Novel Poly(ethylene glycol) Hydrogels from Silylated PEGs

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ABSTRACT: Poly(ethylene glycol) (PEG) and Pluronic® F-127 (PF127) were silylated with 3-isocyanatopropyltriethoxysilane to synthesize PEG-based hydrogels by sol-gel transition of silane. Silanes on different PEG molecules formed covalent bonds by acid-catalyzed hydrolysis and condensation. Addition of monosilylated PEG resulted in the incorporation of dangling PEG chains, which increased the swelling ratio of the hydrogels slightly. PEG hydrogels in microspheres were prepared by emulsifying aqueous silylated PEG solution in oil followed by curing. Crosslinked PF127 hydrogels displayed inverse thermosensitivity. The previously swollen PF127 hydrogels shrank immediately at high temperatures (e.g., 60°C), but the welling of shrunken hydrogels at low temperature (e.g., 5°C) took much longer. The release of fluorescein from the PF127 hydrogels was dependent on the temperature of the environment. The release of fluorescein from the PF127 hydrogels was faster at 45°C than at 5°C. This was most likely due to shrinking of the hydrogels leading to squeezing of the incorporated fluorescein. The ability of hydrogel formation by simple sol-gel transition of silylated PEG can be used to prepare new drug delivery systems and biomaterials.

INTRODUCTION

Poly(ethylene glycol) (PEG) has been known to be highly biocompatible, and for this reason, it has been used extensively in the development of controlled drug delivery systems and biomaterials. PEG-based hydrogels have been prepared by various methods. PEG molecules with polymerizable groups, such as methacryloyl PEG and

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acryloyl PEG, were polymerized in the presence of a crosslinking agent. PEG hydrogels have also been prepared by electron beam irradiation [1,2]. Ionizing radiation generates hydroxy radicals from water by radiolysis. PEG molecules were incorporated into poly(vinyl alcohol) hydrogels by glutaraldehyde after activation using acetic anhydride and diisocyanatohexane [3]. Photoreversible hydrogels were synthesized by photopolymerization of a PEG-based polymer [4]. Branched PEG with four arms was esterificated with cinnamylidene acetyl chloride, and then photodimerized by irradiation at above 300 nm. The crosslinked-PEG hydrogel exhibited phase reversibility with irradiation at 254 nm. In other studies, macromers having a PEG central block, attached with oligomers of α-hydroxy acids such as oligo(*dl*-lactic acid) or oligo(glycolic acid) and terminated with acrylate groups, have been synthesized [5]. The macromers were crosslinked by photopolymerization using nontoxic photoinitiators, such as 2,2-dimethoxy-2-phenylacetophenone and ethyl eosin within a minute.

PEG hydrogels have also been prepared by condensation of silylated PEG or by hydrosilylation of α,ω-diallyl PEG with 2,4,6,8-tetramethyltetrahydrocyclosiloxane [6–8]. Di(methyl-diethoxy) silane PEG was synthesized by the hydrosilylation of telechelic diallyl-PEO with methyldiethoxysilane and further crosslinked by the sol-gel process with a trace amount of acid catalyst [6]. The sol-gel transition of tetraethoxysilane was catalyzed by strong acids (HCl, $HClO_4$, HNO_3, H_2SO_4, *p*-toluene sulfonic acid), weak acids (Cl_3CCOOH, $(COOH)_2$, $ClCH_2COOH$, CH_3COOH, HCOOH), and a base, LiOH [9]. The rate of hydrolysis was dependent on the pH of the solution and not on the chemical structure of the catalyst. However, even a weak acid such as acetic acid catalyzed the sol-gel transition of the silane. Crosslinked silylated PEG hydrogels by polycondensation in the presence of acid catalysts could be useful in various applications since the crosslinking reaction does not require any potentially toxic initiators or a powerful source of irradiation. The focus of this study was to prepare PEG hydrogels from silanated PEGs and a silanated Pluronic® F-127 using a weak acid, such as citric acid. Pluronic® F-127 (PF127) is a triblock copolymer of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) in the form of PEO-PPO-PEO. The number of ethylene oxide units and propylene oxide units in PF127 are 98 and 67, respectively. Since PF127 is known to have inverse thermosensitive properties [10–15], crosslinked PF127 hydrogels also are expected to have the same property. We describe a new approach to synthesize crosslinked PEG hydrogels.

MATERIALS AND METHODS

Materials

PEG (molecular weight of 6000) and mineral oil were obtained from Fluka Chemical Corp. (Milwaukee, WI). Tetrahydrofuran (THF) and citric acid monohydrate were purchased from Mallinckrodt Specialty Chemical Co. (Paris, KY). Fluorescein sodium salt was obtained from Sigma Chemical Co. (St. Louis, MO). Lithium aluminum hydride (LiAlH$_4$), dibutyltin dilaurate, phosphorous pentoxide, monomethoxy poly(ethylene glycol) (m-PEG) (Mw = 5,000), 3-(Trimethylsilyl)-1-propane sulfonic acid sodium salt were purchased from Aldrich Chemical Co. (Milwaukee, WI). Deuterium oxide for NMR spectroscopy was obtained from Cambridge Isotope Laboratories (Woburn, MA). Pluronic® F-127 (PF127, Mw = 13,000) was obtained from BASF Corporation (Parsippany, NJ). For silylation, PEG and PF127 were dried by azeotropic distillation using benzene. THF was purified by refluxing with lithium aluminum hydride overnight and distilling from LiAlH$_4$ to remove water and impurities. Distilled anhydrous THF was kept in a storage flask and used within three days. Other chemicals were used without further purification.

