Preparation of a Novel Poloxamer Hydrogel

HaeYong Kweon,[1,*] Mi-Kyong Yoo,[1] Jin-Hak Lee,[2] Won-Ryang Wee,[2] Young-Gun Han,[2] Kwang-Gill Lee,[3] Chong-Su Cho[1]

[1]*School of Agricultural Biotechnology, Seoul National University, 103 Serdun-dong, Kwonseun-gu, Suwon 441-744, South Korea*
[2]*Department of Ophthalmology, Seoul National University College of Medicine, Seoul Artificial Eye Center, Seoul National University Hospital Clinical Research Institute, Seoul 110-799, South Korea*
[3]*Department of Sericulture and Entomology, National Institute of Agriculture and Technology, Suwon 441-100, South Korea*

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ABSTRACT: Poloxamer hydrogels were prepared by photopolymerization from poloxamer macromer, which was synthesized by reaction of poloxamer 407 with acryloyl chloride. The synthesis of poloxamer macromer was confirmed using NMR and FTIR spectrometry. The gelation behavior and crystalline structure of poloxamer macromer was similar to those of poloxamer 407 itself; however, the amorphous scattering of poloxamer macromer was higher than that of poloxamer itself. Differential scanning calorimetric analysis showed that the melting temperature and enthalpy of poloxamer hydrogel were also lower than those of poloxamer itself. The compressive modulus of poloxamer hydrogels were similar (92.6–101.7 kPa), regardless of the concentration of poloxamer macromer. Equilibrium water uptake of poloxamer hydrogels decreased with an increase of concentration of poloxamer macromer. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 88: 2670–2676, 2003

INTRODUCTION

Hydrogels are polymeric materials that do not dissolve in water at physiological temperature and pH but swell considerably in aqueous medium.[1] Hydrogels are well-known materials used in applications in various biomedical fields because of their permeability of small molecules, soft consistency, low interfacial tension, facility for purification, and high equilibrium water content, which make them similar to the physical properties of living tissue.[2] Therefore, hydrogels can be applied as biomaterials including artificial skin,[3] blood contact materials,[4] and controlled release for bioactive materials.[5,6]

Poloxamer, a triblock copolymer of poly(ethylene oxide) (PEO)–poly(propylene oxide) (PPO)–PEO, is a typical polymeric surfactant used in the pharmaceutical field for controlled drug release and biomedical field including burn wound covering[7] because of its reversible thermal gelation and extremely low toxicity.[8–10] However, gelation of poloxamer needs high concentration. When the gel is implanted in the body, the gel will be diluted by body fluid and finally becomes sol during implant in the body.

Polymerizable biomaterials used as a matrix for incorporation of other polymers, for instance, lysine and hydroxyethylmethacrylate,[11] poly(lactic acid),[12] poly(ϵ-caprolactone),[13] and silk fibroin,[14] have been investigated as scaffold for tissue engineering in the form of semi-interpenetrating polymer networks.

In this study, polymerizable poloxamer macromer was synthesized by the reaction of poloxamer 407 with acryloyl chloride. A three-dimensional hydrogel was formed by photopolymerization of poloxamer macromer, which could be used as matrix for the scaffold and drug delivery system. The synthesis of poloxamer macromer was confirmed by use of nuclear magnetic resonance (NMR) and FTIR spectrometry. The gelation behavior of poloxamer macromer was examined and the crystalline structure was investigated by use of an X-ray diffractometer. Differential scanning calorimetric (DSC) and compressive mechanical properties of poloxamer hydrogels were measured and the equilibrium water content of poloxamer hydrogels was also examined. The poloxamer macromer used had higher viscosity than that of poly(ethylene glycol) (PEG) macromer and reversible thermal gelation behaviors, although the PEG macromer did not have the gelation property before curing. Therefore, the injectable poloxamer macromer can be used in an intraocular lens without leakage.

Correspondence to: C.-S. Cho (chocs@plaza.snu.ac.kr).
**Present address:* Department of Sericulture and Entomology, National Institute of Agriculture and Technology, Suwon 441-100, South Korea.

