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Synthesis and characterization of amphiphilic poly(2-ethyl-2-oxazoline)/poly(ε-caprolactone) alternating multiblock copolymers

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Abstract

Novel amphiphilic alternating multiblock copolymers were synthesized by the polycondensation reaction of α,ω-dihydroxypoly(2-ethyl-2-oxazoline) (HO–PEtOz–OH) with α,ω-dicarboxypoly(ε-caprolactone) (HOOC–PCL–COOH) by varying the block composition. The phase transition and swelling behaviors of multiblock copolymer hydrogels depending on temperature changes were investigated in aqueous media. The crystalline melting of PCL domain and the hydrophobic interaction within the gel could be correlated with the phase transition. Thermosensitive swelling behaviors of hydrogels were investigated in response to temperature changes. The hydrogels exhibited reversible swelling–shrinking behavior, where the higher swelling ratios were obtained at the lower temperature. The higher swelling ratios were obtained for hydrogel containing longer PEtOz blocks, and swelling capacity could be controlled by adjusting the block composition. In mechanical tests, the dried gels and hydrogels of multiblock copolymers prepared from longer oligomeric PCL exhibited maximum strengths in the range of 10.6–12.5 and 3.2–7.3 MPa, and ultimate elongation up to 880–930 and 320–1000%, respectively.

Keywords: Alternating multiblock copolymers; Hydrogels; Reversible swelling–shrinking

1. Introduction

Amphiphilic block copolymers composed of hydrophilic and hydrophobic segments have served as attractive building blocks for versatile application fields such as separation technology and the area of drug delivery [1–5]. Therefore, interests in the preparation and characterization of various types of amphiphilic block copolymers are consistently increasing to tailor their properties to specific applications [6–10]. In particular, hydrogels exhibiting temperature-modulated swelling–shrinking response in water have attracted much attention for controlled drug delivery applications [11–14]. Recently, thermoplastic biodegradable hydrogels prepared from amphiphilic block copolymers were widely investigated [15,16]. These block copolymers consisted of hydrophilic poly(ethylene oxide) (PEO) and hydrophobic, biodegradable poly(L-lactide). They are physically crosslinked hydrogels due to the crystallinity and the hydrophobic interaction of poly(L-lactide) blocks, in which various favorable properties for practical use including processability and biodegradability can be obtained. These studies mainly dealt with the synthesis, physical properties, and time-dependent swelling behavior of block copolymers, while the temperature-dependent swelling–shrinking behaviors were not emphasized. In this work, we aimed to describe the synthesis of novel amphiphilic alternating multiblock copolymers based on hydrophilic poly(2-ethyl-2-oxazoline) (PEtOz) and hydrophobic poly(ε-caprolactone) (PCL), temperature-dependent phase transitions and the swelling–shrinking behavior of their hydrogels. We recently reported the synthesis of amphiphilic AB diblock copolymers of PEtOz and PCL, which were found to disperse to form micelles in an aqueous phase [9]. In this work, water-insoluble but swellable multiblock copolymers based on PEtOz and PCL were prepared. Therefore, in this system, the characteristics of thermoplastic elastomer hydrogels are expected since they consist of hard domain of crystalline PCL and soft domain of amorphous PEtOz [17–21]. Thermoplastic elastomer hydrogels have advantages over chemically crosslinked hydrogels, in that they can be processable in melt or solution, and exhibit favorable mechanical

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properties such as elasticity and tensile strength. The temperature-dependent phase transitions, thermoreversible swelling behavior, and mechanical properties of multiblock copolymer hydrogels were investigated.

