Thermoreversible Gelation of PEG−PLGA−PEG Triblock Copolymer Aqueous Solutions

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ABSTRACT: Aqueous solutions of new biodegradable triblock copolymers, poly(ethylene glycol-*b*-(DL-lactic acid-*co*-glycolic acid)-*b*-ethylene glycol) (PEG−PLGA−PEG), have shown to have sol-to-gel (lower transition) and gel-to-sol (upper transition) transitions as temperature monotonically increases. The lower transition is important for drug delivery application because the solution flows freely at room temperature and becomes a gel at body temperature. In this paper, the mechanism of gelation was proposed, and the structure−property relationship of the sol−gel transition was investigated. The lower transition may be related to micellar growth and intra- and intermicelle phase mixing and packing, while the upper transition involves breakage of micellar structure. Critical gel concentration and critical gel temperature are controlled by polymer molecular parameters, such as block length and composition of PEG−PLGA−PEG triblock copolymers, and additives, such as salts.

I. Introduction

Temperature- or pH-sensitive polymers have been extensively applied to drug delivery systems.[1,2] In particular, polymers showing a sol-to-gel transition by temperature change have been proposed for an injectable drug delivery depot.[3,4] In a previous publication, we reported gel-to-sol phase transition by increasing temperature of aqueous solutions of poly(ethylene oxide) (PEO)−aliphatic polyester diblock and PEO−aliphatic polyester−PEO triblock copolymers.[5] The transition temperature monotonically increased as concentration increased. The shape of the transition curve and its location in the phase diagram were manipulated by polymer block structure, molecular weights of constituting blocks, and the nature of biodegradable aliphatic polyesters such as poly(L-lactic acid) (PLLA), poly(DL-lactic acid) (PDLA), poly(lactic acid-*co*-glycolic acid) (PLGA), and poly(DLLA-*co*-ϵ-caprolactone (CL)). Thus far, the two temperature-dependent sol−gel transitions (designated hereafter as the lower and upper transition curves in the phase diagram) were only found with PEO−poly(propylene oxide) (PPO)−PEO block copolymers (Pluronics) and PEO−poly(butylene oxide) (PBO)−PEO.[6,7] The lower transition curve has been thought to be a unique property of these polymers.

The sol-to-gel transition behavior of Pluronics has been utilized for the delivery of labile drugs such as polypeptides and proteins because such drugs can be formulated in an aqueous solution.[8,9] The formulation forms a gel depot in situ when exposed to body temperature via subcutaneous injection. The incorporated drug is then released into the body in a controlled manner. The gel depot from PEO−PPO−PEO block copolymers dissolved from its surface within 1 day into soluble unimers, which may cause a harmful or toxic effect in the body, thus resulting in difficulties in sustained release in a long-term base. The surface dissolution could be related to its gelation mechanism of micelle packing; packed micelles are subject to dissipation by dilution.

In this report, the sol−gel transition behavior of PEG−PLGA−PEG triblock copolymer aqueous solutions is presented. The transition curves in phase diagram resemble those of PEO−PPO−PEO block copolymers. The formed gels of PEG−PLGA−PEG in rats maintained their integrity longer than 1 month.[10]

In addition to their biodegradability, longer duration of PEG−PLGA−PEG gels is clearly distinguished from PEO−PPO−PEO gels, showing that the PEG−PLGA−PEG gel is not erodible by dilution and is more beneficial for the carriers of polypeptide, proteins, and other pharmaceuticals for long-term delivery.

Transition behavior was monitored by microdifferential scanning calorimetry (microDSC) and ^{13}C NMR. The transition curve was modified by PLGA block composition, block length, and additives. A possible gelation mechanism is proposed to explain gelation behavior and gel stability in an aqueous environment on the basis of the experimental results.

II. Experimental Section

Synthesis. The synthesis of PEG−PLGA−PEG triblock copolymers has been described elsewhere.[11] Briefly, ring-opening polymerization of lactide and glycolide onto monomethoxypoly(ethylene glycol) was performed to synthesize PEG−PLGA diblock copolymers. Diblock copolymers were then coupled using hexamethylene diisocyanate to produce the PEG−PLGA−PEG triblock copolymers.

