

Synthesis and Characterization of Biodegradable Elastic Hydrogels Based on Poly(ethylene glycol) and Poly(ϵ -caprolactone) Blocks

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Abstract: Novel biodegradable elastic hydrogels, based on hydrophilic and hydrophobic polymer blocks, were synthesized via the radical crosslinking reaction of diacrylates of poly(ethylene glycol) (PEG) and poly(ϵ -caprolactone) (PCL). PEG and PCL diols were diacrylated with acryloyl chloride in the presence of triethylamine, with the reaction confirmed by FT-IR and $^1\text{H-NMR}$ measurements. The diacrylate polymers were used as building-blocks for the syntheses of a series of hydrogels, with different block compositions, by simply varying the feed ratios and molecular weights of the block components. The swelling ratio of the hydrogels was controlled by the balance between the hydrophilic and hydrophobic polymer blocks. Usually, the swelling ratio increases with increasing PEG content and decreasing block length within the network structure. The hydrogels exhibited negative thermo-sensitive swelling behavior due to the coexistence of hydrophilic and hydrophobic polymer components in their network structure, and such thermo-responsive swelling/deswelling behavior could be repeated using a temperature cycle, without any significant change in the swelling ratio. *In vitro* degradation tests showed that degradation occurred over a 3 to 8 month period. Due to their biodegradability, biocompatibility, elasticity and functionality, these hydrogels could be utilized in various biomedical applications, such as tissue engineering and drug delivery systems.

Keywords: biodegradable hydrogels, thermo-responsive swelling, PEG, PCL, *in vitro* degradation.

Introduction

Hydrogels are three-dimensional polymer networks capable of absorbing large amounts of water to swell, but are insoluble due to the presence of cross-links which can be formed via either chemical or physical bonds.^{1,2} Since the first report on the biomedical use of poly(2-hydroxyethyl methacrylate) hydrogel,³ hydrogels have been used widely in the biomaterial and pharmaceutical areas for various applications, including tissue engineering⁴ and drug delivery,^{1,5} due to their good biocompatibility.⁶ Recently, the hydrogels were designed to respond to their environmental changes, such as pH, temperature, and specific compounds.^{7,8} These stimuli-responsive hydrogels have gained considerable interest in the pharmaceutical field due to their unique swelling and permeability characteristics that can be changeable in response to a variety of physical, chemical, and biological stimuli,⁹ leading to the concept of intelligent or smart drug delivery systems.

Biodegradable hydrogels have attracted considerable attentions for biomedical uses because they do not require any surgical removal process after the system fulfills its goal.¹⁰⁻¹² In addition, the degradation can be utilized to control the rate of drug release and the physico-chemical properties of the hydrogel systems, and thus to provide flexibility in the design of biomedical devices, such as drug/biomaterials combination products. Most biodegradable hydrogels are typically prepared by chemical or physical crosslinking of water-soluble natural polymers or from segmented block copolymers consisting of hydrophilic polymers and hydrophobic, biodegradable polymers. While the crosslinking method has the advantages of easy processing, it is hard to control their physical and chemical properties including biodegradability. Use of segmented block copolymers may be a better way to control the hydrogel properties, because the multicomponent nature of the system affords versatility in designing hydrogels with well-defined chemical and physical properties. In particular, the polyether-polyester block copolymers constitute a major class of block copolymer hydrogels.¹²⁻¹⁵

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In the family of aliphatic polyesters, polylactide, polyglycolide, and poly(ϵ -caprolactone) (PCL) have been extensively investigated as biocompatible and biodegradable polymers.¹⁶⁻¹⁹ Although their rather high crystallinity may decrease the biocompatibility with soft tissues and lower the biodegradability, the drawbacks can be overcome by copolymerization with other monomers. Poly(ethylene glycol) (PEG) is well known to have the superior properties of flexibility, hydrophilicity and biocompatibility. These properties may be the reason why the PEG is the most frequently used polyether in making block copolymers for biomedical applications. Biodegradable hydrogels are also prepared based on triblock copolymers containing PEG as a central block and D,L-lactic acid which was terminated by diacrylated groups.^{20,21} The degradation rate and permeability of the hydrogels could be altered by changing the composition and concentration of the macromers.

