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Injectable gel: Poly(ethylene glycol)–sebacic acid polyester

Jisun Lee, Min Kyung Joo, Hejin Oh, Youn Soo Sohn, Byeongmoon Jeong *

Division of Nano Sciences, Department of Chemistry, Ewha Womans University, 11-1 Daehyun-Dong, Seodaemun-Ku, Seoul 120-750, South Korea

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Abstract

In order to develop an injectable material for drug delivery that has both formulation advantages of a sol-to-gel transition system and minimal burst release of a drug, a soft thermogel of poly(ethylene glycol)–sebacic acid polyester was synthesized. The polymer aqueous solution (25 wt%) undergoes 'clear sol-to-gel' transition as the temperature increases from 5 to 65 °C. The drug can be mixed in a low viscous sol state at low temperature (< 15 °C). In particular, the thermogel is soft enough to be injected through a 21-gauge syringe needle even as a gel state. The model hydrophilic drug, FITC–dextran (molecular weight: 40,000 Da), was released from the gel over 24 h. The biodegradable poly(ethylene glycol)–sebacic acid polyester soft thermogel is believed to be promising for the hydrophilic drug delivery where an initial burst of a drug might be a concern.

Keywords: Sol–gel transition; Biodegradable polymer; Drug delivery

1. Introduction

An in situ gel-forming polymer has recently been drawing attention as a promising material for minimally invasive therapy [1,2]. Such a system enables pharmaceutical agents or cells to be easily entrapped and form a depot by a simple syringe injection at a target site, where the depot acts as a sustained drug delivery system, or a cell-growing matrix to produce the tissue. In particular, a thermogelling polymer of which the aqueous solution is a sol at room temperature or lower, and forms a gel at body temperature (37 °C) has been suggested for the delivery of cells or biopharmaceuticals that are susceptible to heat or organic solvent [3–5]. The currently reported thermogelling systems are poly(ethylene glycol)/poly(propylene glycol) triblock copolymer (Poloxamer®) [6], poly(ethylene glycol)/poly(butylene glycol) di- and tri-block copolymers [7], poly(ethylene glycol)/poly(lactic acid-*co*-glycolic acid) triblock and graft copolymers [8,9], poly(ethylene glycol)/poly(propylene fumarate) [10], chitosan/glycerol phosphate [11], polyphosphazene [12], and poly(ethylene glycol)/poly(caprolactone) triblock copolymers [13,14].

A soft gel that is injectable even as a gel state may be a choice for a hydrophilic drug because the thermogelling system suffers from an initial burst of the hydrophilic drug unless the sol-to-gel transition temperature is low enough to ensure a fast sol-to-gel transition during the subcutaneous injection of a drug formulation. However, the polymer with a low sol-to-gel transition temperature tends to be an uninjectable gel unless the formulation temperature is low enough to keep the sol state. The modulus of the above thermogelling polymers varies from 100 to 10,000 Pa in the gel state, depending on the concentration of the polymer. A gel cannot be formed in water below a critical gel concentration due to the lack of physical junctions. This fact limits the low value of a gel modulus by the above thermogelling polymers.

We designed a poly(ethylene glycol) (PEG) connected by sebacic esters (SA) of which the aqueous polymer solution is expected to undergo sol-to-gel transition as the temperature increases. The polymer consists of the flexible methylene units of SA and hydrophilic PEG. Therefore, the polymer is expected to be mixed with a drug in the sol state, followed by forming a soft gel that can be injected even as a gel. And, we investigated the release of a hydrophilic model drug, dextran, from the gel. The final degradation products of poly(ethylene glycol)–sebacic acid polyester (PEG–SA) are PEG and sebacic acid. Sebacic acid is clinically used for a polyanhydride component for the anticancer treatment and PEG is a well-known biocompatible hydrophilic polymer [15]. The hydrophilic/hydrophobic balance of the PEG–SA is a key factor in

* Corresponding author. Tel.: +82 2 3277 3411; fax: +82 2 3277 3419.
E-mail address: bjeong@ewha.ac.kr (B. Jeong).

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determining thermosensitive sol–gel transition at a desired temperature. It is expected to be controlled by varying the molecular weight of PEG and the composition of PEG–SA.

2. Experimental section

2.1. Materials

Poly(ethylene glycol) (M_W = 400, 600, and 900), 1,6-diphenyl-1,3,5-hexatriene, sebacoyl chloride, and anhydrous toluene were used as received from Aldrich. Triethyl amine (Aldrich) was dried over potassium hydroxide. FITC–dextran (M_W = 40,000) was purchased from Sigma and was used as received.