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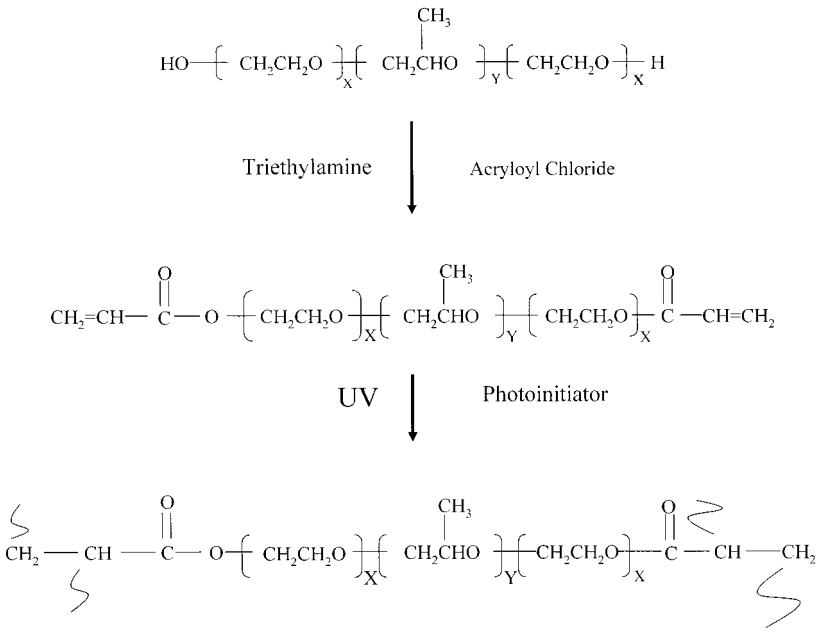

Figure 1 Synthesis scheme of poloxamer hydrogel prepared from poloxamer 407 and acryloyl chloride.

EXPERIMENTAL

Materials

Poloxamer 407, a block copolymer having a molecular weight of 12,600 and a 30 wt % content of PPO, was provided by BASF Korea Inc. (Seoul, Korea) and used without any further purification. Acryloyl chloride (Aldrich, Milwaukee, WI), and triethylamine (Aldrich) were used. All other chemicals used were of reagent grade and were used without further purification.

Synthesis of poloxamer macromer and poloxamer hydrogel

The procedure of poloxamer macromer synthesis is illustrated in Figure 1. Poloxamer, α- and ω-terminated by hydroxyl groups, was end-capped with acrylated groups to form a polymerizable macromer; the synthesis of the poloxamer macromer is as follows. Poloxamer 407 [25.2 g (2 mmol)] was dissolved in 75 mL of benzene in a round-bottom flask. Triethylamine