The purpose of this study is to develop a new biodegradable, elastic block copolymer hydrogel. The physico-chemical properties, such as biodegradability, swelling property, elasticity and amphiphilicity, can be modulated by simply changing the synthetic parameters, e.g., the block composition and ratio. As building-blocks for synthesis of block copolymer hydrogels, various PEG and PCL diacrylates with different molecular weights were prepared by esterification reaction of acryloyl chloride with PEG and PCL diols. Compared to the hydrogels prepared from the segmented block copolymers, the use of two separate polymer blocks of PEG and PCL may provide a more versatile and useful design for various hydrogels with different properties. The prepared diacrylates were used to undergo radical crosslinking reaction to form hydrogels. In this study, the unique physico-chemical properties of the synthesized hydrogels as a function of the block structures were examined.

Experimental

Materials. PEG acrylate ($M_n = 575$ and 700), PEG diol ($M_n = 2,000$), poly(ϵ -caprolactone) diol (PCL, $M_n = 530$ and $1,250$), acryloyl chloride (Ac), triethylamine (TEA), dimethyl sulfoxide (DMSO) and benzene were purchased from Sigma-Aldrich. 2,2-Azobisisobutyronitrile (AIBN) as a radical initiator was purchased from Junsei Chemicals (Japan) and used after purification by recrystallization in methanol. Hexane was purchased from Samchun Chemicals, Korea. The other chemicals were used as received.

Synthesis of PEG and PCL Diacrylates (PEG-DA and PCL-DA). Diacrylation of PEG ($M_n = 2,000$) and PCL ($M_n = 530$ and $1,250$) diols with Ac is illustrated in Figure 1. The required amount of PEG (or PCL) diols was dissolved in benzene in a 100 mL of two-neck round bottom flask equipped with a water condenser and a magnetic stirrer. The calculated amounts of TEA and Ac were added to the reaction flask, and the reaction mixtures were stirred at 80°C for

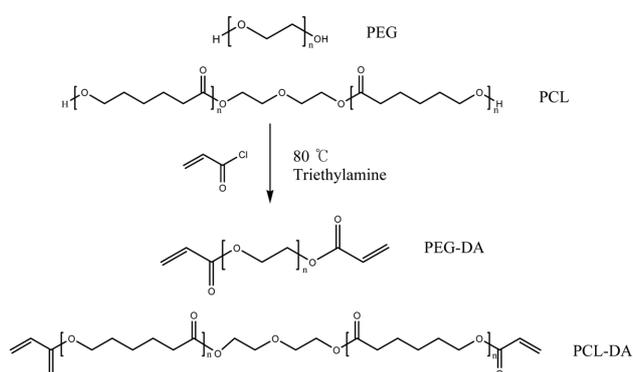


Figure 1. Synthetic methods for diacrylation of PEG and PCL diols.

3 h. The reaction mixtures were filtered to remove triethylamine hydrochloride, and then the filtrate was dropped into excess *n*-hexane to obtain diacrylates. Finally the precipitated PEG diacrylates were dried at 40°C under reduced pressure for 24 h. The prepared diacrylates were characterized by Fourier transform infrared spectroscopy (FT-IR) and $^1\text{H-NMR}$ measurements.

Synthesis of PEG/PCL Block Copolymer Hydrogels.

The chemically crosslinked biodegradable hydrogels with both hydrophilic and hydrophobic components were prepared via radical crosslinking reaction of PEG-DA and PCL-DA with different molecular weights. PEG-DA and PCL-DA were taken in different feed ratios to make various hydrogels with different block compositions as listed in Table I. The prepared diacrylates and AIBN were dissolved in DMSO in the micro centrifuge tubes, which were sealed by Teflon tape. The micro centrifuge tubes were placed in a drying oven at 65°C for 12 h. After the gel formation, both ends of the tubes were cut and the hydrogels were pulled out. The hydrogels were placed in ethanol for 24 h to