2. Experimental

2.1. Materials and equipment

2-Ethyl-2-oxazoline (Aldrich) was dried and distilled over calcium hydride. 1,4-Dibromo-2-butene (Aldrich) was recrystallized twice from *n*-hexane. Poly(caprolactone diol)s (Aldrich) with M_n of 1250 and 2000 were purified by precipitation from methylene chloride into diethyl ether and were used after drying at 40°C under vacuum. Succinic anhydride (Aldrich) was recrystallized from chloroform. *N*,*N*′-dicyclohexylcarbodiimide (DCC) (Tokyo Kasei) and 4-dimethylaminopyridine (DMAP) (Tokyo Kasei) were used as received. Acetonitrile, methylene chloride, and 1,4-dioxane were distilled over calcium hydride. Other solvents such as THF, diethyl ether, and *n*-hexane were used without further purification. ^{1}H NMR spectra were obtained on a Bruker AC 250 spectrometer at 250 MHz. Molecular weights and molecular weight distributions were determined using a GPC equipped with a Waters Associates 410 RI detector, 510 HPLC pump, and μ-Styragel columns with pore sizes of 10^2, 500, 10^3 and 10^4 Å. The eluent was THF and the molecular weights were calibrated with the polystyrene standards. Thermal data were obtained on a Perkin–Elmer DSC 7. Transmittance (%) at 500 nm was measured on a Hewlett–Packard 8452A spectrophotometer. Mechanical properties were estimated from a HOUNSFIELD H25KS universal testing machine.

2.2. Preparation of amphiphilic multiblock copolymers

The multiblock copolymers were prepared by the polycondensation reaction of α,ω-dihydroxypoly(2-ethyl-2-oxazoline) (HO–PEtOz–OH) and α,ω-dicarboxypoly(ε-caprolactone) (HOOC–PCL–COOH). The HO–PEtOz–OH with M_n of 900 was prepared by the following procedure [22,23]. A solution of 2-ethyl-2-oxazoline (20 g, 202 mmol) and 1,4-dibromo-2-butene (4.32 g, 20.2 mmol) in acetonitrile (120 ml) was stirred at reflux for 9 h under nitrogen. After cooling to room temperature, the slight excess of 0.2 N methanolic KOH was added to introduce hydroxyl groups at the both ends of PEtOz chain. After evaporation of the solvent, the crude product in THF was filtered through the silica gel. The product, HO–PEtOz–OH, was then isolated by precipitation into diethyl ether and was dried at 40°C under vacuum. HO–PEtOz–OH with M_n of 2000 was synthesized in an identical manner except that the feed molar ratio of 2-ethyl-2-oxazoline to 1,4-dibromo-2-butene was 20. For the preparation of HOOC–PCL–COOH with M_n of 1800, to a 1,4-dioxane (100 ml) solution of polycaprolactone diol ($M_n = 1250$) (15 g) and succinic anhydride (2.88 g, 28.8 mmol), DMAP (3.52 g, 28.8 mmol) was added. The reaction mixture was stirred at room temperature for 24 h under nitrogen. The crude polymer was isolated by precipitation into *n*-hexane. An aqueous HCl solution was added to a THF solution of crude polymers, and the solution was then poured into distilled water. Finally, the product, HOOC–PCL–COOH was isolated by precipitation from THF into *n*-hexane and was dried at 40°C under vacuum. Multiblock copolymer, (PEtOz900/PCL1800)$_n$, was prepared by the polycondensation reaction of HO–PEtOz–OH ($M_n = 900$) and HOOC–PCL–COOH ($M_n = 1800$) in the presence of DCC and DMAP. To a methylene chloride solution (20 ml) of HO–PEtOz–OH (1 g) and equimolar HOOC–PCL–COOH (2 g), DCC (0.69 g, 3.3 mmol) and DMAP (0.04 g, 0.33 mmol) were added under nitrogen. The reaction was maintained for 24 h at room temperature. The precipitated dicyclohexyl urea was filtered off. The multiblock copolymer was isolated by precipitation into diethyl ether under vigorous stirring. Other multiblock copolymers which have different block composition, (PEtOz900/PCL2500)$_n$ and (PEtOz2000/PCL2500)$_n$, were synthesized in an identical manner.

