Thermogelling Poly(caprolactone-*b*-ethylene glycol-*b*-caprolactone) Aqueous Solutions

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ABSTRACT: Poly(caprolactone-*b*-ethylene glycol-*b*-caprolactone) (PCL−PEG−PCL) triblock copolymer aqueous solution (>15 wt %) undergoes the sol−gel−sol transition as the temperature increases from 10 to 60 °C. The mechanism and structure−property relationship of the sol−gel transition were investigated. In particular, compared with the PEG−PCL−PEG triblock copolymers recently reported by our group, PCL−PEG−PCL has (1) a synthetic advantage without a hexamethylene diisocyanate coupling step, (2) a wider gel window of over 15−32 wt %, and (3) a larger gel modulus. Both PEG−PCL−PEG and PCL−PEG−PCL polymers are an important progress in the biodegradable thermogelling system in that they can be lyophilized in a powder form, are easy to handle, are easy to redissolve to a clear solution, and show little syneresis through the gel phase.

Introduction

Biodegradable thermogelling polymers which undergo the sol-to-gel transition (specifically lower transition) as the temperature increases have gained attention for their potential biomedical applications including drug delivery, cell therapy, and tissue engineering.[1−3] At room temperature or below the sol-to-gel transition temperature, the polymer aqueous solution containing pharmaceutical agents can be mixed in a sol state, whereas it turns into a gel through a subcutaneous or intramuscular injection due to the physiological heat at 37 °C and acts as a slow releasing depot of the drug or a cell growing matrix. Poly(ethylene glycol/poly(lactic acid-*co*-glycolic acid) (PEG/PLGA),[4,5] chitosan/glycerol phosphate,[6] poly(phosphazene)s,[7] and poly(ethylene glycol)/poly(propylene fumarate) (PEG/PPF)[8] have so far been reported as biodegradable thermogelling polymers. However, drug delivery systems using the above polymers suffer from very slow redissolution/reconstitution and sticky paste morphology.

We designed a polycaprolactone (PCL) based system showing the sol-to-gel transition as the temperature increases. PCL is a well-known biodegradable crystalline polymer[9] and can thus be a brittle polymer instead of having the sticky paste morphology. The powderlike polymer is easy to weigh and to transfer. In addition, the reconstitution problem is expected to be solved by heating the aqueous polymer suspension just above the melting point of the polymer. However, in order for a polymer aqueous solution to show the sol-to-gel transition, it was suggested that the polymer should have some hydrophilicity and amorphous morphology as in the case of PEG/PLGA system.[4,5] Otherwise, it would undergo the sol-to-precipitation or gel-to-sol transition (gel melting) instead of the sol-to-gel transition as the temperature increases. Such trends have been reported for poly(phenylalanine-*g*-ethylene glycol) (PP-*g*-PEG), poly(ethylene glycol)/poly(L-lactic acid) (PEG/PLLA) block copolymers, and PEG/PCL multiblock and diblock copolymers.[10−12]

When the PCL block is too large, the polymer is not soluble in water. When PEG block is too large, the aggregation of micelles is hampered and the PEG-containing block polymer aqueous solution does not show the sol-to-gel transition in a biomedically important temperature range of 10−50 °C. The aggregation of micelles has been suggested as a sol-to-gel transition mechanism of the polymers consisting of PEG and hydrophobic blocks such as poly(ethylene glycol)/poly(propylene glycol) (PEG/PPG), poly(ethylene glycol)/poly(butylene glycol) (PEG/PBG), and PEG/PLGA.[4,5,13,14]

On the basis of above consideration, we prepared the PCL−PEG−PCL triblock copolymer with a PEG molecular weight of 1000−1500. The structure−property relationship of PCL−PEG−PCL on the sol−gel transition was investigated, focusing on PCL length, PEG length, and topological variation (ABA vs BAB). Very recently, we reported PEG−PCL−PEG (BAB type) thermogelling polymers,[15] and their phase behavior were also compared in this paper.

Materials and Experimental Methods

Materials. ϵ-Caprolactone, stannous octoate, poly(ethylene glycol) (PEG) (MW = 1000 and 1500), 1,6-diphenyl-1,3,5-hexatriene (DPH), and anhydrous toluene were used as received from Aldrich.