Silylation of PEG and PF127

Forty grams of polymer was dissolved in 250 mL of benzene. Then 100 mL were distilled off to remove water from the polymer by forming an azeotropic mixture. The residual benzene was further distilled out under reduced pressure. As shown in Figure 1, PEG and PF127 were silylated with 3-isocyanatopropyltriethoxysilane (IPTS) in the presence of dibutyltin dilaurate as a catalyst.

A polymer solution (40 g in 400 mL of THF) was prepared in 1,000 mL three-necked, round-bottomed flask under dry nitrogen. IPTS and dibutyltin dilaurate, a catalyst, were added to the polymer solution. The molar ratios of IPTS and dibutyltin dilaurate to polymer (PEG 6,000 and PF127) were 10 and 0.2, respectively (for the silylation of m-PEG, the ratios were 5 and 0.1, respectively). After adding the reactants, the mixture was stirred continuously for 48 h under dry nitrogen. After the reaction, silylated polymer was precipitated from THF with hexane twice, and dried in vacuo.

Elemental Analysis

Calculated for disilylated PEG (Mw = 6000) (C$_{292}$H$_{588}$N$_2$O$_{145}$Si$_2$): C, 53.92; H, 9.11; N, 0.43; Si, 0.86. Found: C, 53.72; H, 8.94; N, 0.46; Si, 1.23.

HO-(CH$_2$CH$_2$O)$_n$-CH$_2$CH$_2$-OH
PEG

CH$_3$O-(CH$_2$CH$_2$O)$_n$-H   +   OCN-CH$_2$CH$_2$CH$_2$Si(OCH$_2$CH$_3$)$_3$
m-PEG   IPTS

HO-(CH$_2$CH$_2$O)$_n$-(CH$_2$CH-O)$_m$-(CH$_2$CH$_2$O)$_n$-H
Pluronic F-127

Dibutyltin dilaurate
Anhydrous THF

CH$_3$O-(CH$_2$CH$_2$O)$_{n-1}$-CH$_2$CH$_2$-OC(O)NH-R
Silylated m-PEG

R-NHC(O)O-(CH$_2$CH$_2$O)$_n$-CH$_2$CH$_2$-OC(O)NH-R
Disilyl PEG

or   R-NHC(O)O-(CH$_2$CH$_2$O)$_n$-(CH$_2$CH-O)$_m$-(CH$_2$CH$_2$O)$_n$-C(O)NH-R
Disilyl Pluronic F-127

R= -CH$_2$CH$_2$CH$_2$Si(OCH$_2$CH$_3$)$_3$

Figure 1. Synthetic reaction scheme of silylated PEG and silylated PF 127.

Calculated for silylated m-PEG (Mw = 5,000) (C$_{239}$H$_{481}$N$_1$O$_{119}$Si$_1$): C, 54.15; H, 9.14; N, 0.26; Si, 0.53. Found: C, 54.18; H, 9.26; N, 0.24; Si, 0.50.

Calculated for disilylated Puronic® F-127 (C$_{615}$H$_{1234}$N$_2$O$_{273}$Si$_2$): C, 56.46; H, 9.51; N, 0.21; Si, 0.43. Found: C, 56.24; H, 9.50; N, 0.22; Si, 0.69.

Preparation of Silanated PEG Hydrogels

One gram of polymer or polymer mixtures was dissolved in 10 mL of deionized distilled water (DDW) and 50% ethanol for making hydrogels from disilylated PEG and PF127, respectively. In the case of disilylated PEG hydrogels, the weight ratio of monosilylated PEG (Mw 5000) to disilylated PEG (Mw 6000) was varied from 0:10 to 8:2. After dissolving polymers or polymer mixtures in solvents, 10 w/w% citric acid monohydrate was added. When HCl was used as an acid catalyst, the pH of the polymer solution was adjusted to pH 2.0 with 0.2N HCl. After mixing the solution for 10 min using a vortex mixer (Model S8223-1, Scientific Products, McGaw Park, IL), the polymer solution was mixed further by sonication for 10 min in a sonicator (Model FS110, Fisher Scientific, Pittsburgh, PA). Polymer solutions were transferred into polystyrene Petri dishes (60 × 15 mm, Scientific Product, MaGaw Park, PA) and left

overnight to allow solvent evaporation. After peeling off polymer films from Petri dishes, they were washed several times with double distilled water (DDW) to remove unreacted polymers and acid catalysts. The swollen hydrogels were dried overnight in a vacuum oven at room temperature.

Characterization of Disilyl PEG Condensation Using Proton NMR

One tenth gram of disilylated PEG and 0.001 g of 3-(trimethyl-silyl)-1-propane sulfonic acid sodium salt as an internal standard were dissolved in 1 mL of deuterium oxide. A sample for NMR experiment was prepared by adding 0.01 g of citric acid monohydrate as the acid catalyst into polymer solution. The control was prepared by the same procedure only without the acid catalyst. NMR spectra of the control and a sample were recorded with Bruker ARX 300 spectrometer 30 min before and after gelation.