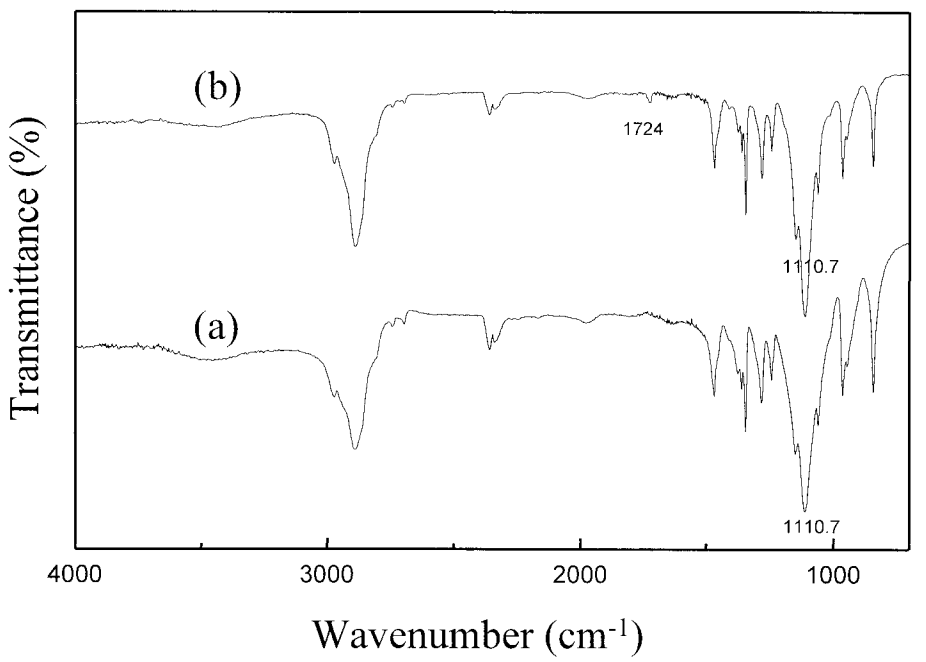

Figure 2 FTIR spectra of (a) poloxamer 407 and (b) poloxamer macromer.