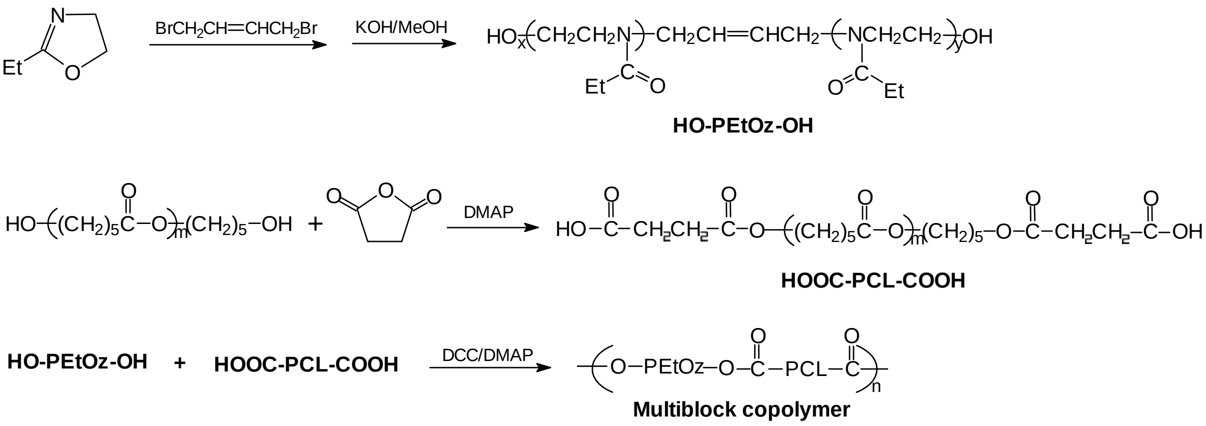
2.3. Thermosensitive behavior of multiblock copolymers

The films of multiblock copolymers were obtained by solvent casting from methylene chloride. Each 15% polymer solution was poured into a Teflon mold, then was dried at room temperature for 24 h and at room temperature in vacuo for 48 h. The polymer film was cut to a desired dimension and was adhered to the wall of UV–Vis spectrophotometer cell. The cell was then filled with distilled water. The transmittances of hydrogels were measured after the equilibrium of swelling at a wavelength of 500 nm with increasing the temperature. To estimate the temperature-dependent swelling behavior of hydrogels, dried polymer films of about $1 \times 1 \times 0.07$ cm^3 were prepared. After immersion in water at desired temperature for a fixed time interval, the hydrogels were tapped with filter paper to remove water on the surface, and then were weighed. The swelling ratio, W_W/W_P was used to evaluate the capacity of water absorption, where W_W is the weight of absorbed water and W_P that of dried polymer film. Swelling–shrinking behaviors of hydrogels in response to temperature fluctuation were investigated by changing the temperature of water. For each multiblock copolymer hydrogel, upper- and lower-bounded temperatures were selected. (PEtOz900/PCL1800)$_n$ was studied at 15–35°C, (PEtOz900/PCL2500)$_n$ at 15–45°C, and (PEtOz2000/PCL2500)$_n$ at 15–47°C, respectively.

3. Results and discussion

3.1. Synthesis and characterization of multiblock copolymers

Amphiphilic multiblock copolymers composed of hydrophilic PEtOz and hydrophobic PCL were prepared as illustrated in Scheme 1.



Scheme 1.