Swelling Kinetics of Disilyl PEG Hydrogels

Swelling ratios of disilylated PEG hydrogels were determined by the gravimetric method. Briefly, dried disilyl PEG hydrogels were cut into a size of about 12 mm × 12 mm and transferred into 30 mL of DDW. The weights of swollen PEG hydrogels were measured at timed intervals. Weights of swelling hydrogels and dry hydrogels were used to determine the swelling ratios using the following equation:

$$\text{Swelling Ratio} = (W - W_o)/W_o$$

where W is the weight of swelling hydrogel and W_o is the weight of a dried hydrogel.

Characterization PEG Microspheres by Atomic Force Microscopy

A 100 mL round-bottomed beaker with a water jacket was charged with 70 mL of heavy mineral oil and 0.2 g of Span 80 (HLB 4.3). After mixing for 10 min at 4000 rpm with a mechanical stirrer (G. K. Heller Corp. Floral Park, NY) equipped with an impeller-type blade, the polymer solution containing citric acid monohydrate was added into the beaker using a disposable glass pipette. After adding the disilylated PEG solution, the mixture was stirred overnight at 7000 rpm. Cured PEG

microparticles were washed consecutively with ethyl-acetate, ethyl-acetate:diethyl ether (1:1), ethyl acetate:diethyl ether (1:2), and diethyl ether. After washing microspheres with diethyl ether twice, PEG microparticles were collected by filtration and dried overnight in a vacuum oven at room temperature.

Dried PEG microspheres were mounted on a steel support, and visualized by an atomic force microscope (Nanoscope III; Digital Instrument, Santa Barbara, CA). Images were obtained by scanning the surface for 10 min in a tapping mode using a single crystal silicon probe (model TESP).

Thermoreversible Swelling of PF127 Hydrogel

A PF127 hydrogel was cut into a size of 12 mm × 12 mm. Three films were put into 100 mL DDW and equilibrated for a day. Fully swollen PEG hydrogel was transferred into 100 mL of DDW previously adjusted to 60°C. The weight of the hydrogel was measured as the hydrogel shrank with time. When the weight of shrinking hydrogel didn't change further, the hydrogel was transferred into 100 mL of DDW previously adjusted to 5°C. The weight of a swelling hydrogel was measured at specific time intervals.

Thermosensitivity of PF127 Hydrogels

In preparation of PF127 hydrogels incorporating silanated PEG, the weight ratio of disilyl PF127 to silylated m-PEG (Mw = 5000) was varied from 10:0 to 6:4. Dried PF127 hydrogels were put into beakers containing 100 mL of water at 5°C, 25°C, 40°C, and 50°C. After equilibrating for 2 h at each temperature, PF127 hydrogels were taken out and weighed to calculate the swelling ratios.

Thermosensitive Release of Fluorescein from PF127 Hydrogel

PF127 hydrogels containing 10 (w/w)% of fluorescein sodium salt were prepared in a film form. Hydrogel films were cut into a size of 12 mm × 12 mm and put into 500 mL of 0.2 M phosphate buffered saline (PBS). Three milliliters of sample was taken from the release test medium with time. Absorbance of a sample at each time point was recorded at 444 nm by Beckman DU-7 Spectrophotometer (Palo Alto, CA). A calibration curve was obtained using fluorescein solutions of different concentrations ranging from 2.0 mg/mL to 12.0 mg/mL in PBS.

RESULTS

Synthesis of Silylated Polymers

PEG and PF127 were successfully silylated by coupling IPTS to the end hydroxyl groups through urethane bonds. Figure 2 shows ^{1}H NMR spectra of silylated PEG with molecular weight of 6,000 (disilylated PEG-6000) and silylated PF127. Some characteristic NMR peaks were observed from the NMR spectra. At 4.1 ppm, a triplet showed up after the reaction, which was assigned as a proton peak of O–CH$_2$ of a urethane bond (–OC(O)NH–). A broad peak appeared at 5.0 ppm which was assigned as the NH peak of a urethane linkage. Because of the IPTS coupling to end the hydroxyl groups, silane proton peaks appeared at 0.55 ppm (–CH$_2$Si), 1.16 ppm (–Si(OCH$_2$CH$_3$)$_3$), 1.55 ppm (–CH$_2$CH$_2$Si), and 3.72 ppm (–Si(OCH$_2$CH$_3$)$_3$)
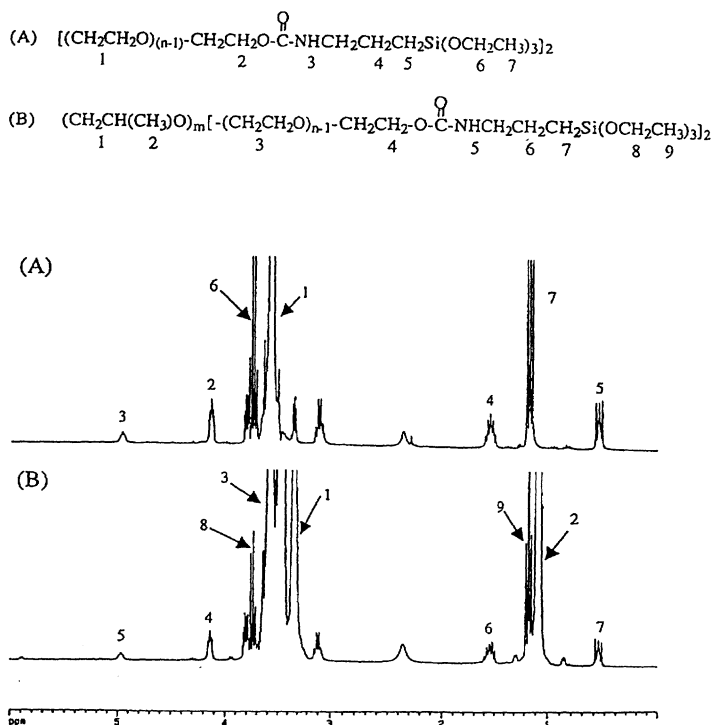
Figure 2. ^{1}H NMR spectra of disilylated PEG 6000 (A) and disilylated PF 127 (B) in CDCl$_3$.