Sol−Gel Transition. The sol (flow)−gel (no flow) was determined by a test tube inverting method with temperature increments of 1 °C per each step.[12,13] Each sample with a given concentration was prepared by dissolving the polymer in distilled water in a 4 mL vial. After equilibration at 4 °C for 12 h, the vials containing samples were immersed in a water bath at a constant designated temperature for 20 min. Inverting the vial determined a gel state when no fluidity in 1 min was visually observed. A minimum shear stress of 62 Pa is needed for the system to flow in a vial.[13] The sol−gel transition

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$$CH_3O(CH_2CH_2O)_x[(COCH_2O)_y(COCH(CH_3)O)_z]OCNH(CH_2)_6NHCO[(OCH(CH_3)CO)_z[(OCH_2CO)_y](OCH_2CH_2)_xOCH_3$$

PEG PLGA Urethane PLGA PEG

Figure 1. Structure of PEG−PLGA−PEG triblock copolymers.

Table 1. List of Triblock Copolymers Studied

block copolymers PEG−PLGA−PEG[a]	M_n(NMR)	M_w(GPC)	M_w/M_n[b]
$EG_{12}-(L_{26}G_7)-EG_{12}$	550−2320−550[c]	3560	1.09
$EG_{17}-(L_{26}G_7)-EG_{17}$	750−2370−750[c]	4190	1.23
$EG_{12}-(L_{29}G_8)-EG_{12}$	550−2600−550[c]	4140	1.24
$EG_{12}-(L_{31}G_9)-EG_{12}$	550−2810−550[c]	4270	1.29
$EG_{12}-(L_{32}G_9)-EG_{12}$	550−2910−550[c]	4580	1.22
$EG_{12}-(L_{31}G_{12})-EG_{12}$	550−2930−550[d]	4510	1.20

[a] EG = ethylene glycol, L = lactic acid, G = glycolic acid. Subscripts indicate the rounded number of the repeating unit. [b] Determined by GPC. [c] Mole ratio of DLLA to GA is 78/22. [d] Mole ratio of DLLA to GA is 72/28.

temperature determined by this method has a precision of ±0.5 °C.

Microcalorimetry. A differential scanning microcalorimeter (DSC, Perkin-Elmer) was used to study heat exchange during the sol−gel transition for 10−60 °C with a heating rate of 1 °C/min. A polymer solution (0.5 g) with a specified concentration was loaded in a cell. A baseline for deionized water was subtracted in each DSC thermogram.

NMR Spectrometry. An NMR spectrometer (Varian, 500 MHz) was used for ^{13}C NMR spectra of PEG−PLGA−PEG triblock copolymers in D_2O (27 wt %) at various temperatures. The solution temperature was equilibrated for 20 min before measurement.

III. Results and Discussion

Figure 1 shows the chemical structure of PEG−PLGA−PEG triblock copolymers. Synthesis and characterization results were reported elsewhere.[11] The molecular weight, polydispersity, and composition of the block copolymers determined by NMR and gel permeation chromatography (GPC) are summarized in Table 1. All GPC traces of triblock copolymers are unimodal and show low polydispersity. This indicates that the purity is high enough for the study of physical properties of these triblock copolymers.

Figure 2 shows a typical transition curve obtained from an aqueous solution of a $EG_{12}-(L_{31}G_9)-EG_{12}$ triblock copolymer. The composition of the PLGA block was 78/22 (LA/GA) in molar ratio. The critical gel concentration (CGC) of the block copolymer was approximately 16 wt %. Above its CGC, the clear polymer solution, e.g. 33 wt %, formed a transparent gel at 30 °C. The viscosity of $EG_{12}-(L_{31}G_9)-EG_{12}$ triblock copolymer aqueous solution at 33 wt % concentration at room temperature was 10 cP, which makes it easy to formulate and inject through a syringe needle. The viscosity abruptly increased at the sol-to-gel transition temperature. The critical gelation temperature (CGT) forms the lower transition curve in the phase diagram. With further increasing temperature, the transparent gel became turbid. This temperature as a function of polymer concentration was presented by cross-marks in the diagram in Figure 2. Another finding was that the opaque gel became translucent in the temperature range 48−52 °C regardless of polymer concentration. Upon further heating, the tanslucent gel turned apaque again, and the gel finally dissolved into an opaque solution at another concentration-dependent critical