The multiblock copolymers were prepared by the polycondensation of HO–PEtOz–OH and HOOC–PCL–COOH. For the preparation of HO–PEtOz–OH, 2-ethyl-2-oxazoline was polymerized with 1,4-dibromo-2-butene as the bifunctional initiator to produce PEtOz with oxazolinium living end groups, which were then terminated by methanolic KOH to introduce hydroxyl groups at both chain ends [22,23]. The chain length of HO–PEtOz–OH could be conveniently controlled by varying the molar ratio of 2-ethyl-2-oxazoline to a cationic bifunctional initiator, 1,4-dibromo-2-butene. The ^{1}H NMR spectra were utilized to determine the molecular weights of HO–PEtOz–OHs from the peak integration ratios of C*H*=C*H* of the initiator part at 5.51 ppm and methyl protons in PEtOz repeating unit at 1.11 ppm.

As listed in Table 1, the molecular weights of HO–PEtOz–OHs are 900 and 2000 with narrow polydispersity. For the preparation of hydrophobic PCLs having carboxyl groups at both chain ends, HO–PCL–OHs with molecular weights of 1250 or 2000 were allowed to react with succinic anhydride in the presence of 4-dimethylaminopyridine. The molecular weights of HOOC–PCL–COOHs were determined from the integration ratios of resonance at 2.28 ppm originating from the CH_2C=O of PCL block and resonance of CH_2CH_2 of terminal succinic moiety at 2.62 ppm in ^{1}H NMR spectra. The molecular weights and polydispersities of HOOC–PCL–COOHs are summarized in Table 1. The amphiphilic multiblock copolymers were synthesized by the DCC-mediated polycondensation reaction of two telechelic oligomers, HO–PEtOz–OH and HOOC–PCL–COOH. The block compositions of multiblock copolymers were easily controlled by appropriately selecting a pair of HO–PEtOz–OH and HOOC–PCL–COOH with different molecular weights. The ^{1}H NMR spectrum of (PEtOz900/PCL2500)$_n$ in Fig. 1 represents characteristic resonance peaks of multiblock copolymers.

Table 1
Molecular weights of HO–PEtOz–OH and HOOC–PCL–COOH

Oligomers	M_n [a]	M_w/M_n [b]
HO–PEtOz900–OH	900	1.10
HO–PEtOz2000–OH	2000	1.10
HOOC–PCL1800–COOH	1800	1.50
HOOC–PCL2500–COOH	2500	1.50

[a] Estimated by ^{1}H NMR.
[b] Estimated by GPC.

The methylene protons of EtOz unit adjacent to PCL block CH_2CH_2–OCO–PCL appear at 4.20 ppm together with methylene protons of ethylene oxy unit used as an initiator in the synthesis of HO–PCL–OH. The molar ratios of repeating units in PEtOz and PCL blocks were determined by the integration ratio of methyl protons in the PEtOz block and methylene protons (CH_2C=O) of PCL block. Fig. 2 shows gel permeation chromatograms of two telechelic oligomers, HO–PEtOz–OH ($M_n = 900$), HOOC–PCL–COOH ($M_n = 1800$), and a resulting multiblock copolymer (PEtOz900/PCL1800)$_n$.

The molecular weights and block compositions of the multiblock copolymers are summarized in Table 2.

3.2. Temperature-dependent phase behavior of multiblock copolymer hydrogels

All the PEtOz/PCL amphiphilic multiblock copolymers prepared in this work were water-insoluble but swellable due to physical crosslinking mainly from PCL crystalline domain and hydrophobic interactions along the polymer chains. When fabricated as a certain shape, these multiblock copolymers retained their shape in water and thus were found to show characteristics of water swellable hydrogel. As in the case of water-soluble polymer system, it is expected that the balance between hydrophilicity and hydrophobicity in hydrogels affects the phase transition of hydrogel [24,25]. The temperature-dependent phase transitions of multiblock copolymer hydrogels were investigated by observing the change of transmittance at 500 nm as shown in Fig. 3.