Synthesis. The PCL−PEG−PCL triblock copolymers were prepared by ring-opening polymerization of caprolactone in the presence of PEG. Stannous octoate was used as a catalyst. For example, to synthesize the PCL−PEG−PCL (980−1000−980) triblock copolymer, PEG (15.0 g, 15.0 mmol, M_n = 1000) 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. ϵ-Caprolactone (23.7 g, 207.6 mmol) and stannous octoate (49 μL, 0.12 mmol) were added to the reaction mixtures and stirred at 120 °C for 24 h. The product was isolated by precipitation into diethyl ether. The polymer was redissolved in the 30 mL of methylene chloride

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Table 1. List of PCL−PEG−PCL Triblock Copolymers Studied

	PCL−PEG−PCL[a]	EG/CL[a]	M_n(NMR)	M_n[b]	PDI[b]
PI	$(CL)_{4.7}-(EG)_{22.7}-(CL)_{4.7}$	2.4	540−1000−540	2030	1.1
PII	$(CL)_{6.0}-(EG)_{22.7}-(CL)_{6.0}$	1.9	690−1000−690	2380	1.3
PIII	$(CL)_{8.5}-(EG)_{22.7}-(CL)_{8.5}$	1.3	980−1000−980	2710	1.2
PIV	$(CL)_{9.9}-(EG)_{22.7}-(CL)_{9.9}$	1.1	1130−1000−1130	3250	1.1
PV	$(CL)_{5.6}-(EG)_{34}-(CL)_{5.6}$	3.1	650−1500−650	2360	1.1
PVI	$(CL)_{14.2}-(EG)_{34.1}-(CL)_{14.2}$	1.2	1650−1500−1650	4100	1.3

[a] Determined by ^{1}H NMR in $CDCl_3$ based on ethylene glycol (EG) unit (4H, 3.6 ppm) and caprolactone (CL) unit (2H, 2.2 ppm) of the polymers. [b] Determined by GPC. In the GPC, tetrahydrofuran was used as an eluting solvent and PEGs were used as the molecular weight standards. Polydispersity index (PDI) was defined by weight-average molecular weight divided by number-average molecular weight of the polymers.

and precipitated by slowly adding diethyl ether. The residual solvent was removed under vacuum.

^{1}H NMR ($CDCl_3$) of PCL-PEG-PCL: δ 1.35 ($-OCH_2CH_2-\boldsymbol{C}\mathbf{H}_2CH_2CH_2CO-$), δ 1.62 ($-OCH_2\boldsymbol{C}\mathbf{H}_2\boldsymbol{C}\mathbf{H}_2CH_2\boldsymbol{C}\mathbf{H}_2CH_2CO-$), δ 2.30 ($OCH_2CH_2CH_2CH_2\boldsymbol{C}\mathbf{H}_2CO$), δ 3.60 ($-O\boldsymbol{C}\mathbf{H}_2CH_2-$), δ 4.06 ($-O\boldsymbol{C}\mathbf{H}_2CH_2CH_2CH_2CH_2CH_2CO-$), δ 4.20 ($-CH_2\boldsymbol{C}\mathbf{H}_2O-COCH_2CH_2CH_2CH_2CH_2CO-$).

Gel Permeation Chromatography. The gel permeation chromatography (GPC) system (Waters 515) with a refractive index detector (Waters 410) was used to obtain the molecular weights and molecular weight distributions of the PCL−PEG−PCL triblock copolymers. Tetrahydrofuran was used as an eluting solvent. The PEGs in a molecular weight range of 400−10 000 Da were used as the molecular weight standards because tetrahydrofuran is a good solvent not only for the PEG in this molecular weight range but also for the PEG−PCL−PEG. Styragel HMW 6E and HR 4E columns (Waters) were used in series.

NMR Study. A 500 MHz NMR spectrometer (Varian) was used for ^{1}H NMR (in $CDCl_3$) to study composition of the polymer and ^{13}C NMR (in D_2O) to see the spectral change of the PCL−PEG−PCL triblock copolymer as a function of temperature. The solution temperature was equilibrated for 20 min before the measurement.

Sol−Gel Transition. The sol−gel transition was determined by the test tube inverting method. The 4 mL vials (diameter 1.1 cm) containing 0.5 mL of PCL−PEG−PCL triblock copolymer solutions were immersed in a water bath at a designated temperature for 20 min. The transition temperatures were determined by a flow (sol)−no flow (gel) criterion when the vial was inverted with a temperature increment of 1 °C per step.[5,15] The precision of the sol−gel transition temperature was ±1 °C.