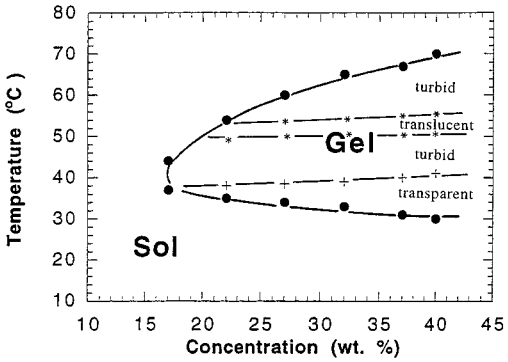

Figure 2. Phase diagram of $EG_{12}-(L_{31}G_9)-EG_{12}$ triblock copolymer aqueous solutions. Filled circles indicate sol−gel transition temperature, and the cross-bar is the temperature at which the transparent gels become turbid. The gel passes through a translucent region (*) and finally becomes turbid again with increasing temperature.

temperature, seen as the upper critical transition curve in the phase diagram.

The lower transition temperature showed a weak concentration dependency and gradually decreased from 36 to 30 °C as the polymer concentration increased from 17 to 40 wt %. The upper transition temperature was more influenced by concentration. In the same concentration range, the transition temperature increased from 44 to 70 °C.

The lower transition curve is particularly interesting for drug delivery applications. The weak concentration dependency in lower transition curve, located in the range 30−36 °C, should allow a safe formulation of labile drugs with a polymer solution at room temperature without phase transition problem. After the gel forms, the water content in the gel will determine its degradation rate and the release rate of incorporated pharmaceuticals in the body. Another interesting feature is that the gel formed remained transparent at the body temperature. This permits a homogeneous gel phase at body temperature and will minimize uncontrolled gel properties such as degradation and diffusion properties due to gel heterogeneity. The sol-to-gel transition temperature of Pluronic F127, PEO−PPO−PEO (4300−3300−4300), varies from 50 to 5 °C in a similar polymer concentration range.[6] This implies that above a concentration for which the gelation temperature is 20 °C (occurring at a concentration about 25%) may require refrigeration during formulation which is of inconvenience.

The gelation mechanism of Pluronic polymers has been investigated by using a variety of instrumentation such as ultrasound velocity, light scattering, small-angle neutron scattering, rheometry, and microcalorimetry.[14−16] The Pluronic polymers form micelles that are equilibrated with monomeric polymers. The equilibrium shifts to micelle formation with increasing temperature. Above a CGC, the micelles pack together to occupy the entire volume, resulting in gel formation. According to this mechanism, the formed gel is subject to dissolution upon dilution from its surface, because when diluted, the interaction forces between packed micelles are not strong enough to keep an integrated mass, resulting in dissociation. This allows surface erosion of the gel, which has been utilized as a means for near-zero-order release of incorporated drugs for a short period of time.[9] However, the observation of integrity of the PEG−PLGA−PEG gel in rats even after 1 month may imply

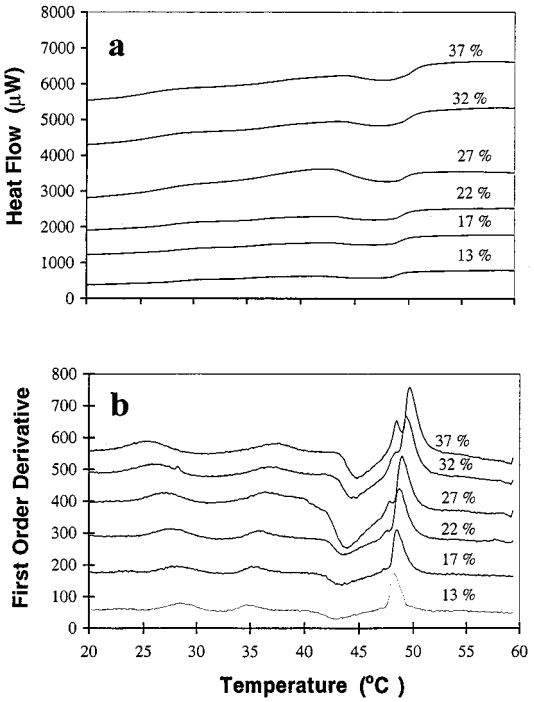

Figure 3. (a) Concentration-dependent DSC thermogram of aqueous solutions of $EG_{12}-(L_{31}G_9)-EG_{12}$ triblock copolymer, obtained from microdifferential scanning calorimetry. The heating rate was 1 °C/min. The baseline of deionized water was subtracted for each thermogram. (b) First-order derivatives of thermogram with respect to temperature.

that the gelation mechanism or gel structure is different than that of Pluronic, or if follows the same mechanism, the interactions between packed micelles are in a different order than those found in Pluronics.[10]