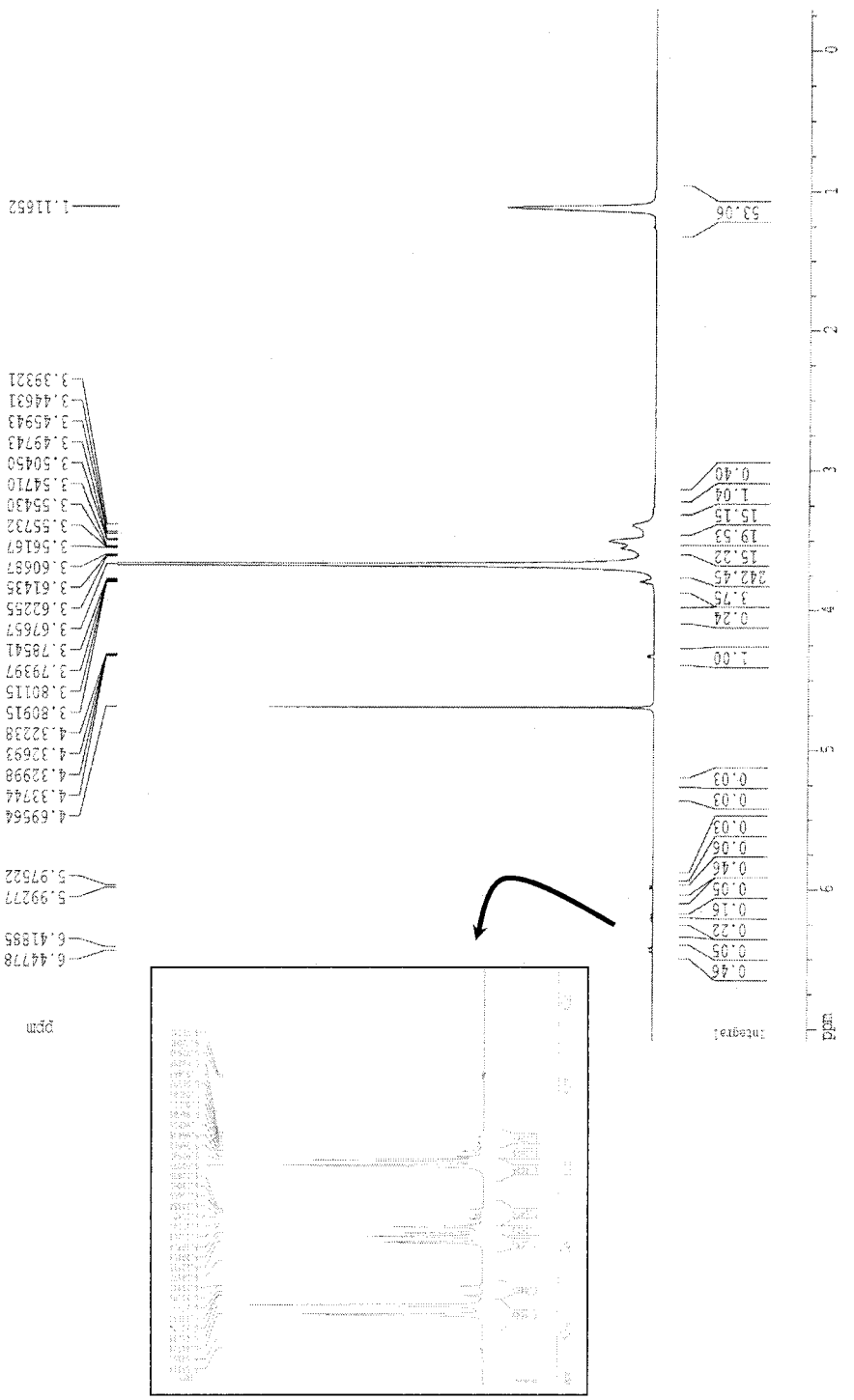

Figure 3 ^{1}H-NMR spectrum of poloxamer macromer.

[0.59 mL (4.23 mmol)] and acryloyl chloride [0.34 mL (4.18 mmol)] were added to the flask, and the reaction mixture was stirred for 3 h at 80°C. The reaction mixture was filtered to remove triethylamine·hydrochloride, and then the macromer was obtained by pouring the filtrate into an excess of *n*-hexane. Finally, it was dried at 40°C under reduced pressure for 24 h.

The poloxamer hydrogel was prepared from poloxamer macromer by the UV polymerization method. Poloxamer macromer was dissolved in distilled water in a cold room maintained at 5°C. Photoinitiator solution (25 μg; 100 mg of 2,2-dimethoxy-2-phenylacetophenone dissolved in 1 mL of *N*-vinyl pyrrolidone) was added to the acrylated poloxamer aqueous solution. The solution mixture was irradiated for 5 min using a low-intensity LWUV lamp (FL 20 LB chemical lamp; wave range, 300–400 nm; maximum intensity, 360 nm; Toshiba, Tokyo, Japan), and the resulting gel was lyophilized.

Measurements

FTIR spectra were obtained by use of a Midac M series spectrometer to confirm the formation of poloxamer macromer and hydrogel. The NMR measurement was performed by use of a 600-MHz high-resolution NMR spectrometer (AVANCE 600; Bruker, Rheinstten, Germany).

The gelation temperature of 1 mL of poloxamer 407 and poloxamer macromer was determined as the temperature at which the sample did not drop or slip from inverted vials.

X-ray diffraction (XRD) analysis was performed by small-angle X-ray scattering with a general area detector diffraction system (GADDS; Bruker-AXS, Karlsruhe, Germany) using Cu–K_α radiation.

The DSC experiment was carried out by use of a DSC 2910 (TA Instruments, New Castle, DE) to measure the melting temperature and enthalphy. The measurement was carried out at a scanning rate of 10°C/min and a nitrogen gas flow rate of 50 mL/min. The melting point was determined at the maximum of the melting endotherm.

The compressive mechanical properties of the poloxamer networks were examined using a Minimat (Rheometric Scientific, New Castle, DE) with circular disc (diameter 6 mm) and a crosshead speed of 1 mm/min. The compressive modulus was calculated as the slope of the initial linear portion of the stress–strain curve. The compressive strength at yield was defined as the intersection of the initial linear line and steep linear line.

To measure water content, preweighed hydrogels were immersed in phosphate buffer (pH 7.4) at 37°C. After the excess surface water was removed with filter paper, the weight of the swollen samples was measured until equilibrium hydration degree was reached. The equilibrium water uptake was calculated according to following equation:

$$\text{Water uptake (\%)} = \frac{(W_s - W_d)}{W_d} \times 100$$

where W_s is the weight of the swollen samples and W_d is the weight of the dry samples.