Table I. Various Kinds of Hydrogels Based on PEG and PCL Blocks

Hydrogel Samples	PEG-DA	PCL-DA	PEG/PCL (w/w)
PEG575/PCL530	PEG ₍₅₇₅₎ -DA	PCL ₍₅₃₀₎ -DA	1/1
PEG575/PCL530	PEG ₍₅₇₅₎ -DA	PCL ₍₅₃₀₎ -DA	2/1
PEG575/PCL1250	PEG ₍₅₇₅₎ -DA	PCL ₍₁₂₅₀₎ -DA	1/1
PEG575/PCL1250	PEG ₍₅₇₅₎ -DA	PCL ₍₁₂₅₀₎ -DA	2/1
PEG700/PCL1250	PEG ₍₇₀₀₎ -DA	PCL ₍₁₂₅₀₎ -DA	1/1
PEG700/PCL1250	PEG ₍₇₀₀₎ -DA	PCL ₍₁₂₅₀₎ -DA	2/1
PEG700/PCL1250	PEG ₍₇₀₀₎ -DA	PCL ₍₁₂₅₀₎ -DA	4/1
PEG2000/PCL1250	PEG ₍₂₀₀₀₎ -DA	PCL ₍₁₂₅₀₎ -DA	1/1
PEG2000/PCL1250	PEG ₍₂₀₀₀₎ -DA	PCL ₍₁₂₅₀₎ -DA	2/1
PEG2000/PCL1250	PEG ₍₂₀₀₀₎ -DA	PCL ₍₁₂₅₀₎ -DA	4/1
PEG575	PEG ₍₅₇₅₎ -DA	-	1/0
PEG700	PEG ₍₇₀₀₎ -DA	-	1/0
PEG2000	PEG ₍₂₀₀₀₎ -DA	-	1/0

remove residual impurities, followed by drying in a vacuum oven at room temperature for 2-3 days.

Characterization. The presence of the ester carbonyl group in the prepared diacrylates was confirmed by FT-IR (Nicolet, USA). ¹H-NMR spectra of PEG-DA and PCL-DA were obtained on a JNM-AL400 spectrometer (Jeol Ltd, Akishima, Japan) at 400 MHz. The break point during elongation of PEG/PCL hydrogels in the dried state was measured using a universal testing machine (LR30K, LLOYD instruments, UK). The film-type hydrogel was prepared and cut into a dimension of 30 mm × 4 mm × 2 mm. The sample length between jaws was 10 mm and the crosshead speed was 10 mm/min.

Swelling Test. To determine the swelling properties, the prepared hydrogels were cut into disks (5 mm in diameter and 3 mm in thickness) and then dried under vacuum for 24 h. The samples were immersed in distilled water to reach their equilibrium swelling, and weighed after removal of excessive surface water by lightly tapping the samples with a filter paper. The weight swelling ratio (*S*) was calculated from the following equation:

$$S = W_s/W_d$$

where, *W_s* and *W_d* are the weights of swollen and dried hydrogels, respectively. All measurements were performed in triplicates and the standard deviation is reported (average ± SD). To observe thermo-reversible swelling properties of the hydrogels the changes in swelling between two fixed temperatures were obtained by alternatively placing the samples in two water baths with different temperatures.

In Vitro Degradation Test. Hydrogel disc samples were immersed in an excessive amount of distilled water and incubated at room temperature and at 37 °C. The change in the swelling ratio and the weight loss of the hydrogels was monitored gravimetrically at timed intervals.

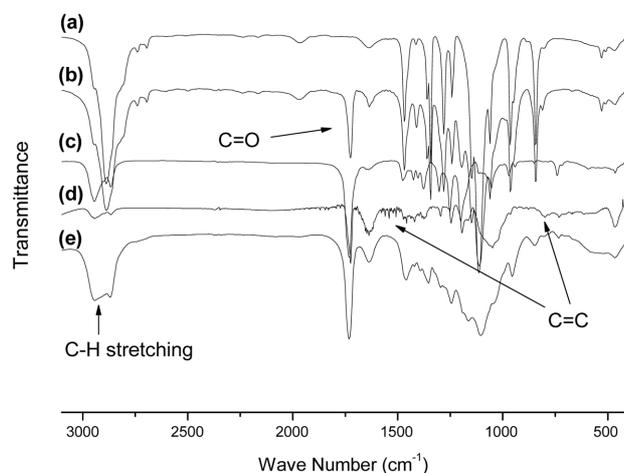


Figure 2. FT-IR spectra of (a) PEG, (b) PEG-DA, (c) PCL, (d) PCL-DA, and (e) PEG/PCL hydrogels.