The micelle formation and change in the micellar structural change of PEG−PLGA−PEG at low concentrations were investigated by ^{13}C NMR, dye solubilization method, and light scattering.[11] Abrupt changes in micellar diameter and aggregation number at 30 °C were found. The second virial coefficient sharply decreased at 30 °C, indicating a sudden increase in polymer−polymer attraction at the critical temperature. The critical micelle concentration (cmc) of Pluronics decreased one hundredth over 20−45 °C while that of PEG−PLGA−PEG decreased one-half over 20−50 °C, implying a different mechanism of gelation.[11]

The DSC thermogram of an aqueous solution of $EG_{12}-(L_{31}G_9)-EG_{12}$ as a function of polymer concentration is presented in Figure 3a. The first derivative of the thermogram with regard to temperature clearly shows the transition (Figure 3b). Each curve shows two endotherms and one exotherm. As the concentration increases, the first endotherm gradually shifted to lower temperature, while all other changes in heat capacity shifted to higher temperature. Because the thermograms were obtained at a scanning rate of 1 °C/min, the heat capacity changes do not exactly coincide with the phase transition temperatures which were obtained after equilibration at each temperature for 15 min presented in the phase diagram of Figure 2. However, on the basis of the temperature dependency and the heat capacity peak location, it seems that the first endotherm is related to the sol-to-gel transition and the second to the gel turbidity change (a clear to an opaque gel). The large change in heat capacity occurred in the gel phase at 48 °C, and this is related to the turbidity

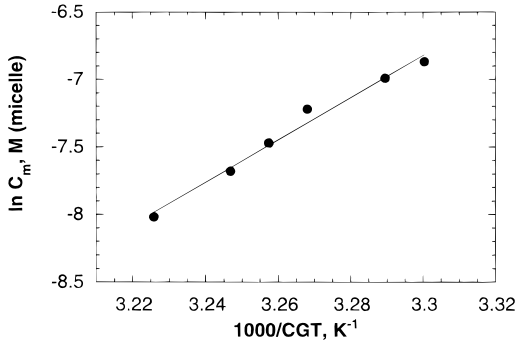

Figure 4. Calculation of enthalpy change during sol-to-gel transition $EG_{12}-(L_{31}G_9)-EG_{12}$ triblock copolymer aqueous solutions.

change of the gel from opaque to translucent to opaque in a brief temperature range. The enthalpy change at 48−50 °C was increased with increasing polymer concentration. The enthalpy change (ΔH(exotherm)) was almost the same when normalized by the weight of polymer, that is, $\Delta H = -31.75 \pm 7.46$ J/mol of polymer. At this temperature, the gel became translucent again. All these observations are not fully understood; however, the transitions in the gel phase are probably associated with restructuring of micelles in the gel phase.

On the basis of the assumption of a micelle model, the standard states for sol to gel transition can be taken as the micelles in an ideal dilute solution at unit molarity and micelles in gel state.[15] The standard enthalpy change involves gelation of a mole of micelles. The thermodynamic functions, free energy (ΔG°_{gel}), enthalpy (ΔH°_{gel}), and entropy (ΔS°_{gel}) of gelation, can be written as follows.

$$\Delta G^\circ_{gel} = RT(\ln C_m)$$

$$\Delta H^\circ_{gel} = R\{\mathrm{d}(\ln C_m)/\mathrm{d}(1/T)\}$$

$$\Delta S^\circ_{gel} = (\Delta H^\circ_{gel} - \Delta G^\circ_{gel})/T$$

R is the gas constant. C_m is the micellar concentration in mol/L or the concentration of polymer (C) divided by aggregation number. The aggregation number is a function of temperature and should be considered in the calculation of C_m. Assuming the micelles are intact during the sol-to-gel transition as is assumed for the Pluronic case, the aggregation number is a function of temperature. ln C_m is plotted against reciprocal temperature in Figure 4.