2.2. Synthesis

PEG–SA was synthesized by simple condensation polymerization. To synthesize the PEG–SA (PII in the Table 1), the poly(ethylene glycol) (6.01 g, 10.02 mmol, M_W = 600) was dissolved in anhydrous toluene (80 mL), and the solvent was distilled off to a final volume of 30 mL to remove the residual water adsorbed to the polymer. Sebacoyl chloride (2.39 g, 10.0 mmol) and triethyl amine (2.79 mL, 20.0 mmol) were added to the reaction mixture, and stirred at 25 °C for 18 h. The product was isolated by precipitation into diethyl ether. The polymer was dissolved in methylene chloride and fractionally precipitated by slowly adding diethyl ether and the residual solvent was removed under vacuum. The final yield was 60%.

^{1}H NMR ($CDCl_3$) of PEG–SA: δ 1.2 (–OOCCH$_2$CH$_2$CH$_2$-*CH$_2$CH$_2$*CH$_2$CH$_2$CH$_2$COO–), δ 1.6 (–OOCCH$_2$CH$_2$*CH$_2$*CH$_2$-CH$_2$*CH$_2$*CH$_2$CH$_2$COO–), δ 1.8 (–OOCCH$_2$*CH$_2$*CH$_2$CH$_2$CH$_2$ CH$_2$*CH$_2$*CH$_2$COO–), δ 2.30 (–OOC*CH$_2$*CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$-CH$_2$*CH$_2$*COO–), δ 3.60 (–O*CH$_2$CH$_2$*–), δ 4.20 (–CH$_2$*CH$_2$*-OOCCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$COO*CH$_2$*CH$_2$–).

Other PEG–SAs were synthesized in a similar way by varying the composition or molecular weight of the starting PEG. The high molecular weight PEG–SA (PVII) was prepared by reacting an equivalent amount of PEG (6.00 g, 10.0 mmol, M_n = 600) and sebacoyl chloride (2.39 g, 10.0 mmol).

Table 1
List of PEG–SA polyesters studied

	Molecular weight of PEG	Molecular weight of PEG–SA (M_n)[a]	(M_W/M_n)[a]
PI	400	17,200	3.4
PII	600	12,000	1.6
PIII	600/900 (95/5)[b]	18,900	2.1
PIV	600/900 (90/10)[b]	18,500	2.1
PV	600/900 (85/15)[b]	17,600	3.1
PVI	900	11,000	3.0
PVII	600	53,000	2.6

[a] Determined by gel permeation chromatography. Tetrahydrofuran was used as an eluting solvent and poly(ethylene glycol)s were used as the molecular weight standards.

[b] The composition of poly(ethylene glycol)s of the PEG–SA was determined by ^{1}H NMR ($CDCl_3$) by the Eqs. (1) and (2) described in the text.

2.3. Gel permeation chromatography

The gel permeation chromatography system (Waters 515) with a refractive index detector (Waters 410) was used to obtain molecular weight and molecular weight distributions of PEG–SA. Tetrahydrofuran was used as an eluting solvent. Poly(ethylene glycol)s were used as the molecular weight standards. Styragel® HMW 6E and HR 4E columns (waters) were used in series.

2.4. NMR and FTIR study

A 500 MHz NMR spectrometer (Varian®) was used for ^{1}H NMR (in $CDCl_3$) to study the composition of the polymer and ^{13}C NMR to see the spectral change of the PEG–SA polyester (25 wt% in D_2O) as a function of temperature. ^{13}C NMR spectra in *N*,*N*-dimethyl form amide (DMF-d_7) were compared as a control. The solution temperature was equilibrated for 20 min before the measurement. Changes in functional groups of the polymers and sebacoyl chloride were monitored using FTIR spectrometer (BioRed).

2.5. Sol–gel transition

The sol-to-gel transition temperature of the polymer aqueous solution was investigated by dynamic rheometry (Thermo Haake, Rheometer RS 1) [9,11,14]. The aqueous polymer solution was placed between parallel plates of 25 mm diameter and a gap of 0.5 mm. The data were collected under a controlled stress (4.0 dyn/cm^2) and a frequency of 1.0 rad/s. The heating rate was 0.2 °C/min.

2.6. UV–vis spectroscopy

The lower critical solution temperature was shown by an abrupt increase in the absorbance in a visible range (400 nm) of the polymer aqueous solution or gel.