RESULTS AND DISCUSSION

Synthesis of poloxamer macromer and gel

The poloxamer macromer was synthesized through reaction of poloxamer 407 with acryloyl chloride. The

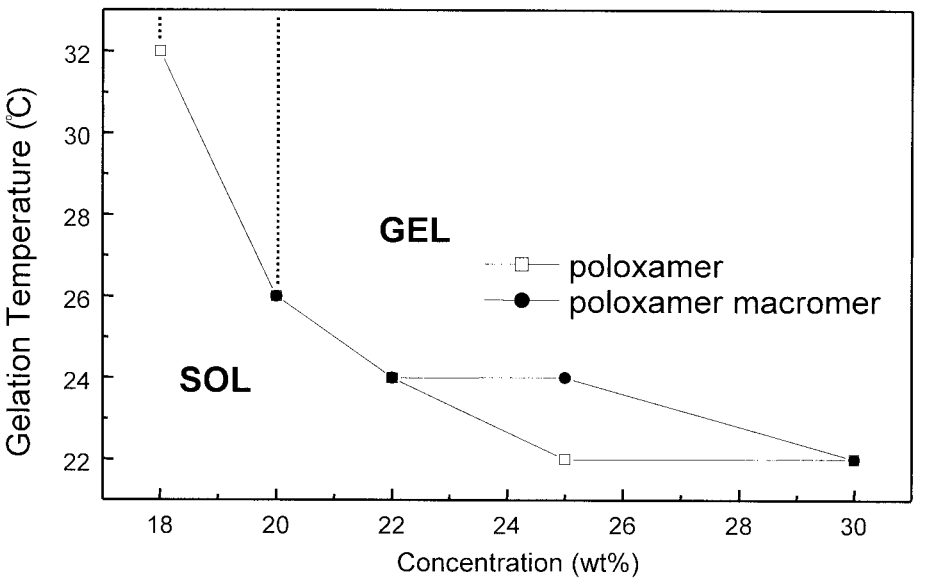

Figure 4 Gelation temperatures of poloxamer and poloxamer macromer according to the concentration.

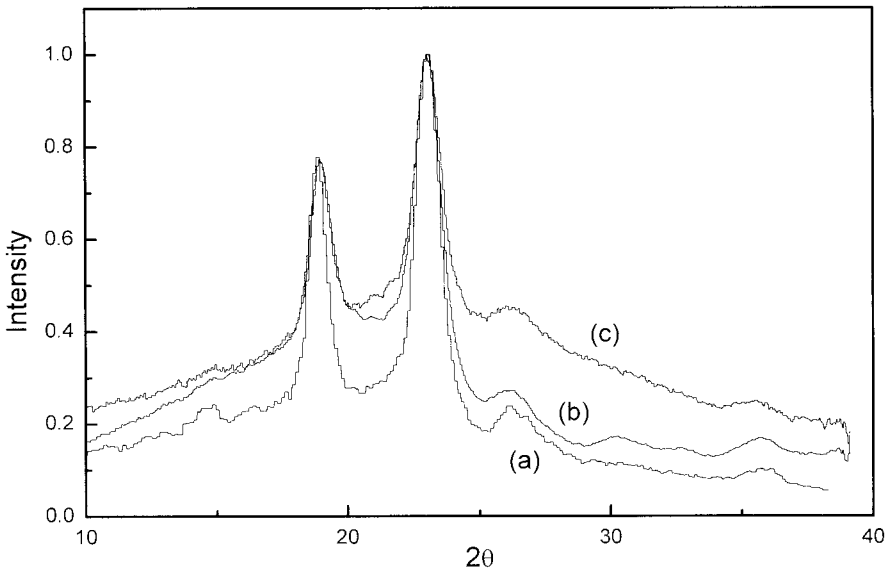

Figure 5 X-ray diffraction patterns of (a) poloxamer, (b) poloxamer hydrogel, and (c) poloxamer macromer.

FTIR spectra of poloxamer and poloxamer macromer are shown in Figure 2. The poloxamer macromer showed a new absorption band at 1724 cm^{-1}, assigned to the C═O stretching band because of acrylation, which was absent in poloxamer 407 itself (Fig. 2). Both poloxamer and the poloxamer macromer showed an absorption band at 1110.7 cm^{-1}, attributed to the characteristic C—O—C stretching band.[15] The formation of poloxamer macromer was confirmed through ^{1}H-NMR spectrometry. As shown in the ^{1}H-NMR spectrum (Fig. 3), protons in the vinyl groups of the poloxamer macromer encapped with acrylate appeared in the δ 5.79–6.43 ppm range.