Results and Discussion

PCL Diacrylation. PCL-DA was synthesized by reaction of PCL diol with acryloyl chloride as shown in Figure 1. FT-IR spectra of PCL diol and PCL-DA are shown in Figure 2. PCL-DA showed absorption bands at 1635 and 813 cm^{-1} assigned to C=C due to acrylation of PCL diol, respectively. Those peaks were not observed in PCL diol itself (Figure 2). The absorption bands at around 1750 and 1110 cm^{-1} , which were present in both PCL diol and PCL-DA, were attributed to ester and ether stretching peaks, respectively. Formation of PCL-DA was also confirmed through ¹H-NMR spectrometer. As shown in ¹H-NMR spectrum (Figure 3), the vinyl groups of the PCL-DA appeared in the 5.79-6.43 ppm range. From the above results, the terminal hydroxyl groups in the PCL diol were subsequently converted to acrylate groups by reacting with acryloyl chloride. Since PCL diol has two hydroxyl groups per molecule, the number of acrylic groups in PCL-DA should be 2. The number of acrylic groups that was calculated from

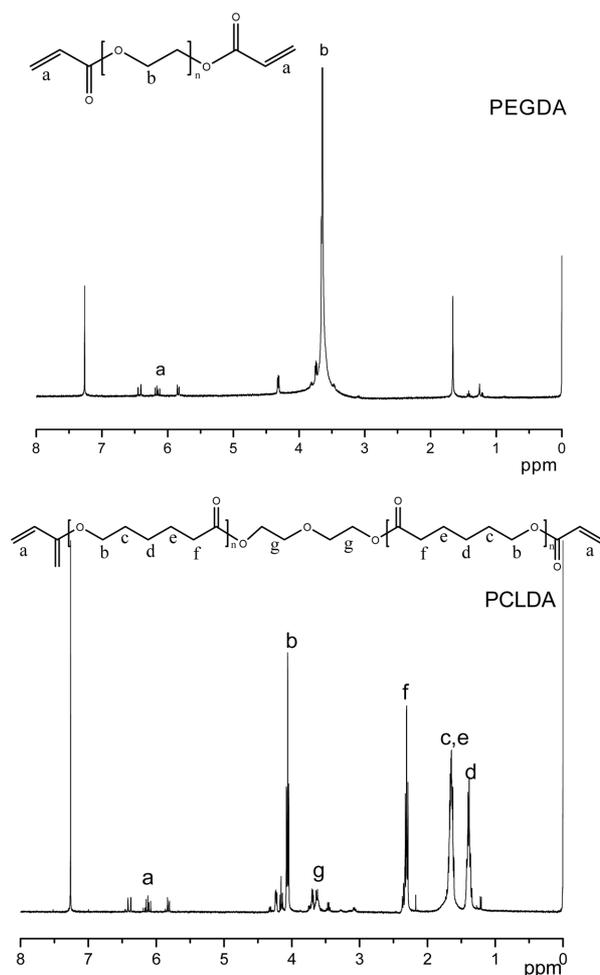


Figure 3. ¹H-NMR spectra of diacrylates of PEG and PCL.

the peak integration of $^1\text{H-NMR}$ spectra, was more than 1.8 for all PCL-DA products (Yield = 32% for PCL530-DA and 78% for PCL1250-DA).