2.7. Micellization

Micelle formation was investigated by the dye solubilization method [16,17]. 1,6-Diphenyl-1,3,5-hexatriene solution in methanol (10 μL at 0.4 mM) was injected into an aqueous polymer solution (1.0 mL) in a concentration range of 0.0005–10.0 wt%. The absorption spectra of these solutions were recorded from 320 to 400 nm. The micelle formation of the PEG–SA (PII 1.0 wt% in water) was also studied by a dynamic light scattering instrument (ALV 5000-60x0) [13,14]. A YAG DPSS-200 laser (Langen, Germany) operating at 532 nm was used as a light source. Measurements of scattered light were made at an angle of 90 ° to the incident beam. The results of dynamic light scattering were analyzed by the regularized CONTIN method. The decay rate distributions were transformed to an apparent diffusion coefficient (D). From the apparent diffusion coefficient, the hydrodynamic radius (r) of a micelle can be obtained by the Stokes–Einstein equation.

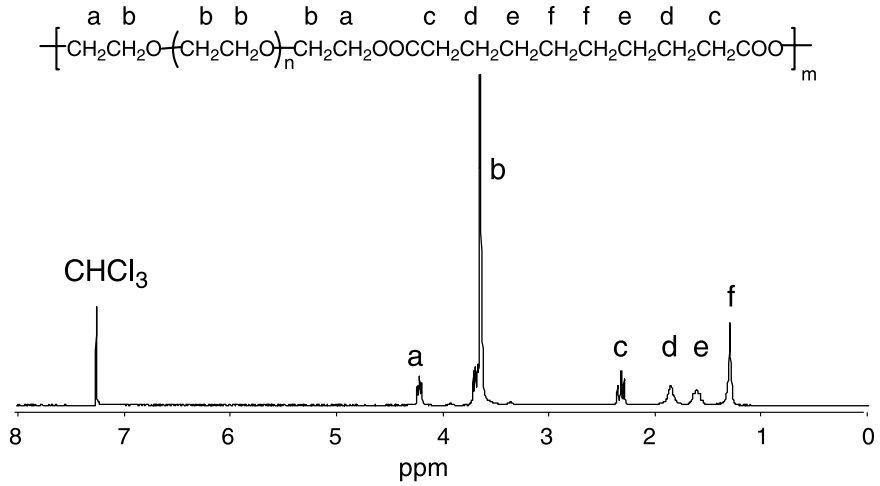

Fig. 1. ^{1}H NMR (in $CDCl_3$) spectra of the PEG–SA (PII).

2.8. In vitro drug release

FITC–dextran (M_W = 40,000 Da) was dissolved in a PEG–SA copolymers (PII or PV) aqueous solution (25.0 wt%) at a concentration of 5.0 mg/mL at 4 °C. All preparations were clear solutions. They turned into gels at 37 °C. The polymer gel containing FITC–dextran (0.5 mL) was injected through a syringe with 21-gauge into a 4.0 mL vial (inner diameter = 12 mm), which was thermostated in a shaking water bath (90 strokes/min) at 37 °C. The total FITC–dextran mass loaded was 2.5 mg. After 2 min, 3.0 mL of release medium (150 mM phosphate buffer saline, pH 7.4) at 37 °C was added to the preformed gel. The release medium was replaced by a fresh one (3.0 mL) at designated sampling intervals. The amount of released FITC–dextran was determined by the fluorescence spectroscopy (Shimadzu, RF-5301 PC; excitation wave length: 493 nm, emission wave length: 515 nm). The concentration was calculated against the standard curve of FITC–dextran in the release medium.

2.9. Syneresis

The polymer aqueous solution (25 wt%, 2.0 mL) was injected into a test tube with an inner diameter of 5.0 mm. The change in the height was investigated in a thermostatic water bath at 37 °C.

2.10. Gel formation and injectability test

A syringe containing aqueous solution (0.5 mL) of PEG–SA (25 wt%) was taken out of the refrigerator (4 °C) and kept at 37 °C for 2 min to form a gel. The gel was injected through a 21-gauge syringe needle into water at 37 °C to test the gel stability and injectability. To confirm the in vivo applicability of the PEG–SA as a depot system, the same procedure was applied to the rats and investigated the gel stability.

2.11. Degradation of the polymer

Aqueous solutions (0.3 mL) of PEG–SA (25 wt%) was kept at 37 °C for 2 min to form a gel. Three milliliters of phosphate buffer saline (pH 7.4, 37 °C) was added to the gel. The remaining polymer was freeze dried at a given time interval,

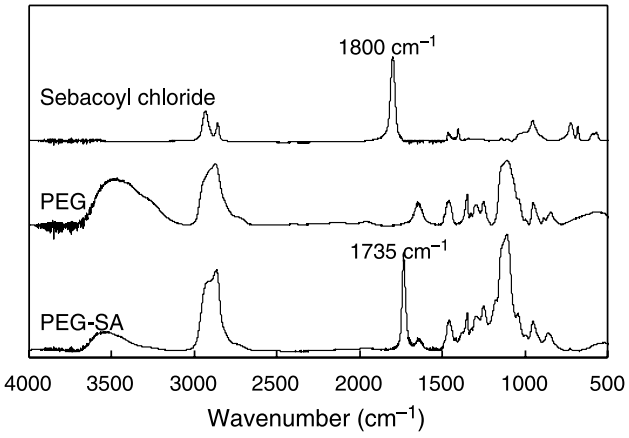

Fig. 2. FTIR spectra of the sebacoyl chloride, PEG, and PEG–SA (PII).