The terminal hydroxyl groups in poloxamer 407 were subsequently converted to the acrylate groups by a reaction with acryloyl chloride. From measurement of solubility of the poloxamer hydrogel in water after photopolymerization, the substitution degree of the poloxamer macromer was 99.8 wt %.

Gelation

Thermoreversible sol–gel transition is one of the unique characteristics of poloxamer, which depends on the composition and molecular weight of PEO in the poloxamer.[16] To observe the effect of modification on the gelation of poloxamer, the gelation temperatures of poloxamer and poloxamer macromer were examined with respect to the concentration (Fig. 4). The gelation temperature decreased with increasing concentration of poloxamer and poloxamer macromer. Poloxamer macromer showed similar gelation behavior with poloxamer itself, except that 18 wt % of poloxamer macromer could not form a gel because of the modification of terminal OH groups of PEO chains. Gelation of poloxamer is known as a micelle packing and entanglement mechanism.[15] In light of our results, the effect of terminal group modification on the gelation of poloxamer 407 is not significant.

XRD

XRD analysis was used to study crystalline structure, which affects various properties in the solid state. XRD patterns of poloxamer and poloxamer macromer are shown in Figure 5. The poloxamer showed typical diffraction peaks at Bragg angles of 19.2, 23.5, and

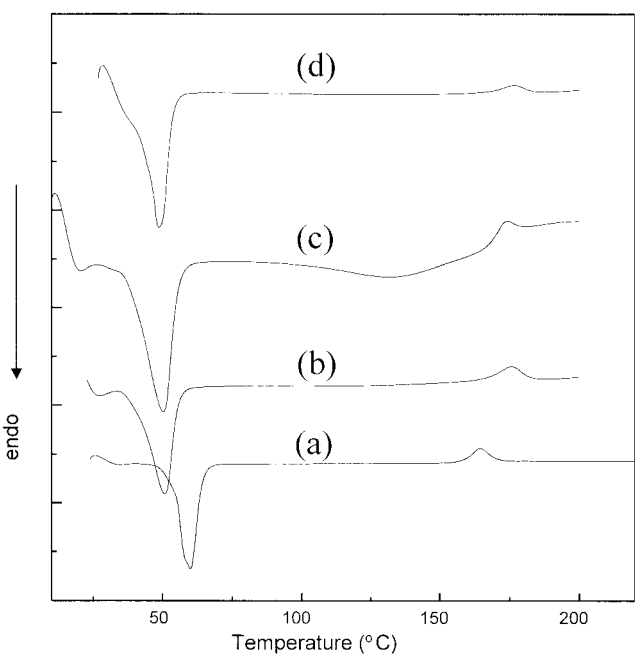

Figure 6 DSC thermograms of (a) poloxamer 407 and poloxamer hydrogel (in wt %): (b) 14, (c) 20, and (d) 22.

TABLE I
Mechanical Properties of Poloxamer Gel After Irradiation According to Concentration of Poloxamer Macromer[a]

Concentration (wt %)	Initial modulus (kPa)
14	92.6 ± 17.5
18	101.7 ± 23.7
22	99.7 ± 16.2

[a] $n = 5$.

26.2°, corresponding to the crystalline spacing of 5.15, 3.78, and 3.40 Å, respectively.[17] Figure 5 shows that the modification of the terminal group did not affect the crystalline spacings of poloxamer but the amorphous scattering of poloxamer was increased as a result of the insertion of bulky acrylate groups into the PEO chains of poloxamer.

Differential scanning calorimetry

Figure 6 shows the DSC thermograms of poloxamer 407 and poloxamer hydrogels. The melting temperature (T_m) of poloxamer hydrogel (50°C) is lower than that of poloxamer 407 itself (60°C) because of the modification of the terminal group. Moreover, poloxamer hydrogels showed lower melting enthalpy (60 J/g) than that of poloxamer 407 (106 J/g) itself. These results are in good agreement with the increase of amorphous scattering of X-ray diffraction analysis.