Upon heating, the transmittance of the (PEtOz900/PCL1800)$_n$ hydrogel increased in the range of 30–35°C,

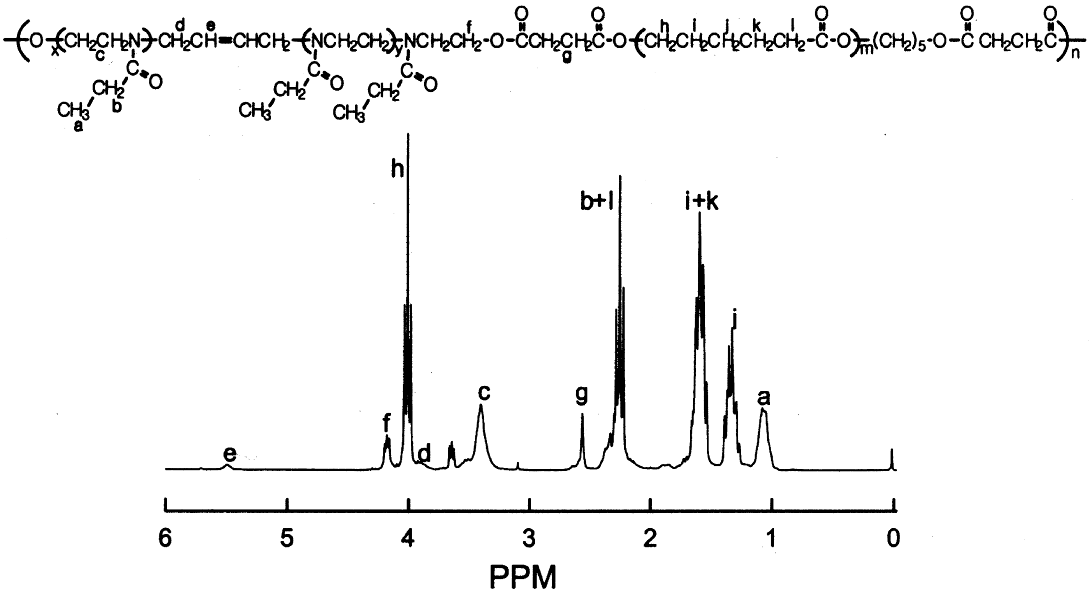


Fig. 1. ^{1}H NMR spectrum of $(PEtOz900/PCL2500)_n$.

but further heating resulted in decrease of transmittance in the range of 36–45°C. The hydrogels of $(PEtOz900/PCL2500)_n$ and $(PEtOz2000/PCL2500)_n$ also exhibited two distinct transitions at somewhat higher temperature ranges than those of the $(PEtOz900/PCL1800)_n$ hydrogel. The change of optical transmittance in hydrogels might be dominantly influenced by the PCL block. The first transitions, where gradual increase in optical transmittance was observed, could be ascribed to the crystalline melting of the PCL microdomain, which was supported by the existence of an endotherm in the similar temperature range in the DSC experiment as shown in Fig. 4.

The second transition, where a sudden decrease in optical transmittance occurred, might be induced by the promotion of hydrophobic interaction along the hydrophobic PCL chains. The hydrophilic PEtOz is known to show lower critical solution temperature (LCST) in water [26]. However, the LCST range of PEtOz with M_n of 900 or 2000 in water is beyond our experimental temperature range and thus, the effect of PEtOz on the phase transition of the hydrogels in water could be excluded.

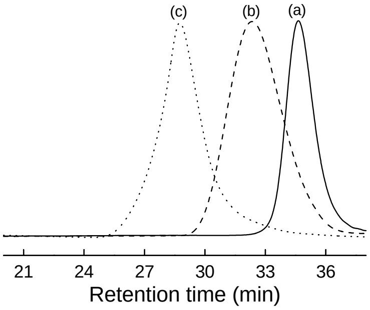


Fig. 2. Gel permeation chromatograms of: (a) HO–PEtOz900–OH; (b) HOOC–PCL1800–COOH and (c) $(PEtOz900/PCL1800)_n$.