PEG Diacrylation. PEG-DA was synthesized by reacting PEG diol with acryloyl chloride as shown in Figure 1. The FT-IR spectra of PEG diol and PEG-DA are shown in Figure 2. From the FT-IR spectrum of PEG-DA an ester

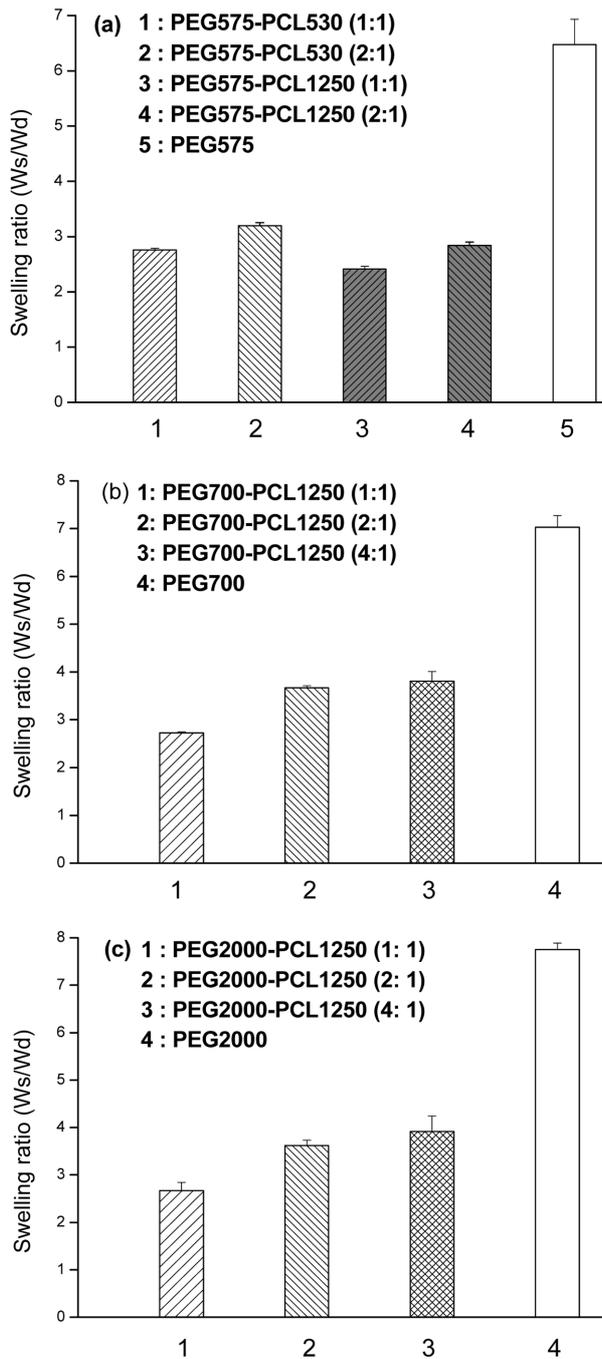


Figure 4. Comparison of the swelling ratios of PEG/PCL hydrogels with different block compositions.

carbonyl band appears at around 1760 cm^{-1} and for PEG a C-H stretching band appears at 2885 cm^{-1} . From the $^1\text{H-NMR}$ spectrum (Figure 3), the vinyl group protons of the PEG-DA were observed in the range of 5.79 to 6.43 ppm on the PEG diacrylate spectrum and it was not present on the