The sol-to-gel transition of the polymer aqueous solution was also investigated by dynamic mechanical analysis (Thermo Haake, rheometer RS 1).[5,15] 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.

Micelle Formation. Micelle formation was determined by the dye solubilization method at room temperature (20 °C).[13] The hydrophobic dye (DPH) has a significantly lower absorptivity in an aqueous environment compared with that in the hydrophobic environment. Therefore, with the formation of micelles, the hydrophobic dyes are preferentially partitioned into the hydrophobic core of micelles, resulting in the increase in the absorbance of the dye. DPH solution in methanol (10 μL at 0.4 mM) was injected into an aqueous polymer solution (1.0 mL) in a concentration range of 0.000 05−0.1 wt %. The absorption spectra (Shimadzu UV 2450) of these solutions were recorded from 330 to 400 nm.

Dynamic Light Scattering. The size of a micelle was studied by a dynamic light scattering (DLS) instrument (ALV 5000-60x0) as a function of temperature at 1.0 wt %. 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 DLS 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.

Differential Scanning Calorimetry. A differential scanning calorimeter (DSC, Perkin-Elmer DSC 7) was used to study melting and recrystallization behavior of the polymers in a temperature range of 10−60 °C with a heating and cooling rate of 5.0 °C/min. A polymer (about 5.0 mg) was loaded in a cell, and heat exchange was recorded during the heating and cooling cycle.

pH Effect on Gel Modulus. To investigate the pH effect on the sol−gel transition, the polymer solution was prepared at 20 wt %. About 10−80 μL of 1.0 M hydrochloric acid or 1.0 M sodium hydroxide solution was added to a well-stirred vial containing polymer solution (10.0 mL) in the ice bath. The polymer aqueous solution shows a transparent sol phase during the procedure. To eliminate the polymer degradation effect, pH was adjusted just before the dynamic mechanical analysis (Thermo Haake, rheometer RS 1) experiment. The aqueous polymer solution (20 wt %) 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.

Results and Discussion

The PCL−PEG−PCL triblock copolymer was prepared by ring-opening polymerization of ϵ-caprolactone on the PEG in the presence of stannous octoate as a catalyst.[9] The ethylene peak of ethylene glycol ($C\mathbf{H}_2C\mathbf{H}_2O$) units at 3.60 ppm and the methylene peak of caprolactone ($COC\mathbf{H}_2CH_2CH_2CH_2CH_2O$) units at 2.30 ppm in the ^{1}H NMR ($CDCl_3$) spectra were used for the determination of number-average molecular weight (M_n) of the PCL−PEG−PCL triblock copolymer. The peak area ratio of connecting ethylene glycol units at 4.20 ppm ($-CH_2\boldsymbol{C}\mathbf{H}_2O-COCH_2CH_2CH_2CH_2CH_2CO-$) to PEG ethylene glycol ($C\mathbf{H}_2C\mathbf{H}_2O$) units at 3.60 ppm shows that both hydroxyl groups of PEG are connected to polycaprolactone. In the case of α,ω-dihydroxyalkane, the two hydroxyl end groups show the same reactivity when the number of methylene units between the hydroxyl groups is over 6.[16] PEG (MW = 1000) has 22.7 ethylene glycol repeating units between two hydroxyl end groups; the principle of equal reactivity could be valid. Thus, the PCL blocks in the PCL−PEG−PCL were assumed to have the same molecular weight. Table 1 summarizes the polymers investigated in this study. The total molecular weight and polydispersity (M_n/M_w) of the PCL−PEG−PCL triblock copolymer, determined by gel permeation chromatography (GPC), were in the ranges of 2000−4100 and 1.1−1.3, respectively. PI and PV are quite hydrophilic and freely soluble in water, whereas PIV is too hydrophobic and is partially soluble in water in a biologically important temperature range of 4−50 °C. Aqueous solutions (18−32 wt %) of PII, PIII, and PIV showed the sol-to-gel transition (lower transition) and gel-to-sol transition (upper transition) as the temperature increased. Figure 1 shows the phase dia-

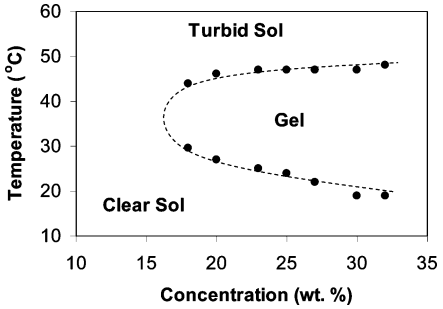

Figure 1. Phase diagram of PCL−PEG−PCL triblock copolymers (PII) in deionized water. The temperature of the bath was changed in steps of 1 °C. Conditions of flow (sol) or no flow (gel) were determined by inverting the vial vertically in the bath. The precision of the measurements was within ±1 °C.