According to our previous report,[14] the T_m of PEG networks prepared by photopolymerization of PEG macromer was a little lower than that of PEG itself. Because poloxamer is composed of PEO and PPO, the formation of crystallization was restricted by modification of the terminal group.

Mechanical properties

To determine the mechanical performance of poloxamer hydrogel in the wet state, compressive mechanical tests were performed under a constant compression rate. The compressive stress was increased slowly as the force was applied to the samples and then quickly increased after an initial compressive period. The initial compressive moduli of poloxamer hydrogels calculated from the stress–strain curves of compressive mechanical test are shown in Table I. Values of the compressive modulus of poloxamer hydrogels are similar (92.6–101.7 kPa), regardless of the concentration of hydrogels.

Equilibrium water uptake

Equilibrium water contents of poloxamer hydrogels prepared from photopolymerization of poloxamer macromer are shown in Figure 7. Water uptakes of poloxamer hydrogels decreased with increasing concentration of poloxamer macromer as a result of the formation of network structure by photopolymerization and an increase of crosslinking density.

CONCLUSIONS

The formation of a novel poloxamer macromer, synthesized from poloxamer 407 and acryloyl chloride, was confirmed using FTIR and NMR spectrometry. The gelation temperature of the poloxamer macromer

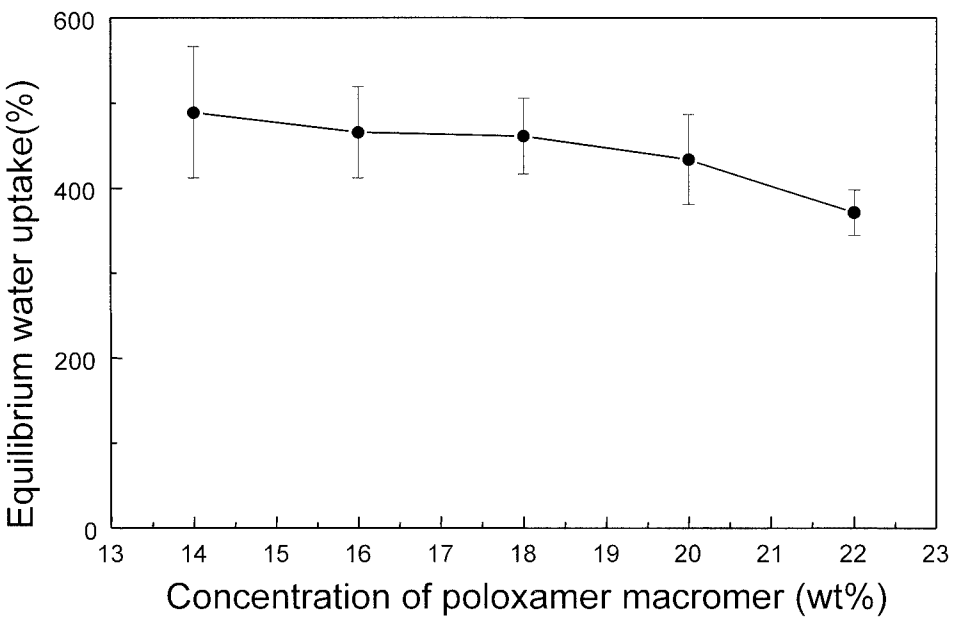

Figure 7 Equilibrium water uptake of poloxamer hydrogels.

was similar to that of poloxamer itself. XRD results showed that the crystalline structure of poloxamer was not affected by the modification of the terminal group but the crystallinity was decreased. This result was also confirmed through DSC, in which melting temperature and enthalpy (50°C, 60 J/g) were lower than those of poloxamer itself (60°C, 106 J/g). The compressive moduli of poloxamer hydrogels were about 100 kPa, regardless of the concentration of hydrogels. However, the equilibrium water content of poloxamer hydrogel decreased with increasing concentration of poloxamer macromer because of an increase of crosslinking density and the formation of network structure by photopolymerization. From the above results, poloxamer hydrogels could be used as a matrix for controlled drug release, intraocular lens, and a scaffold for tissue engineering.

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