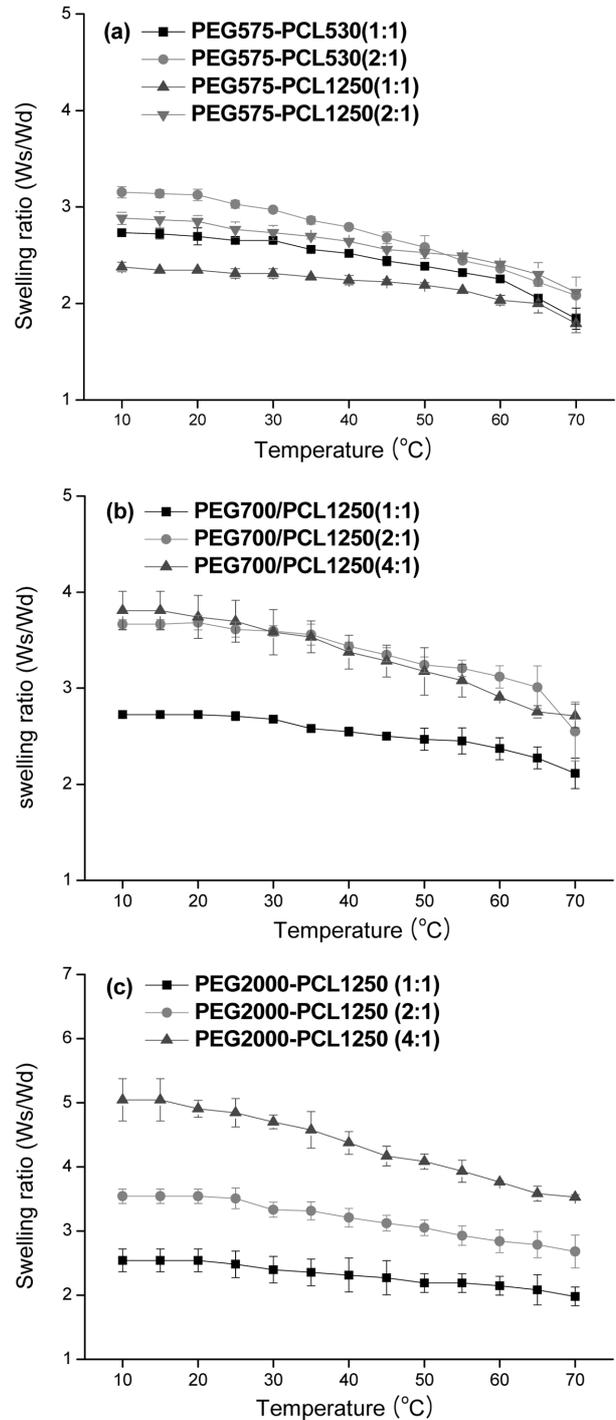


Figure 5. Changes in the swelling ratio of PEG/PCL hydrogels as a function of temperature.

PEG diol spectrum. From the $^1\text{H-NMR}$ results, about more than 90% of the hydroxyl end groups of the diol was modified with acryloyl chloride to produce PEG-DA (Yield = 77%).

Swelling Studies. The weight swelling ratio of the PEG/PCL block copolymer hydrogels with various block compositions and lengths was measured and the results are illustrated in Figure 4. Usually the swelling of hydrogels significantly depends on the hydrophilicity and the degree of crosslinking density. The swelling ratio of the PEG/PCL hydrogels ranged from 2 to 4, and could be controlled by the relative balance between the hydrophilic and hydrophobic polymer blocks. As expected, the swelling increased with the increasing content of hydrophilic PEG and the decreasing length of the PCL block. The hydrogels prepared from the PEG block only showed the highest swelling ratio. If the molecular weight of the PCL block was higher than the PEG block, the equilibrium swelling ratio of the hydrogels was smaller than others. The swelling ratio decreased with the increasing block length of hydrophobic PCL when the molecular weights of the polymer blocks were close to each other, as observed by others.²²

Temperature Effect on Swelling Ratio. The prepared hydrogels were kept to equilibrate in water for a day. The swelling ratio of the hydrogels was measured as a function of temperature (up to 70 °C). The immersion time of the samples in distilled water was 10 min. Figure 5 shows the effect of temperature on the swelling ratio. It was observed that the hydrogels exhibited a negative thermo-responsive swelling behavior. Upon increasing the temperature, the hydrogel gradually shrank in volume even though the change was not so large and not so drastic as other previously reported thermo-responsive hydrogels, such as poly(*N*-isopropylacrylamide) (PNIPAAm) hydrogels which are chemically crosslinked hydrogels without the hydrophobic block.²³

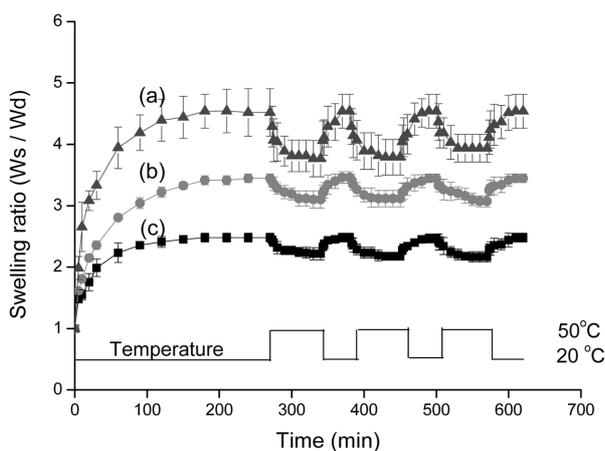


Figure 6. Thermo-reversible swelling properties of hydrogels: (a) PEG2000/PCL1250 (4/1), (b) PEG2000/PCL1250 (2/1), and (c) PEG2000/PCL1250 (1/1).

