers led to rapid swelling in water and the rapid mass erosion was mainly caused by the fast cleavage of the PEO block by hydrolysis.

Conclusions

The crosslinked scaffold network films (GL-PEGs) having the glycerol-lactide triacrylate (GL-Ac) and various PEG monoacrylates (PEG-Ac) were prepared by simple UV copolymerization. The Tg of all networks after biodegradation relatively decreased and the trend was similar to that before biodegradation, whereas the $Td_{1/2}$ increased in all networks to a certain degree. The tensile strength of GL scaffolds increased with increasing the lactide content and the tensile strength decreased as the PEG was incorporated and as the molecular weight and content of PEG increased due to the soft PEG. After biodegradation of the networks in PBS at 80 • for 1 day, the GL-PEG networks have shown to be degraded faster than GL one, as PEG is incorporated and its content increased. In addition, the molecular weight of PEG was not related to the degree of biodegradation in GL-PEG networks. It was also confirmed from morphological change of their surfaces by SEM observation. The preparation of *in situ* porous scaffolds and the grafting of bioactive ligands such as RGD, REDV, and YIGSR are presently in progress to obtain further functional polymer scaffolds and barriers for tissue engineering. Thus, these network films are expected to be useful as polymer scaffolds.

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