[Figure 2(A)]. In the spectrum of silylated PF127, two proton peaks from PF127 appeared at 1.1 ppm and 3.35 ppm [Figure 2(B)].

Condensation of Disilyl PEG

Shown in Figure 3 is NMR spectra of disilyl PEG (Mw = 6000) solution with and without citric acid. The addition of citric acid shifted $-CH_2CH_2\underline{CH_2}Si(OCH_2CH_3)_3$ proton peak (triplet) from 0.73 to 0.63 ppm, $-CH_2CH_2CH_2Si(OCH_2\underline{CH_3})_3$ proton peak (triplet) from 1.23 to 1.17 ppm, $-CH_2CH_2CH_2Si(O\underline{CH_2}CH_3)_3$ proton peak (quartet) from 3.90 to 3.63 ppm [Figure 3(A) and (B)]. The NMR spectrum of the hydrogels formed by citric acid in Figure 3(C) was the same as Figure 3(B). Upfield shifts of the proton peaks exhibited the hydrolysis of disilylated PEG, since the hydrolysis of the silane released ethanol as shown in Figure 4. Proton peaks of the released ethanol appeared upfields in comparison with the ethoxy protons of the silane because hydrogen was more electropositive than $-CH_2CH_2\underline{CH_2}Si(OCH_2CH_3)_2-$ group. After gelation, the proton
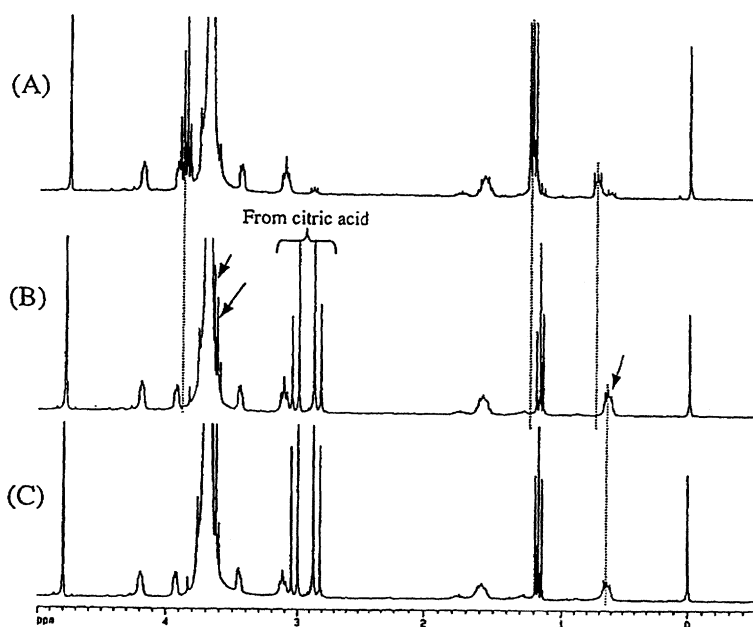
Figure 3. ^{1}H NMR spectra of disilylated PEG in D_2O without citric acid (A), with citric acid (B), and after gelation with citric acid (C).

$$n \; \text{-CH}_2\text{CH}_2\text{CH}_2\overset{\displaystyle \text{OCH}_2\text{CH}_3}{\underset{\displaystyle \text{OCH}_2\text{CH}_3}{\text{Si}}}\text{-OCH}_2\text{CH}_3 \;\; + \;\; \text{H}_2\text{O}$$