The enthalpy of gelation calculated calculate from the slope was $\Delta H^\circ_{gel} = 130.15$ kJ/mol (micelle). The aggregation number from static light scattering was calculated to be 98 at 30 °C, and the molecular weight of $EG_{12}-(L_{31}G_9)-EG_{12}$ triblock copolymer was 3910.[11] Therefore, $\Delta H^\circ_{gel} = 1.32$ kJ/mol (chain) at 30 °C. $\Delta G^\circ_{gel} = -0.18$ kJ/mol (chain), and $\Delta S^\circ_{gel} = 4.94$ J/(mol K) (chain) at 30 °C. This small endotherm is comparable with that of Pluronic F127, 1−2 kJ/mol (chain).[15] In the case of Pluronics, a huge endotherm caused by micellization overshadowed the small endotherm caused by the sol-to-gel transition. Yu et al. claimed that such a small enthalpy of gelation resulted from the minor change in hydration of the PEO block in micellar fringe, and gelation is simply packing of independently formed micelles and practically athermal process.[15] In both

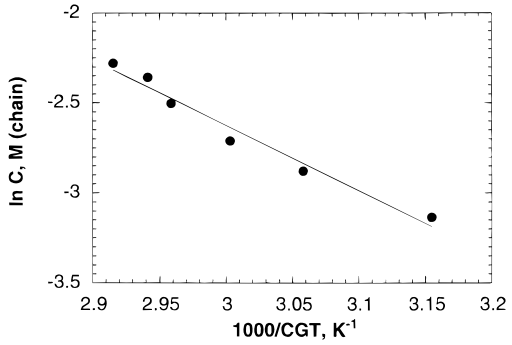

Figure 5. Calculation of enthalpy change during sol-to-gel transition (upper transition, but opposite to gel melting) of EG_{12}−($L_{31}G_9$)−EG_{12} triblock copolymer aqueous solutions.

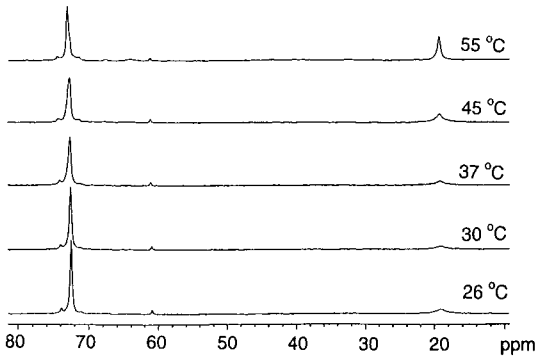

Figure 6. ^{13}C NMR spectra of 27 wt % EG_{12}−($L_{31}G_9$)−EG_{12} triblock copolymer in D_2O as a function of temperature. The solution was equilibrated for 20 min at the setting temperature before measurement.

PEG−PLGA−PEG and PEO−PPO−PEO cases, the positive enthalpy terms make unfavorable contributions to gelation. Therefore, the entropy term is the driving force in the sol-to-gel transition. This is in contrast with the gelation of gelatin where the enthalpy term (−67 kcal/mol) is the dominant force in gelation.[17]

Thermodynamic functions for the gel-to-sol transition (upper transition) of PEG−PLGA−PEG triblock copolymer aqueous solutions can be regarded in a different manner. Now, the standard states for the gel-to-sol transition are assumed to be polymer aggregates and chain molecules instead of micelles because micelles are broken at this high temperature due to dehydration followed by phase mixing. Therefore, the thermodynamic equations can be rewritten with C (polymer concentration) instead of C_m (micelle concentration).

A plot of ln C versus reciprocal temperature gives the enthalpy of the gel-to-sol transition (Figure 5). From the slope, the enthalpy of gel melting was calculated to be 30 kJ/mol (chain). Similarly, $\Delta G = -6$ to -8 kJ/mol (chain) and $\Delta S = 70$ J/mol (chain). The gel-to-sol transition is an endothermic process (opposite to gelation) as shown in the negative slope.