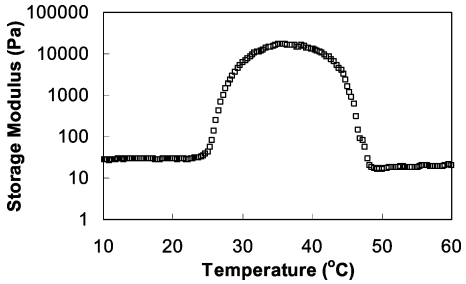

Figure 2. Dynamic mechanical analysis of PCL−PEG−PCL triblock copolymer (PII) aqueous solutions (20 wt %) as a function of temperature. The thermogram was obtained with a heating rate of 0.2 °C min^{-1}.

gramof PII aqueous solutions. The general phase behavior of PIII and PIV was similar to that of PII and will be compared in this paper. The lower transition at about 17−28 °C accompanies transparent solution-to-turbid gel formation, whereas the upper transition at 44−47 °C causes the turbid gel-to-turbid suspension of the polymer in water, similar to the PEG/PLGA system.[4,5] Contrary to the PLGA/PEG system, the upper transition temperatures of PCL−PEG−PCL aqueous solution were nearly constant in a concentration range of 18−30 wt %. The lower transition temperature is dependent on the concentration.

The sol−gel transition accompanies a large change in modulus. Figure 2 shows the change in storage modulus (G') of PII aqueous solution (20 wt %) as a function of temperature. An abrupt increase in G' by the sol-to-gel transition, followed by a decrease in G' by the gel-to-sol transition, was clearly shown as the temperature increased.

The micelle formation of the PCL−PEG−PCL triblock copolymers was proven by hydrophobic dye solubilization and dynamic light scattering. The partitioning of the hydrophobic dye (DPH) into a micelle core enhances the absorption coefficient of the dye at 343, 358, and 379 nm above a certain polymer concentration (Figure 3a). The critical micelle concentration of PII determined by the dye solubilization method[13,15] was in the range of 0.0005−0.005 wt %. The micelle size of PII in water (1.0 wt %) was investigated by dynamic light scattering as a function of temperature (Figure 3b). At low temperature (below the sol-to-gel transition temperature), the radius of a micelle was about 6 nm. The micelle size slightly decreases as the temperature increases up to 20 °C. However, the significant increases in the micelle size and micelle size distribution were observed above 25−40 °C. Above 44 °C, the micelles were aggregated

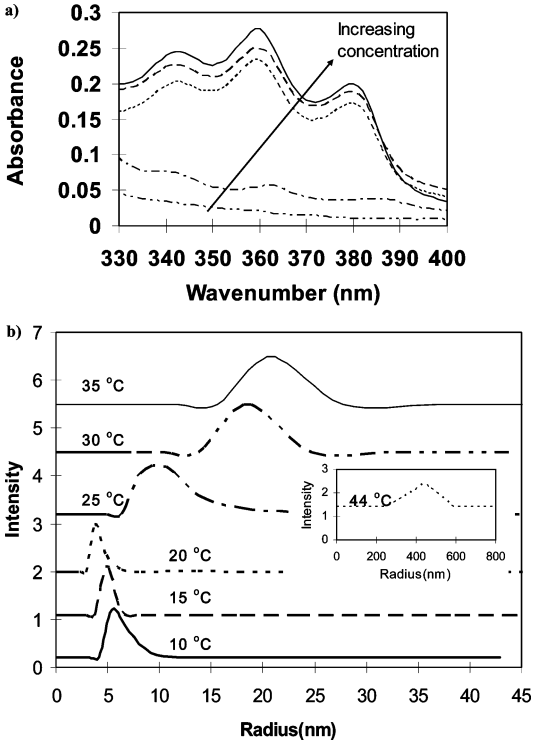

Figure 3. (a) UV−vis spectra of DPH as a function of polymer (PII) concentration (0.00005 wt % (− · · −), 0.0005 wt % (− · −), 0.005 wt % (· · ·), 0.05 wt % (- - -), 0.1 wt % (—)) in water. The increases in the absorbance at 343, 358, and 378 nm indicate the hydrophobic domain (micelle) formation. (b) Radius of a PCL−PEG−PCL (PII) micelle determined by dynamic light scattering. The aqueous polymer solution (1.0 wt %) was investigated at 10, 15, 20, 25, 30, 35, and 44 °C (inset).