$$\Updownarrow \text{H}^+$$

$$\begin{array}{l}
\text{-CH}_2\text{CH}_2\text{CH}_2\overset{|}{\underset{|}{\text{Si}}}\text{-O-}\overset{|}{\underset{|}{\text{Si}}}\text{CH}_2\text{CH}_2\text{CH}_2\text{-} \\
\qquad\qquad\quad\text{O}\qquad\text{O} \\
\text{-CH}_2\text{CH}_2\text{CH}_2\overset{|}{\underset{|}{\text{Si}}}\text{-O-}\overset{|}{\underset{|}{\text{Si}}}\text{CH}_2\text{CH}_2\text{CH}_2\text{-}\qquad + \quad 3n\;\text{CH}_3\text{CH}_2\text{OH} \\
\qquad\qquad\quad\text{O}\qquad\text{O} \\
\text{-CH}_2\text{CH}_2\text{CH}_2\overset{|}{\underset{|}{\text{Si}}}\text{-O-}\overset{|}{\underset{|}{\text{Si}}}\text{CH}_2\text{CH}_2\text{CH}_2\text{-}
\end{array}$$
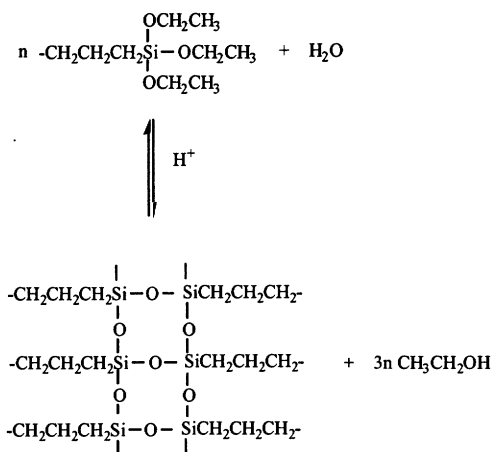
Figure 4. Schematic representation of silane condensation.

NMR spectrum of the sample did not change from that of hydrolyzed disilylated PEG, which may indicate the formation of hydrogel by weak interaction such as hydrogen bonds between silanols. The formation of a fragile hydrogel strongly indicated the participation of silanols by the gelation of hydrolyzed silanated PEGs. For covalent bonds between silanes, removal of ethanol and water is required.

Swelling Kinetics of Disilylated PEG Hydrogels

Shown in Figure 5 are swelling kinetics of disilylated PEG hydrogels prepared in the presence of HCl. As the amount of silylated m-PEG-5000 in the hydrogel increased from 50% to 80%, the equilibrium swelling ratio increased from 6.0 to 10.7, respectively. When the ratio of disilylated PEG and silylated m-PEG-5000 changed from 5:5 to 4:6 and from 4:6 to 3:7, the equilibrium swelling ratio increased from 6.0 to 6.9 and from 6.9 to 7.6, respectively. The more silylated m-PEG-5000 in the hydrogel displayed more equilibrium swelling, since free PEG chains allowed more excluded volume than crosslinked PEG chains by greater flexibility. The thickness of the PEG hydrogel film ranged from 0.3 to 0.5 mm. All films reached the plateau swelling ratio within 30 min after the hydrogels started to swell.

The swelling kinetics of disilylated PEG hydrogels prepared by citric acid-catalyzed condensation is shown in Figure 6. The PEG hydrogels from citric acid-catalyzed silane also showed an enhanced equilibrium swelling ratio with increasing amounts of silylated m-PEG-5000. When
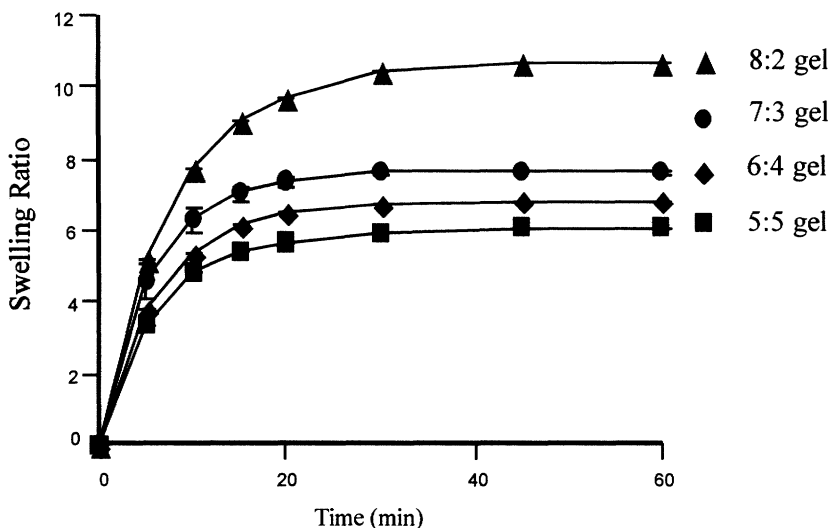
Figure 5. Swelling kinetics of disilylated PEG hydrogels. The hydrogel was prepared by silane condensation with HCl. The amount of silylated m-PEG-5000 was increased from 50 to 80 w% of total polymer. As the amount of silanated PEG-5000 increased, the swelling ratio of the hydrogel increased from 6.0 to 10.7.
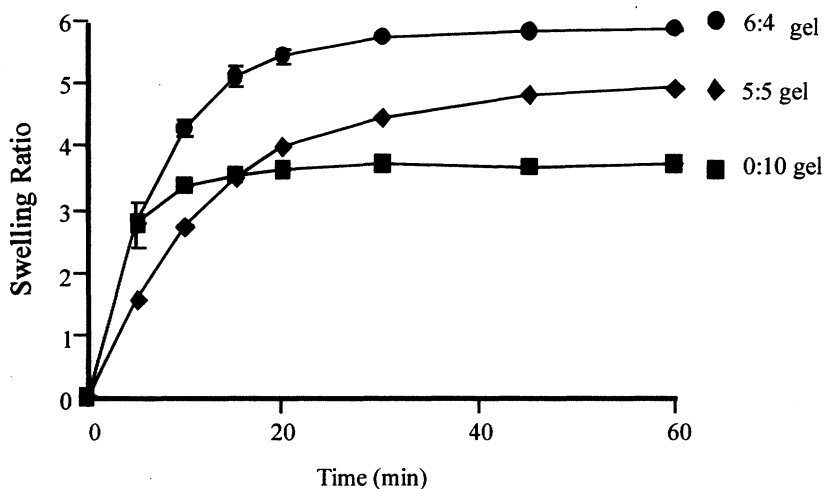