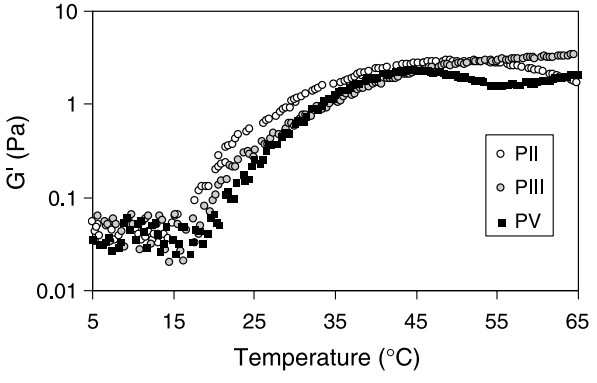

Fig. 3. Changes in storage modulus of the PEG–SA aqueous solutions (25 wt%) as a function of temperature: effect of composition.

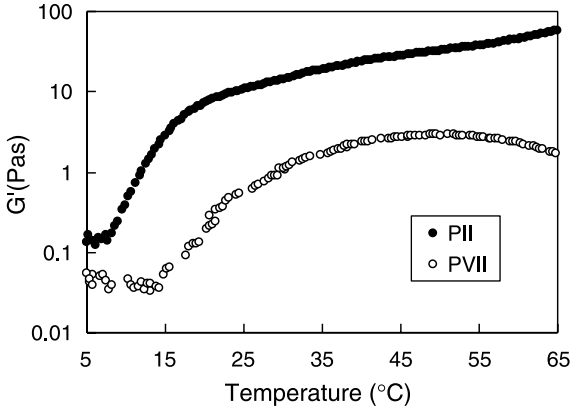

Fig. 4. Changes in storage modulus of the PEG–SA aqueous solutions (25 wt%) as a function of temperature: effect of molecular weight.

and redissolved in tetrahydrofuran for gel permeation chromatography (Waters 410). Poly(ethylene glycol)s were used as the molecular weight standards. Tetrahydrofuran was used as an eluting solvent and the flow rate was 1.0 mL/min.

3. Results and discussion

The polyester was prepared by a simple condensation reaction between poly(ethylene glycol) and sebacoyl chloride. The formation of the polyester was confirmed by ^{1}H NMR, FT-IR, and gel permeation chromatography. ^{1}H NMR spectra of PEG–SA (PII) shows the peaks of SA at 1.0–2.3 ppm, PEG at 3.6 ppm, and the connecting methylene at 4.2 ppm (Fig. 1). The polymer structure can be rewritten as follows when PEG 600 [$(CH_2CH_2O)_{13.6}$] and PEG 900 [$(CH_2CH_2O)_{20.5}$] were copolymerized.

$[(CH_2CH_2O)_{13.6}]_l[(CH_2CH_2O)_{20.5}]_m[(COCH_2CH_2CH_2CH_2\text{-}CH_2CH_2CH_2CH_2COO)]_n$

$$l + m = n \tag{1}$$

$$A_{2.3}/A_{3.6\text{–}4.2} = n/(13.6l + 20.5m) \tag{2}$$

l, m, and n are the number of repeating units of PEG (M_W = 600), PEG (M_W = 900), and sebacoyl ester,

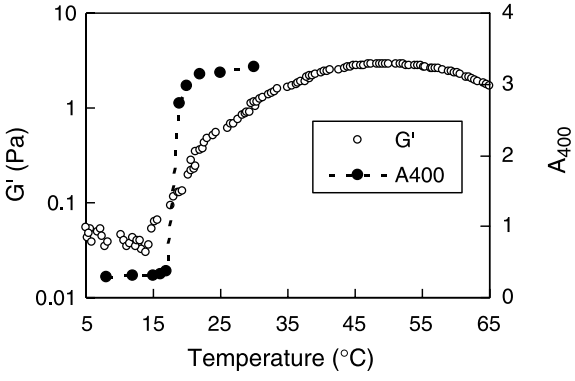

Fig. 5. Comparison of the absorbance at 400 nm and storage modulus (G') of the PEG–SA (PII) aqueous solutions (25 wt%) as a function of temperature.