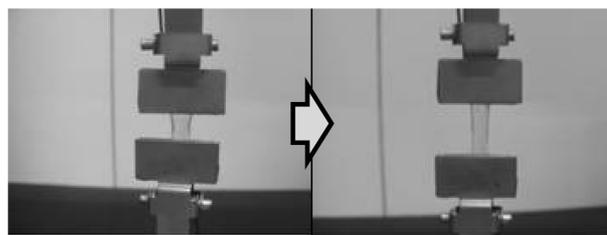


Figure 7. Elastic property of a dried PEG/PCL hydrogel.

Such thermo-responsive swelling appeared more clearly with the high PEG content and for most PEG/PCL hydrogels.

To confirm the thermo-responsive properties, the swelling ratio was measured during temperature fluctuations. The hydrogel samples were alternatively placed in the thermostat baths at 20 and 50 °C, and their swelling changes were examined (Figure 7). When the initially dried hydrogel samples were placed in distilled water at 20 °C, the equilibrium swelling reached within 2-3 h. Exposure of the hydrogels to a higher temperature (50 °C) led to deswelling of the hydrogels. When the hydrogels were exposed to 20 °C again, they recovered their initial swelling ratio. Swelling of the hydrogels was reversibly changed between the two temperatures, low swelling at high temperature and high swelling at low temperature.

There are many polymers that exhibit a negatively thermo-responsive property. It has been well known that such a negative thermo-responsive property results from the enhanced hydrophobic interaction at higher temperatures. PNIPAAm, of which monomer itself has both hydrophilic and hydrophobic moieties, is a well-known negative thermo-responsive polymer. Negatively thermo-responsive hydrogels of alternating multiblock copolymers of PEG and poly(L-lactic acid) (PLLA) were also reported previously.²² It is worth noting that the thermo-responsive property could be achieved from the balance based on hydrophilic and hydrophobic blocks. While the PEG/PLLA hydrogels are physical gels (not covalently cross-linked), our PEG/PCL hydrogels are chemical gels with a chemically cross-linked hydrogel network. The PEG/PCL hydrogels exhibited a negative thermo-sensitive swelling behavior due to the balanced coexistence of hydrophilic and hydrophobic block components in their network structure. Even though the thermo-responsive behavior in the PEG/PCL hydrogels is not so strong as in other polymer systems, it is meaningful that the negative thermo-sensitivity can be expanded to chemically cross-linked block copolymer network structures. In addition, it is notable that the thermo-responsive swelling could be repeated without any significant change in the initial swelling ratio.

Mechanical Property. Typical hydrogels are glassy and brittle in the dry state and thus it is very difficult to change the shape and size of the dried state. Even though the hydro-

gels can show elastic behavior to some degree in swollen state, their mechanical strength in the swollen state becomes too weak to change their shape by using physical forces or devices such as scissors or knives. Therefore, it is very useful to make flexible and elastic hydrogels even in the dried state so that they can be reshaped and adjusted as necessary for corresponding applications. PEG is a hydrophilic polymer and its glass transition temperature is very low due to the flexible chain structure. When PEG was used as a building block for preparing hydrogels with other biodegradable polyesters, such as PGA, PLA and PCL, the hydrogels can show flexible and/or elastic properties even in the dried state. All the PEG/PCL hydrogels were flexible and elastic in the dried state, and so they remain intact even after repeated bending or stretching. As shown in Figure 7, the hydrogels can be stretched to almost twice the original length without breaking (Elongation at break: 60-90%).