3.3. Temperature-dependent swelling behavior of multiblock copolymer hydrogels

The PEtOz/PCL amphiphilic multiblock copolymers prepared in this work show the characteristics of water-swellable hydrogels, in which the hard domain constructed from the hydrophobic segment of crystalline PCL acts as physical crosslinks. As the balance between hydrophilicity and hydrophobicity in hydrogel is expected to be modulated by adjusting temperature of surrounding media, the swelling capacity of hydrogels also can be controllable depending on the temperature change. Therefore, the swelling behavior of multiblock copolymer hydrogels in water was investigated in response to temperature change. Fig. 5 shows temperature-dependent swelling behavior of $(PEtOz900/PCL1800)_n$ hydrogel in water in response to consecutive temperature change between 15 and 35°C.

The hydrogel shows reversible thermonegative swelling behavior depending on the temperature change, where the higher swelling ratios were obtained at lower temperature. At 15°C, the hydrogel swells exclusively by the hydration of amorphous PEtOz via hydrogen bonding with water. On the other hand, a temperature increase to 35°C weakens the

Table 2
Molecular weights and compositions of multiblock copolymers

Multiblock copolymers	M_n [a]	Composition ratio [b] ([CL]/[EtOz])	M_w/M_n [a]
$(PEtOz900/PCL1800)_n$	19000	0.63	1.5
$(PEtOz900/PCL2500)_n$	16000	0.70	2.6
$(PEtOz2000/PCL2500)_n$	23000	0.54	1.9

[a] Estimated by GPC.
[b] Molar composition ratio of the repeating units of PCL to that of PEtOz by ^{1}H NMR.

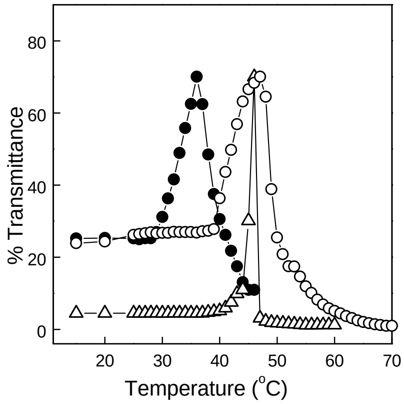


Fig. 3. Light transmittance change of PEtOz/PCL multiblock copolymer hydrogels as a function of temperature in water. ●: (PEtOz900/PCL1800)$_n$ hydrogel, △: (PEtOz900/PCL2500)$_n$ hydrogel, and ○:(PEtOz2000/PCL2500)$_n$ hydrogel.

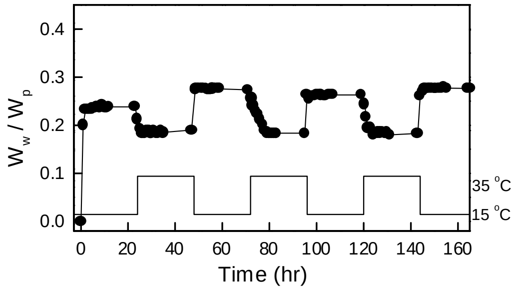


Fig. 5. Reversible changes in swelling ratios of (PEtOz900/PCL1800)$_n$ hydrogel in response to consecutive temperature change between 15 and 35°C.

hydrogen bonding, while the hydrophobic interaction within the hydrogel is enhanced [27]. The temperature dependency of hydrogen bonding of PEtOz might be understood as in the case of PEO because Iza et al. demonstrated that the equilibrium swelling ratios of hydrogels of poly(ethylene oxide) (PEO) were decreased by increasing the temperature, even with a slight temperature change, e.g. from 10 to 25°C [27]. PEtOz and PEO have a similar feature in that they form hydrogen bonding with water and their aqueous solutions exhibit phase separation to form polymer precipitates at lower critical solution temperature (LCST) [26,28]. In Figs. 6 and 7, temperature-dependent swelling and shrinking behaviors of hydrogels of (PEtOz900/PCL2500)$_n$ and (PEtOz2000/PCL2500)$_n$ were shown.