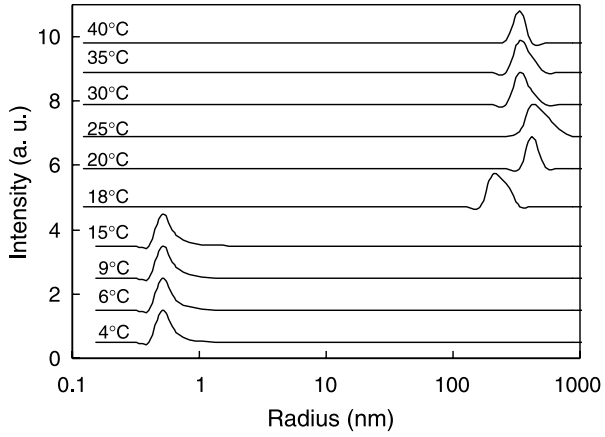

Fig. 6. Dynamic light scattering study of PEG–SA (PII) aqueous solution (1.0 wt%) as a function of temperature.

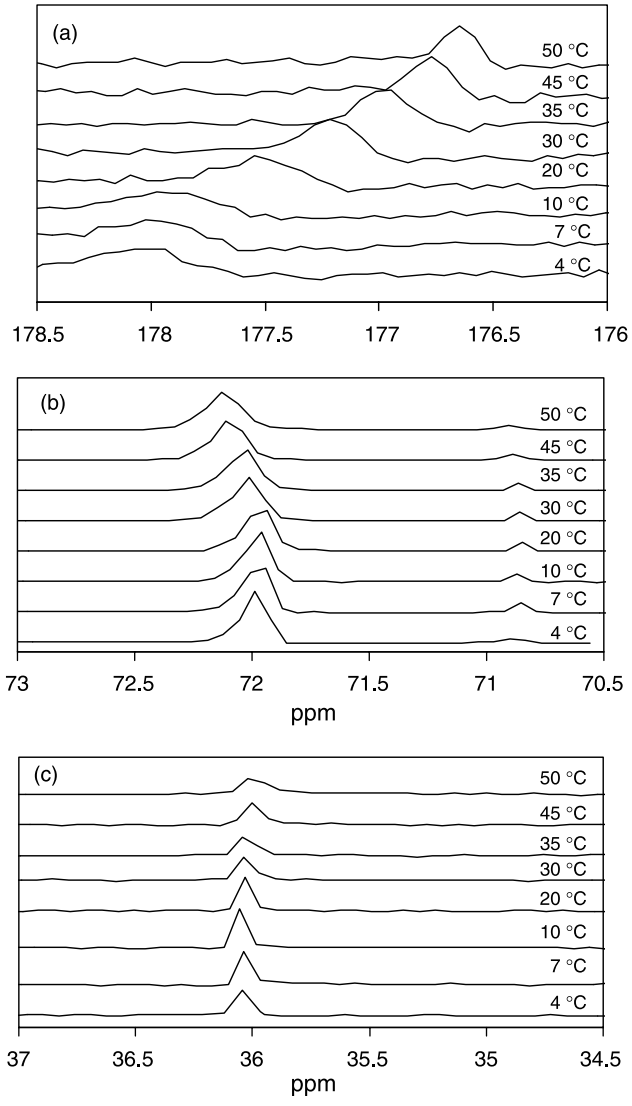

Fig. 7. ^{13}C NMR spectra of PEG–SA (PII) aqueous solutions (25 wt%) as a function of temperature. Top: change in the ester carbonyl peak at 177 ppm, the ethylene glycol (PEG) peak at 72 ppm and the methylene (SA) peak at 36 ppm.