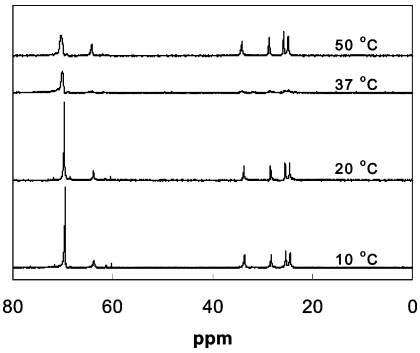

Figure 4. ^{13}C NMR spectra of PCL−PEG−PCL (PII) aqueous solution (20 wt %) as a function of temperature. The change in the peak shape at 10 °C (lower sol phase), 20 °C (lower sol phase), 37 °C (gel phase), and 45 °C (upper sol phase) is related to the sol−gel transition.

to 400 nm in radius. On the basis of this observation, we can conclude that micellar aggregation leads to the sol-to-gel transition (lower transition) as the temperature increases. Also, higher extent of aggregation is involved in the gel-to-turbid sol transition.

^{13}C NMR spectra of PII (20 wt % in D_2O) are shown as a function of temperature (Figure 4). Below the sol-to-gel transition temperature (10 and 20 °C), the sharp PEG peak and collapsed PCL peaks also indicate that PCL−PEG−PCL form a core (hydrophobic PCL)−shell (hydrophilic PEG) structure (micelle) in water. At the gel phase (37 °C), the PEG peak at 73 ppm are collapsed and the PCL peaks at 20−35 ppm in ^{13}C NMR (D_2O) are much more collapsed, indicating that the molecular

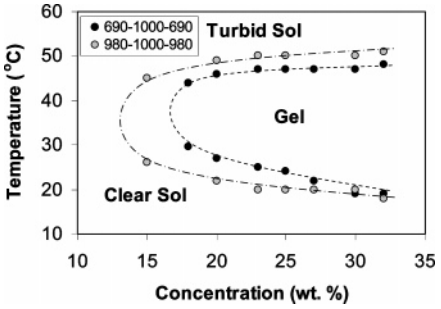

Figure 5. Effect of PCL length on the phase diagram of PCL−PEG−PCL triblock copolymer (PII and PIII) aqueous solutions. The precision of the measurements was within ±1 °C.

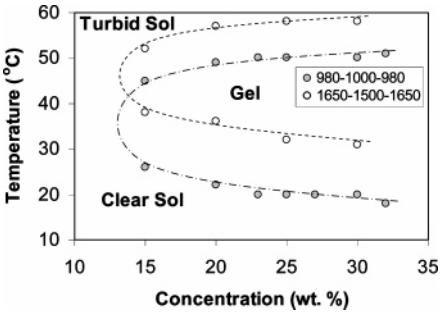

Figure 6. Effect of PEG length on the phase diagram of PCL−PEG−PCL triblock copolymer (PIII and PIV) aqueous solutions. The precision of the measurements was within ±1 °C.

motion is restricted in the gel phase while keeping the core−shell structure. The PCL peaks are pronouncedly increased compared with PEG peak above the gel-to-sol transition (50 °C). This observation and the increase in molecular aggregate size more than 400 nm at 44 °C (Figure 3b) support that the core−shell structure of the polymer might be destroyed at the gel-to-sol transition temperature.

The structure−property relationship of the sol−gel transition was studied not only for PCL length effect and PEG length effect for the PCL−PEG−PCL triblock copolymer but also for topological variation effect of BAB-type vs ABA-type. With the increase in PCL molecular weight of the PCL−PEG−PCL triblock copolymer, the sol-to-gel transition temperature decreased and the gel window, the temperature range where the gel phase persists, increased (Figure 5). By increasing the PEG length of PCL−PEG−PCL at a similar ratio of ethylene glycol (EG) to caprolactone (CL), the sol−gel phase diagram shifted to a higher temperature (Figure 6). On the basis of these observations, the increase in hydrophobic moiety and the decrease in the PEG length are critical for designing a thermogelling polymer with a gel window at around the physiological temperature (37 °C).