The hydrogels also exhibited thermally reversible swelling and shrinking behaviors. In the experimental temperature range, the swelling ratios of the hydrogels become higher by increasing the length of hydrophilic PEtOz block. Therefore, by adjusting the block composition of multiblock copolymers, the thermosensitive swelling–shrinking capacity of their hydrogels could be controlled, which would be a useful feature of thermosensitive hydrogels for temperature-sensitive delivery applications. It is interesting to note that the hydrogel of (PEtOz2000/PCL2500)$_n$ exhibited remarkable enhancement of swelling ratio from 0.44 to 0.83 after the first treatment at 47°C. This behavior might be related to the thermal properties of the hydrogels in water. As shown in the first-scan DSC thermograms of the hydrogels (Fig. 4), the multiblock copolymer hydrogels retain their crystallinity even in the swollen state in water at 15°C. For the hydrogels of (PEtOz900/PCL1800)$_n$ and (PEtOz900/PCL2000)$_n$, in the second-scan thermograms, their crystallinity was preserved. However, the hydrogel of (PEtOz2000/PCL2500)$_n$ lost its crystallinity in the second-scan thermogram (Fig. 4), and thus, the first temperature cycle (Fig. 7) from 15 to 47°C induces amorphous hydrogel of (PEtOz2000/PCL2500)$_n$. Therefore, the hydration of amorphous PCL domain as well as hydrophilic PEtOz might be enhanced, and thus a remarkable increase of swelling ratio for the hydrogel of (PEtOz2000/PCL2500)$_n$ is observed.

3.4. Mechanical properties of multiblock copolymers

The mechanical properties of dried gels and hydrogels including tensile strength and elasticity are critical factors in their practical applications. The PEtOz/PCL multiblock

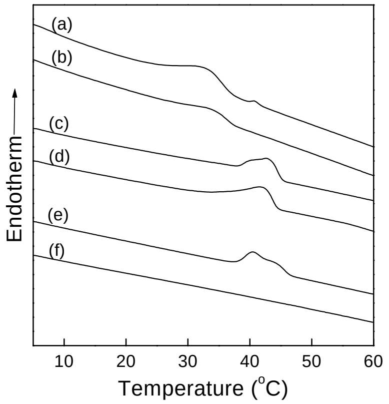


Fig. 4. DSC thermograms of PEtOz/PCL multiblock copolymer hydrogels: (a) First scan of (PEtOz900/PCL1800)$_n$; (b) second scan of (PEtOz900/PCL1800)$_n$; (c) first scan of (PEtOz900/PCL2500)$_n$; (d) second scan of (PEtOz900/PCL2500)$_n$; (e) first scan of (PEtOz2000/PCL2500)$_n$, and (f) second scan of (PEtOz2000/PCL2500)$_n$.

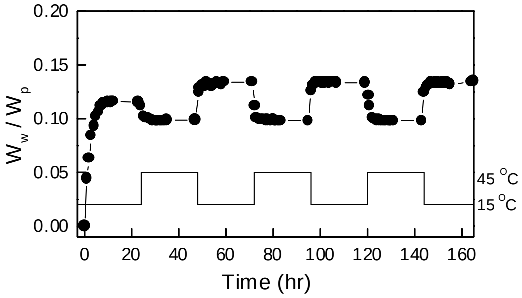


Fig. 6. Reversible changes in swelling ratios of (PEtOz900/PCL2500)$_n$ hydrogel in response to consecutive temperature change between 15 and 45°C.