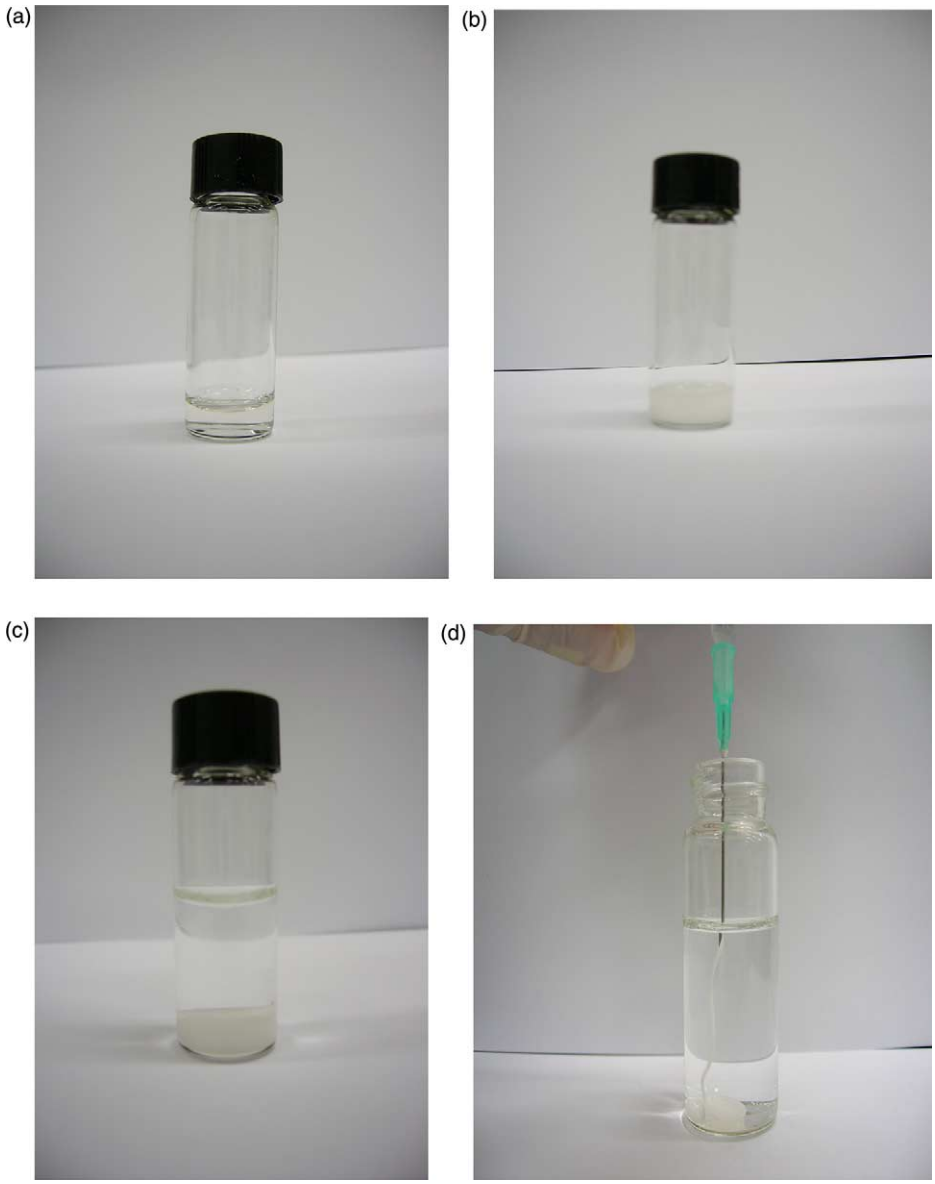

Fig. 8. In situ gel formation from PEG–SA aqueous solution (PII; 25 wt%). (a) Polymer solution at room temperature, (b) the gel at 37 °C, (c) stability of the gel at 37 °C after adding excess water, (d) the gel injection through a 21-gauge needle.

respectively. A2.3 and A3.6–4.2 are the integrated area under the peak at 2.3 and 3.6–4.2 ppm in the ^{1}H NMR. From a peak integration ratio of the 2.3 ppm (SA) to 3.6–4.2 ppm (PEG), a ratio of l to m of the PEG–SA was calculated to be coincided with the feeding ratio of PEG 600 to PEG 900 (Eqs. (1) and (2)). This finding suggests that the reactivities of hydroxyl end groups of PEG 600 and PEG 900 are same. The principle of equal reactivity was reported for the α,ω-dihydroxy alkane for acyl chloride when alkane chain length is greater than 6 [18]. The hydroxyl end groups of PEG 600 and PEG 900 were shown to be another example of the principle of equal reactivity.

The FTIR spectra of PEG–SA (Fig. 2) also confirmed the formation of ester by the peaks at 1730 cm^{-1} (C=O stretching) and 1000–1200 cm^{-1} (C–O stretching). The carbonyl peak of sebacoyl chloride at 1800 cm^{-1} shifted to 1735 cm^{-1} by forming ester.

PEG–SAs investigated in this study are listed in Table 1. Except for PVII, the molecular weight and polydispersity (M_W/M_n) was in a range of 11,000–18,900, and 1.6–3.4, respectively. The high molecular weight polymer (PVII; M_n–53,000) was prepared by a strict control of stoichiometry of the reactants and was investigated for the molecular weight effect on the sol–gel transition.