PCL−PEG−PCL (980−1000−980) and PEG−PCL−PEG (550−2190−550) have a similar composition and total PEG and PCL block length. The numbers in the parentheses are the molecular weight of each block determined by ^{1}H NMR. PCL−PEG−PCL (ABA-type) has a lower sol-to-gel transition temperature and larger gel window compared with PEG−PCL−PEG (BAB-type) (Figure 7). Both PEG−PCL−PEG and PCL−PEG−PCL form micelles at low concentration.[15] The hydrophobic block (PCL) tends to be located in the micelle core, and the hydrophilic block (PEG) is exposed to the shell of the micelle. However, the BAB-type polymers form regular micelles with a hydrophobic block core and a

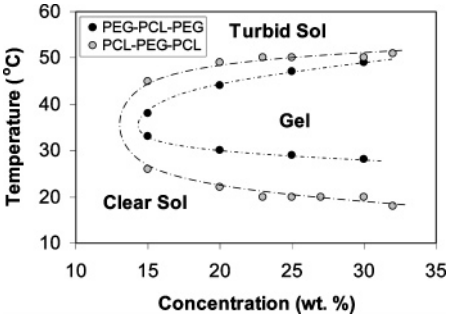

Figure 7. Effect of topology on the phase diagram of triblock copolymer aqueous solutions. Phase diagrams of PEG−PCL−PEG (550−2190−550) and PCL−PEG−PCL (980−1000−980) were compared. The precision of the measurements was within ±1 °C.

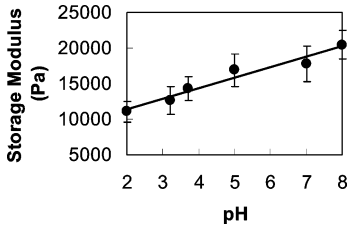

Figure 8. Effect of pH on the gel modulus of triblock copolymer (PII) at 37 °C where the gel shows maximal modulus in a pH range of 2−8. The data points are the averages of three measurements.

hydrophilic block shell, whereas the ABA-type polymers form micelles with loops or intermicellar bridges.[13] The intermicellar bridging of the ABA-type polymer leads more easily to molecular clustering than BAB-type.[17] These interactions are more significant in a high concentration region where the sol-to-gel transition occurs; thus, ABA-type triblock copolymers have a lower sol-to-gel transition temperature and a wider gel window compared with BAB-type polymers. In addition, the intermicellar bridges of PCL−PEG−PCL gives PCL−PEG−PCL (10 000 Pa·s) gel higher storage modulus (G') than PEG−PCL−PEG (100 Pa·s) gel even though both polymers' solutions (20 wt %) show a maximal modulus at around 37 °C. Considering the fact that the cell proliferation is improved in the high-modulus gel,[18] the PCL−PEG−PCL can be a promising material.

Considering biomedical application as a depot system in a specific site, pH is an important parameter. The vaginal pH is 3.7−4.5 and increases during the menstrual cycle.[19] The tumoral pH also varies from 5.2 to 7.4, and gastric pH varies from 2 to 8 along the gastrointestinal track.[20] As the pH increased from 2 to 8, the gel modulus of the PII aqueous solution (20 wt %) doubled, while all the solutions showed maximal modulus at around body temperature (37 °C) (Figure 8). The sol-to-gel transition temperature decreased from 30 to 24 °C as the pH increased from 2 to 8. At pH = 2, the hydronium ions (H_3O^+) as well as water (H_2O) can form hydrogen bonds to ethylene glycol units of the PEG,[21] resulting in an increase in the solubility of the PCL−PEG−PCL triblock copolymers and a softening of the gel modulus. When the pH increases to 8, hydronium ion concentration is negligible and gel modulus increases. Such a trend was also observed for multiblock poloxamer.[3]

A DSC thermogram of PCL−PEG−PCL triblock copolymers (Figure 9) shows one melting transition at

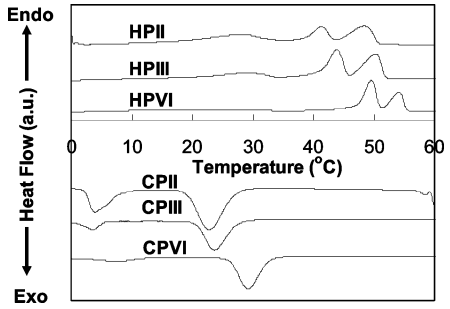

Figure 9. DSC thermogram of PCL−PEG−PCL triblock copolymers. HPII, HPIII, and HPVI are the heating curves of PII, PIII, and PVI, respectively. CPII, CPIII, and CPVI are the cooling curves of PII, PIII, and PVI, respectively. The heating and cooling rate was 5 °C/min.