Figure 6. Swelling kinetics of disilylated PEG hydrogels. The hydrogel was prepared by silane condensation with citric acid. The amount of silylated m-PEG-5000 was increased from 0 to 60 w% of total polymer. As the amount of silanated PEG I-5000 increased, the swelling ratio of the hydrogel increased from 3.7 to 5.9.

a PEG hydrogel are prepared only with disilylated PEG, the equilibrium swelling ratio was 3.7. An increase in the silanated PEG I-5000 from 0 % to 50% and 60%, caused the equilibrium swelling ratio of the hydrogel to increase from 3.7 to 4.9 and 5.9, respectively. The PEG hydrogel prepared by citric acid-catalyzed condensation also reached swelling ratio plateau within 30 min after the hydrogel began swelling. The difference in acid catalyst for silane condensation did not cause substantial difference in swelling kinetics or the swelling ratio of the PEG hydrogel.

Preparation of PEG Microspheres

Condensation of disilylated PEG by citric acid resulted in PEG microspheres. Shown in Figure 7 are AFM images of PEG microspheres. The shapes of crosslinked PEG particles were spherical and an estimated size ranged from 2 to 5 µm [Figure 7(A)]. The surfaces of microspheres were rather rough [Figure 7(B)]. Washing with diethyl ether, an anti-solvent for PEG, causes fast precipitation of PEG chains on the surface resulting in rough surface topography.

## Thermoreversible Swelling of PF127 Hydrogel

PF127 undergoes thermoreversible gelation at concentrations higher than 20 w/v% in water [10,12]. The PF127 is fluid at 4°C, but are highly viscous gels at room temperature and above. The PF127 hydrogel obtained by citric acid-catalyzed silane condensation displayed repetitive thermoreversibility (Figure 8). The thickness of the crosslinked PF127 hydrogel ranged from 0.3 to 0.5 mm. At 60°C the crosslinked PF127 hydrogel shrank immediately and reached the minimum swelling ratio within 30 min. The swelling ratio decreased from 6.1 to 1.8 within 30 min at 60°C. When the temperature was changed to 5°C, the hydrogel started swelling again. The swelling process was slower than the shrinking process. After 2 h at 4°C, the swelling ratio was 5.9, which was almost the same as the original value. Repetitive temperature changes displayed cycles of swelling and shrinking of the crosslinked PF127 hydrogel. The thermoreversible swelling of the crosslinked PF127 hydrogel is a result of the thermosensitivity of PF127. In cold water PF127 displays higher solubility than in hot water since the polymer experienced extensive hydrogen bonding between water molecules and ethereal oxygen of PF127. On the other hand, the solubility of the polymer decreased with increases in temperature since breakage of hydrogen bond caused less extensive hydration.

(A)