The PEG–SA (PI in Table 1) prepared from PEG 400 was not soluble in water, whereas that from PEG 900 (PVI in Table 1) showed the thermosensitive transition above 60 °C in water, and did not form a gel in a physiologically important temperature range of 10–50 °C. The aqueous solution of the PEG–SA (PII–PV in Table 1) prepared from PEG 600 underwent a clear solution (sol)-to-gel transition at 18–26 °C as the temperature increased, which accompanied a 100-fold increase in the storage modulus (G') at the transition temperature. An increase in modulus is a typical phenomenon

for sol-to-gel transition [9,11,19]. However, the gel modulus was less than 5 Pa and formed a very flexible and soft gel. The gel had little difficulty in injecting through a syringe with a 21-gauge needle. However, the gel was stable at 37 °C for 3 weeks and was not disintegrated in the presence of excess amounts of water in a shaking bath. As the ratio of PEG 600 to PEG 900 decreased from 100/0 to 85/15, the sol-to-gel transition temperature increased due to the increased hydrophilicity of the polymer (Fig. 3). To confirm the reversibility of the sol–gel transition, the aqueous polymer solution (PIII: 25 wt%) was heated at 65 °C for 5 min. A turbid gel was formed, and then it was redissolved at 4 °C. The modulus vs. temperature curve of the polymer solution was not significantly affected by the two times of such thermal treatments, suggesting that the sol–gel transition is reversible.

As the molecular weight of PEG–SA increased from 12,000 (PII) to 53,000 (PVII), the sol-to-gel transition temperature of the polymer aqueous solution decreased from 18 to 10 °C whereas gel modulus increased from 1–5 to 10–80 Pa (Fig. 4). The increase in modulus and decrease in sol–gel transition temperature by increasing the molecular weight of a polymer were also reported for multiblock poloxamer aqueous solutions [20].

The turbidity of the polymer aqueous solution abruptly increased at sol-to-gel transition temperature. This finding suggest that the lower critical solution temperature defined by an abrupt increase in turbidity is correlated with the sol-to-gel transition temperature of the polymer solution (Fig. 5).

To understand the molecular mechanism of the sol-to-gel transition of the polymer aqueous solution, dynamic light scattering (DLS) at low concentration (1.0 wt%) and ^{13}C NMR (D_2O) at high concentration (25 wt%) were investigated. An abrupt increase in an apparent polymer size at around transition temperature was observed by a dynamic light scattering experiment (Fig. 6). This fact indicates the aggregation of the polymers at the transition temperature. However, a typical micelle size of 5–100 nm peak was not observed in the sol state [6,8,13,14]. The increase in absorbance of a hydrophobic dye (1,6-diphenyl hexatriene) at 300–400 nm, which is an indication of micelle formation [16,17], was not observed in a sol state over the concentration range of 0.0005–10.0 wt%, either. The micelle aggregation was suggested for the sol-to-gel transition mechanism of poly(ethylene glycol)/poly(lactide/glycolide) and poly(ethylene glycol)/polycaprolactone systems [8,13,14,21]. PEG–SA aqueous solution is not a micellar system. Therefore, it can be suggested that sol-to-gel transition occurs through aggregation of the polymers and water is entrapped among the polymer chains.

^{13}C NMR data were analyzed for the carbonyl group at 176–178 ppm, the ethylene glycol (EG) group at 70–73 ppm, and the methylene (sebacoyl ester) group at 34–37 ppm. Compared with a small down field shift of the ethylene glycol group, a large upfield shift and a change in band broadening of the carbonyl group was noticeable as the temperature increases (Fig. 7). Little changes were observed in a chemical shift of the methylene group (sebacic group). The change in chemical shift of ^{13}C NMR in *N*,*N*-dimethyl formamide-d_7 was not observed in this temperature range. From these data, the change in the chemical environment of hydrophilic parts including the ester of SA and the PEG of PEG–SA are involved in the sol-to-gel transition. This induces the hydrophobic aggregation (heterogeneity) of the polymer, accompanied by the increase in turbidity, and drives the sol-to-gel transition as in the case of methyl cellulose [22].

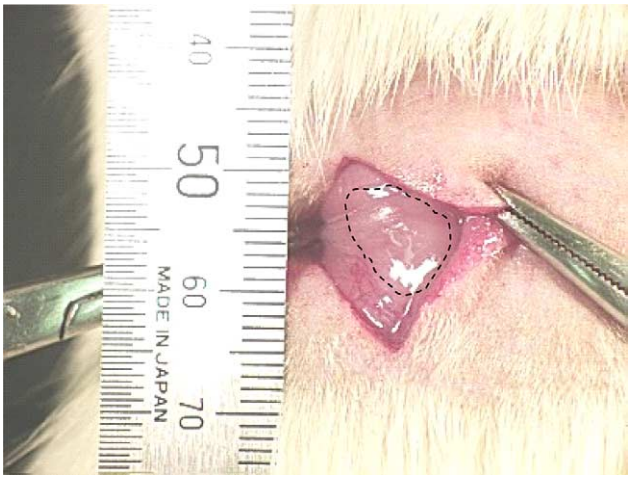

Fig. 9. The depot system formed by a subcutaneous injection of PEG–SA (PII) gel (0.5 mL; 25 wt% in water) to rats through a syringe with a 21-guage needle. The photo was taken by surgery 1 h after the injection.