In Vitro Degradation Test. *In vitro* degradation test of the hydrogels was conducted at room temperature and at 37°C for more than 230 days. Figure 8 shows the weight

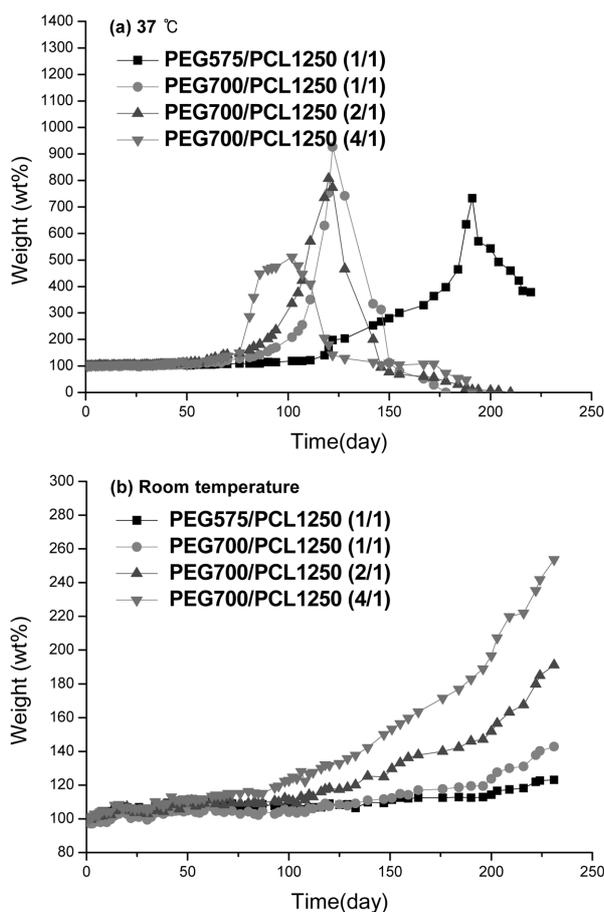


Figure 8. *In vitro* degradation of PEG/PCL hydrogels at room temperature (a) and at 37°C (b).

loss of the PEG/PCL hydrogels as a function of time. As shown by degradation at 37°C, there was no considerable change in the weight of all the hydrogels for up to 70 days. The weight of a PEG700/PCL1250 hydrogel with the block composition ratio of PEG/PCL (4/1) slightly increased from 50 days and significantly increased after about 80 days. Degradation of biodegradable PCL blocks in the hydrogel network led to decreased crosslinking density, which increased the hydrogel swelling ratio. From a certain time point, however, the hydrogel mass abruptly decreased to almost zero. As the degradation proceeded further, the network structure finally broke down so that the hydrogel mass was disintegrated into soluble degradation products. The other hydrogels showed the similar degradation patterns, but with different degradation rates depending on their block composition. Generally, the high content of hydrophobic PCL block led to a delayed degradation behavior. Also, the hydrogels prepared from a short block length showed a delayed degradation property due to the high cross-linking density. The PEG575/PCL1250 (1/1) hydrogel did not show any significant change in weight until more than 120 days and took more than 200 days for degradation. Also, it was not degraded completely to soluble products, but remained as small hydrogel fragments. Such fragments were considered to be residual cross-linked PEG moieties that could not degrade any more.

Degradation of the hydrogels at room temperature progressed much slowly. Even after more than 220 days, practical disintegration of the hydrogel mass was not observed. The increasing swelling ratio of the hydrogels indicates that the degradation was in process. The degradation rate at room temperature was dependent on the block composition as degradation at 37°C, and the high PEG content led to a faster degradation than the other hydrogels. These hydrogels will be highly useful to applications where delayed swelling of hydrogel is desirable.

Conclusions

Diacrylates of PEG and PCL were synthesized by the esterification reaction using acryloyl chloride in the presence of TEA. A series of biodegradable elastic hydrogels based on hydrophilic PEG and hydrophobic PCL blocks were prepared by radical cross-linking reaction. The swelling and degradation properties of the hydrogels could be controlled easily by varying the block composition. Thermo-responsive swelling could be confirmed in a cross-linked hydrogel network structure, which had a balanced hydrophilic and hydrophobic block ratio, and the swelling/deswelling was repeated many times without any change in the initial swelling ratio. These block copolymer hydrogels will be highly useful for applications in drug delivery and tissue regeneration where delayed swelling of hydrogels is desired.

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