(B)
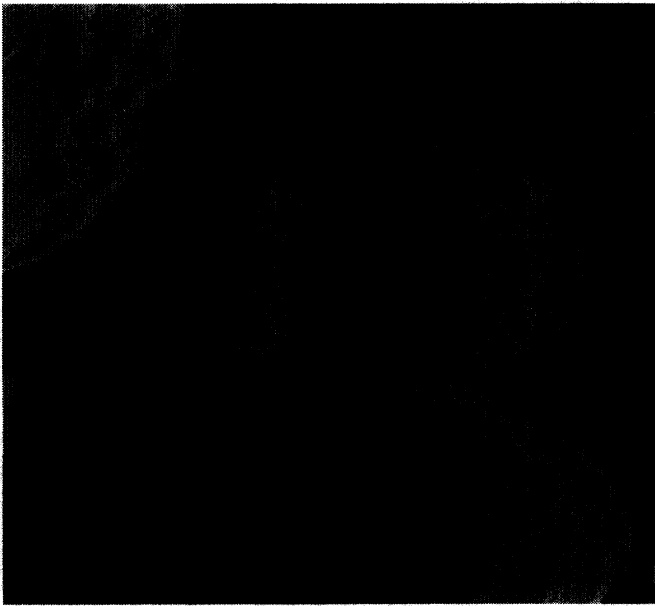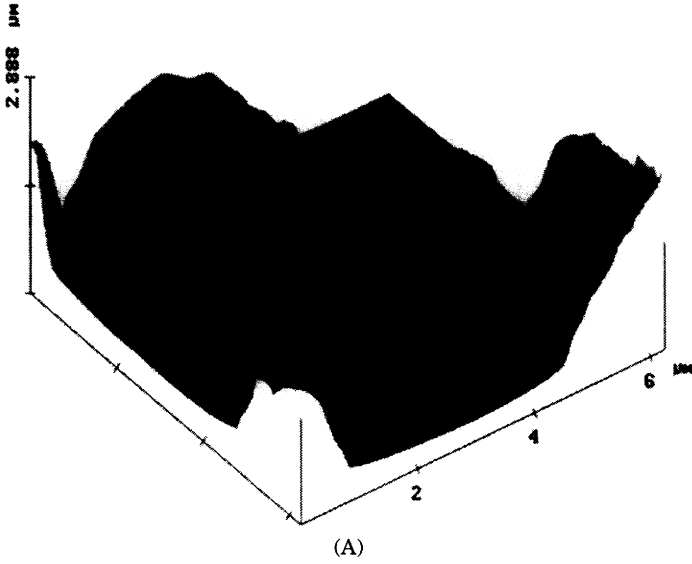
Figure 7. Three-dimensional (A) and two-dimensional (B) images of PEG microspheres obtained by atomic force microscopy.
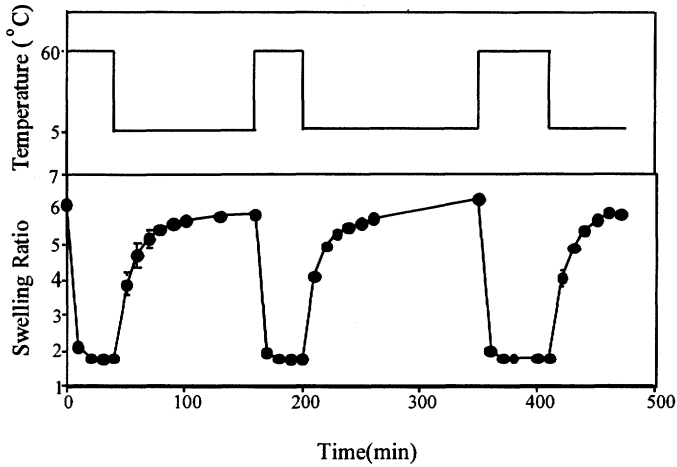
Figure 8. Thermoreversible swelling of the crosslinked PF127 hydrogel. The swelling and deswelling cycle of crosslinked PF127 hydrogel was repeated by alternating the temperature between 5°C to 60°C.
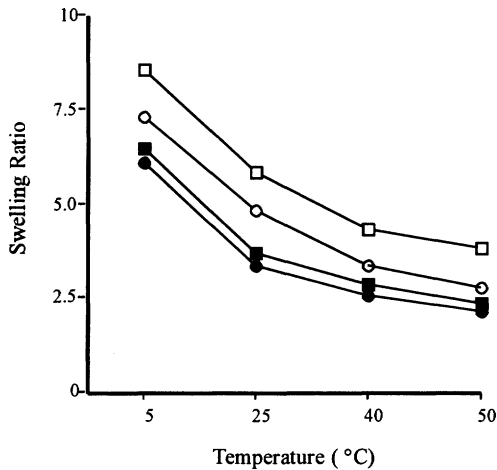
Figure 9. The inverse thermosensitivity of the crosslinked PF127 hydrogel was observed as the temperature was increased from 5°C to 50°C. The weight ratios of disilylated PF127 to silylated m-PEG-500 were 10:0 (●), 9:1 (■), 8:2 (○), and 6:4 (□).

Thermosensitivity of Crosslinked PF127 Hydrogel

Shown in Figure 9 is thermosensitivity of the crosslinked PF127 hydrogel. The ratio between disilylated PF127 and silylated m-PEG-5000 was varied from 10:0 to 6:4. The crosslinked PF127 hydrogel with the 10:0 ratio shrank when temperature increased from 5°C to 50°C. With an increase in temperature from 5°C to 25°C, the swelling ratio of the hydrogel decreased from 6.1 to 3.4. As the temperature increased to 40°C and 50°C, the swelling ratio of the hydrogel decreased more gradually to 2.5 and 2.1, respectively. With the incorporation of silylated m-PEG-5000 into the hydrogel, overall swelling ratio at each temperature was increased, while the transition of swelling ratio with temperature was not changed. As the amount of silylated m-PEG-5000 increased from 0 to 10, 20, and 40 w% of total polymer weight, the swelling ratios at 5°C increased from 6.1 to 6.5, 7.3, and 8.6, respectively. Similarly, swelling ratios at 50°C increased from 2.1 to 2.3, 2.8, and 3.8, respectively. An increase in hydrophilicity of the hydrogel by incorporation of monosilylated PEG only increased the overall swelling ratios without changing the thermal transition behavior of the crosslinked PF127 hydrogel. The crosslinked PF127 hydrogel reflected a thermal gelation of PF127 with increase in temperature.
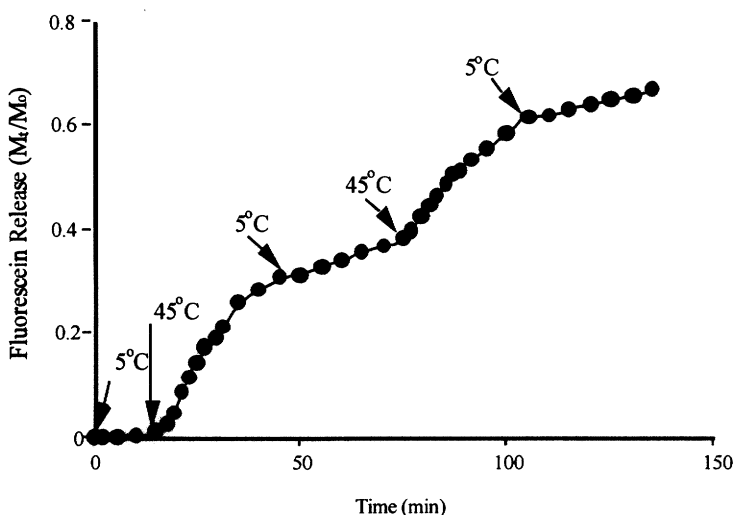
Figure 10. Pulsatile release of fluorescein from the crosslinked PF127 hydrogel in response to temperature changes between 5°C and 45°C.