Fig. 8 shows the sol (a)-to-gel (b) transition of the polymer (PII) aqueous solution (25 wt%) when the temperature changed from room temperature to 37 °C. When the excess amount of water (37 °C) was added on the top of the gel, the gel was not dissolved out and kept its three dimensional mass at 37 °C (c). To investigate the feasibility of the polymer as a drug delivery matrix, a syringe containing aqueous solution (0.5 mL) of PEG–SA (25 wt%) was taken out of the refrigerator (4 °C) and kept at 37 °C for 2 min to form a gel. The gel was injected through a 21-gauge syringe needle into water at 37 °C and the gel maintained its stability (d) in the excess amount of water. To confirm the applicability of the PEG–SA as a depot system, the gel was subcutaneously injected to the rats and investigated the in vivo gel stability. The photo of the gel that was taken by surgery 1 h after the injection showed the in vivo stability of the gel (Fig. 9).

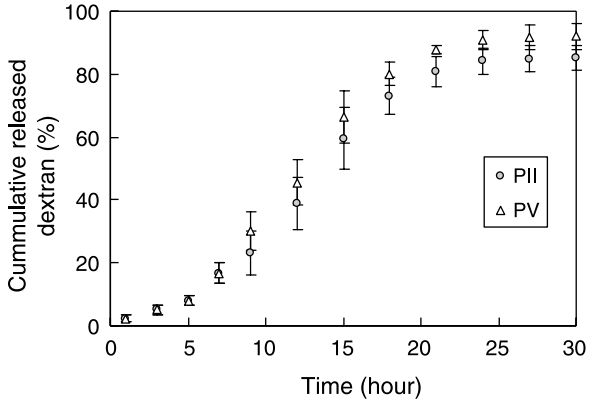

Fig. 10. Cumulative release of dextran 40,000 from the PEG–SA hydrogel of PII and PV. Initial polymer concentration was 25 wt%.

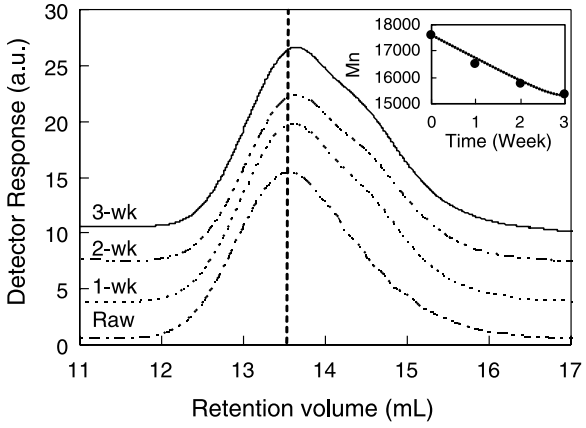

Fig. 11. The gel permeation chromatogram of the PEG–SA (PV) before degradation (raw), the sample taken in 1-week (1-wk), 2-week (2-wk), and 3-week (3-wk) during the degradation study. The change in the number average molecular weight of the polymer is inserted in the figure.

To investigate the usefulness of the soft gel as a hydrophilic drug delivery system, FITC–dextran (M_W = 40,000 Da) was chosen as a model drug. The release profile of the model drug from the gel was investigated over 24 h (Fig. 10). The release profile showed almost constant release of FITC–dextran from the gel over 5–24 h. The sigmoidal release pattern might come from surface thickening of the injected gel due to the higher experimental temperature (37 °C) compared with LCST (26 °C). The gel kept its integrity and the change in volume was less than 2% during the release experiment.

The in vitro degradability of the PEG–SA (PV) was investigated in phosphate buffer saline (pH 7.4) over 3 weeks. The gel permeation chromatogram of the polymer showed a shift in the peak maximum at 13.6 mL as well as an increase in the low molecular weight peak (shoulder) at 14.7 mL during the degradation. The number average molecular weight decreased from 17,600 to 15,300 over 3 weeks (Fig. 11).

4. Conclusions

A thermogelling PEG–SA was prepared by the simple polycondensation reaction of PEG and sebacoyl chloride. The sol-to-gel transition temperature could be controlled from 10 to 26 °C by varying composition and molecular weight of the polymer. The gel was soft enough to be injected through a 21-gauge syringe while the gel was stable in an excess amount of water at 37 °C. This material is expected to be useful as an injectable drug delivery system.

Acknowledgements

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