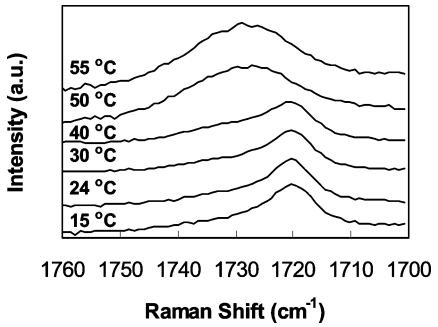

Figure 10. Carbonyl stretching band in the Raman spectra of PCL−PEG−PCL triblock copolymer (PIII) as a function of temperature. Resolution was 1 cm^{-1}.

20−33 °C and two melting transitions at 37−57 °C in the heating curves (HPII, HPIII, and HPVI). In the cooling curves (CPII, CPIII, and CPVI), two crystallization peaks at 0−10 and 20−30 °C were observed. As the molecular weight of PCL (of the PCL−PEG−PCL triblock copolymer) decreased, the peak size at 0−10 °C increased in the cooling curve, indicating that the crystallization peaks at 0−10 and 20−30 °C come from the PEG and PCL, respectively. As the PCL molecular weight increases, the fast crystallizing PCL block freezes the following whole structure and hampers the crystallization process of the PEG.[22,23] Therefore, the crystallization peak of PEG at 0−10 °C in the cooling curve as well as its corresponding melting peak at 20−33 °C in the heating curve decreased as the molecular weight of PCL increased. Compared with HPIII, the thermogram of PII (HPII) with a smaller PCL molecular weight gave a lower melting transition temperature. The fact that the Raman peak of carbonyl (PIII) shifted from 1720 to 1727 cm^{-1} above 50 °C also supports the transitions at 37−57 °C coming from the melting of PCL block (Figure 10). In the crystalline state, the PCL carbonyls are arranged to maximize the dipole−dipole interactions. The carbonyl peak moves to a lower frequency region due to such interactions. However, the carbonyl groups are randomly oriented in the liquid state and independently behave above the PCL melting point. Thus, the carbonyl peak moves to a higher frequency region. Therefore, the lower melting transition at 20−33 °C and the higher melting transitions at 37−57 °C could be assigned to be PEG and PCL, respectively. The two endothermic peaks were also reported for PEG/PCL multiblock copolymers, which were assigned for PCL melting transitions related to melting and recrystallization of PCL during the heating cycle.[22]

The powder morphology of this material is clearly distinguished from previous thermogelling polymers such as PEG/PLGA, PEG/PPF, and polyphosphazene in that it allows comfortable handling in weighing and transferring. In particular, fast dissolution of the powder sample was possible in a couple of minutes, whereas several hours was needed to dissolve the previous thermogelling materials.

Conclusions

The PCL−PEG−PCL triblock copolymer aqueous solution undergoing the sol−gel−sol transition as the temperature increases was prepared by optimizing the molecular weight of the PCL and PEG blocks. The mechanism of the clear sol-to-gel transition seems to be micellar aggregation, whereas the gel-to-turbid sol transition seems to be driven by an increase in the molecular motion of PCL accompanying the core−shell (micelle) structure breakage. The gel formation is driven by the hydrophobic interactions as supported by the finding that sol-to-gel transition temperature decreases and gel window increases by the increase in hydrophobic block length. The topological variation from PEG−PCL−PEG to PCL−PEG−PCL also decreased the sol-to-gel transition temperature and increased gel window and gel modulus which seem to be related to the intermicellar bridges of the PCL−PEG−PCL.

Both PEG−PCL−PEG and PCL−PEG−PCL polymers are an important progress in the thermogelling system in that they could be lyophilized in a powder form and are easy to handle and easy to dissolve to a clear solution in a couple of minutes. In addition, PCL−PEG−PCL has a synthetic advantage over PEG−PCL−PEG because a hexamethylene diisocyanate coupling step is not needed.

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