Thermosensitive Release of Fluorescein from PF127 Hydrogel

Crosslinked PF127 hydrogels released incorporated sodium fluorescein in response to changes in the environmental temperature. Figure 10 displays thermosensitive release of fluorescein from the hydrogel with repetitive temperature changes. At 5°C, the hydrogel released fluorescein slowly since fluorescein had to diffuse a longer distance than at the higher temperatures. When temperature was changed from 5°to 45°C, the release of fluorescein from the crosslinked PF127 hydrogel increased immediately since fluorescein was squeezed from the hydrogel by the shrinking hydrogel. Repetitive temperature changes displayed cycles of slow and fast release of fluorescein from the crosslinked hydrogel.

DISCUSSION

The sol-gel transition of silylated polymers allows easy preparation of PEG-based hydrogels [16]. Silylated PEGs are crosslinked by condensation of end silanes as shown in Figure 4. Silanes at both ends of PEG were hydrolyzed by acid catalysis and released alcohol. After hydrolysis, silanols formed hydrogen bonds with each other and experienced condensation [9,17,18]. Removal of water and ethanol could favor condensation of silane. Various polymers with functional groups such as poly(vinyl alcohol) and poly(propylene glycol) can be crosslinked by water and acid catalysts. Even biodegradable polymers, such as poly(DL-lactide), poly(glycolide), and polycaprolacton]e diols, can be silylated either by chemical coupling of silanes or by hydrosilylation. Silylated degradable polymers should be useful for the preparation of various drug delivery systems for proteins or vaccines since they can be simply crosslinked by weak acids such as citric acid and acetic acid. The easy and safe crosslinking method can find many applications in biomedical sciences, such as in the development of controlled drug delivery systems and environment-sensitive biomaterials.

PEG hydrogels were successfully prepared from disilylated PEG or disilylated PEG copolymer. Silanated PEG derivatives can be used to prepare PEG hydrogels in various sizes and shapes, such as microspheres and films. The silanated PEG hydrogels prepared in this study did not swell much, but silanated PEGs with silanes of one or two hydrolyzable groups provided highly swellable PEG hydrogels. Disilylated PEG 6000 used in this study had six hydrolyzable groups since 3-isocyanatopropyltriethoxysilane is trivalent for condensation. Six crosslinkable groups of the PEG provided highly crosslinked polymer hydrogels, thus low swelling

hydrogels. Possible silanes for the preparation of highly swellable PEG hydrogels are 3-aminopropyldimethylethoxysilane, 3-aminopropyl-methyldiethoxysilane, N-(2-aminoethyl)-3-aminopropylmethyldimethoxy silane. Silylated PEGs for PEG hydrogels can be prepared by hydrosilylation of diallyl PEG with silanes such as dimethylethoxysilane and methyldiethoxysilane [6]. Silylated PEGs with less hydrolyzable groups can decrease the crosslinking density of PEG hydrogels, thus increase the swelling ratio. Free PEG chains were easily incorporated into the PEG hydrogels with a slight increase in swelling ratios of the hydrogels by using silylated m-PEG-5000. Incorporation of free PEG can provide steric repulsion to the hydrogel by the free flexible PEG chains, thus improve the biocompatibility of the hydrogel.

Crosslinked PF127 hydrogel from the silylated PEG copolymer displayed an inverse thermosensitivity. With various Pluronics® of different gelation temperature, thermoreversible hydrogels of different thermal transitions can be prepared by the simple sol-gel process. Crosslinked Pluronic® hydrogels could be useful for the controlled release of biologically active compounds responding to temperature changes.

Silylated PEGs can also be prepared as partially crosslinked PEG hydrogels either by aging through moisture adsorption or by controlled crosslinking in the presence of acid catalysts. The partially crosslinked PEG can find important applications in the pharmaceutical industry as an excipient for the drug formulation since PEG has showed very useful properties in pharmaceutical processes such as good wettability and lubricity. High lubricity of PEG could make it possible for partially crosslinked PEG to find applications as a disintegrant or filler for direct compression in the preparation of tablets containing water-sensitive drugs.

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