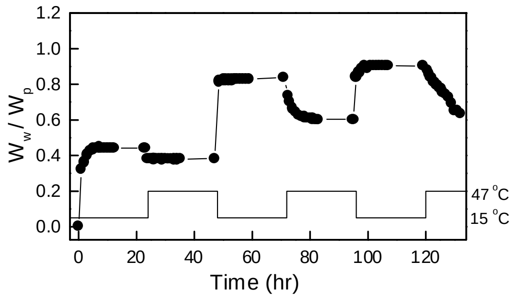


Fig. 7. Reversible changes in swelling ratios of $(PEtOz2000/PCL2500)_n$ hydrogel in response to consecutive temperature change between 15 and 47°C.

copolymers may behave like thermoplastic elastomer since they consist of crystalline hard domains of PCL and amorphous soft domains of PEtOz. In this system, the crystalline PCL domains are expected to serve as physical crosslinks, which mainly contribute to the mechanical strength and elasticity by holding together soft domains in a network structure. The mechanical properties of dried gels and hydrogels of $(PEtOz900/PCL2500)_n$ and $(PEtOz2000/PCL2500)_n$ are summarized in Table 3.

The dried gel and hydrogel of $(PEtOz900/PCL1800)_n$ with segmented PCL of low molecular weight ($M_n = 1800$) were not strong enough to give reliable values of tensile strength or ultimate elongation. The $(PEtOz900/PCL2500)_n$ and $(PEtOz2000/PCL2500)_n$ gels exhibited tensile strength in the range of 10.6–12.5 MPa and ultimate elongation of up to 880–930% in dried state. For the amphiphilic multiblock copolymers of PEO and polybutadiene (PB) reported by Xie et al., the tensile strength and ultimate elongation were reported in the range of 0.57–12.4 MPa and 460–900%, respectively, depending on the feed ratio of PEO to PB [20]. The tensile strengths of $(PEtOz900/PCL2500)_n$ and $(PEtOz2000/PCL2500)_n$ hydrogels, which experienced the cycle of temperature change, 15–45°C (or 47°C)–15°C, decreased probably due to the reduction in the crystallinity of PCL domain. It is noteworthy that the hydrogels from $(PEtOz900/PCL2500)_n$ exhibited ultimate elongation similar to that of dried gel, but the elongation of hydrogels from $(PEtOz2000/PCL2500)_n$ was remarkably reduced. These results might be inferred from the fact that the hydrogel of $(PEtOz900/PCL2500)_n$ preserved its crystallinity after temperature cycle of swelling experiment as clearly shown in the second scan of DSC experiment (Fig. 4), but the hydrogel of $(PEtOz2000/PCL2500)_n$ did not recover the crystallinity after melting during the cycle of temperature change.

Table 3
Mechanical properties of multiblock copolymer gels

Gels	Tensile strength (MPa)	Ultimate elongation (%)
Dried state		
$(PEtOz900/PCL2500)_n$	10.6	930
$(PEtOz2000/PCL2500)_n$	12.5	880
Swollen state		
$(PEtOz900/PCL2500)_n$	7.3	1000
$(PEtOz2000/PCL2500)_n$	3.2	320

4. Conclusion

Novel thermoplastic hydrogels based on alternating multiblock copolymers of hydrophilic poly(2-ethyl-2-oxazoline) and hydrophobic poly(ε-caprolactone) were prepared. The hydrogels exhibited phase transitions depending on the temperature increase. Upon heating, the optical transmittance of hydrogel increased but further heating induced the decrease in the transmittances. The melting of the crystalline PCL domain and the hydrophobic interaction within the hydrogel could be correlated with the increase and decrease in optical transparency, respectively. The hydrogels exhibited reversible thermonegative swelling-shrinking behavior. The swelling capacity of hydrogels could be manipulated by adjusting the block composition. The dried gels and hydrogels of multiblock copolymers prepared from HOOC–PCL–COOH with M_n of 2500 exhibited maximum strength in the range of 10.6–12.5 and 3.2–7.3 MPa, and ultimate elongation of up to 880–930 and 320–1000%, respectively. The detailed study on the relation of degradation to swelling properties of hydrogels are under investigation.

Acknowledgements

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