The change in micellar structure with increasing temperature can be inferred by ^{13}C NMR spectra (Figure 6). The peak observed at 19−20 ppm from CH_3 of PLGA block remained unchanged until the temperature reached 37 °C. At 45 and 55 °C the peak height was significantly enhanced, whereas the peak at 73−74 ppm from PEO block was a little broadened with temperature and its height a little reduced. Both peaks slightly shifted to downfield at elevated temperatures. The gradual changes in the peaks may reflect that there is no considerable change in the micellar nature during the sol−gel transition and that the core−shell structure is preserved. However, the aggregation number and size of micelles which increased abruptly at 30 °C as shown in the low-concentration study may drive the sol-to-gel transition.[11] Also, with increasing temperature the hydrophobic core is more exposed to the water by gradually increased degree of intermixing with the PEG corona.[5] This structural change may influence interactions between the micelles as shown in microcalorimetry study resulting in the sol-to-gel transition, turbidity change in the gel phase, and finally leading to the gel-to-sol transition. Such a trend can be supported by ^{13}C NMR above 45 °C. By phase mixing between PEG and PLGA, and an increase in the molecular motion of PLGA, the micellar structure is broken and PLGA blocks are exposed to water, resulting in enhanced methyl peak at high temperature. The phase mixing tendency at higher temperatures between PEG and PLGA may be responsible for the stability of the gel against dilution in water. When the PLGA core in the micelle is partially exposed to PEG corona by phase mixing, this may also lead to enhanced intermicellar interactions between PEG and PLGA by hydrophobic interaction or by intermicellar penetration of PEG chains. On the basis of this fact, it is thought that the gelation may result from the close packing of partially phase-mixed micelles acting as a "soft sphere", which allows the overlapping of the micelles during the gelation process. The CGC calculated on the basis of the "hard sphere model" accoding to ref 7 was approximately 8 wt %, while the experimentally determined CGC was 16 wt %. This suggests again that the gelation may occur via the close packing of soft micelles with significant micellar overlapping.

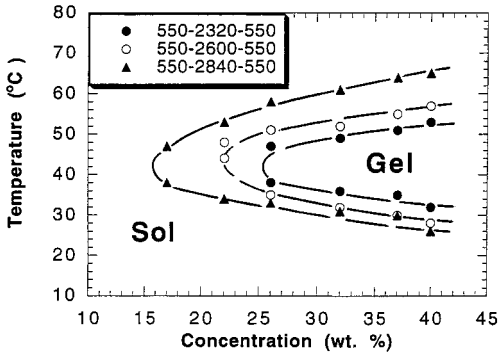

Figure 7. Phase diagram of PEG−PLGA−PEG triblock copolymers with various PLGA lengths: (●) EG_{12}−($L_{26}G_7$)−EG_{12}; (○) EG_{12}−($L_{29}G_8$)−EG_{12}; (▲) EG_{12}−($L_{31}G_9$)−EG_{12}. The legend in the graph indicates molecular weight of constituting block.

The effect of PLGA block length on the sol−gel transition curve, while PEG block length and PLGA composition were kept constant at PEG M_w 550 and LA/GA ratio 78/22, is presented in Figure 7. With increasing PLGA block length, the curve shifted to lower temperatures, while the overall curve shape remained almost unchanged. The increase of 500 Da in molecular weight of PLGA caused the transition curve to shift to lower concentrations by about 10 wt %. In other words, with increasing hydrophobic block length, the gelation takes place at lower concentration and lower temperature while the temperature region for gel phase was widened at a given polymer concentration. The increase in PLGA block length may result in larger micelles, which tend to pack to form a gel at lower concentrations and improve gel stability at a given concentration when

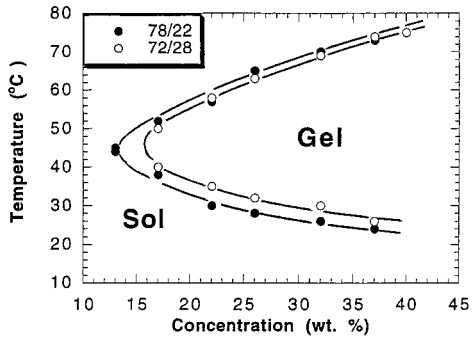

Figure 8. PLGA composition effect on the phase diagram of PEG−PLGA−PEG (550−2900−550) triblock copolymers: (●) $EG_{12}-(L_{32}G_9)-EG_{12}$; (○) $EG_{12}-(L_{31}G_{12})-EG_{12}$. The legend in the graph indicates the mole ratio of DLLA to GA.

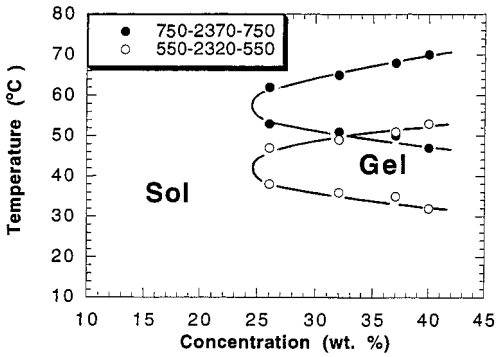

Figure 9. PEG length effect on the phase diagram of PEG−PLGA−PEG triblock copolymer aqueous solutions: (●) $EG_{17}-(L_{26}G_7)-EG_{17}$; (○) $EG_{12}-(L_{26}G_7)-EG_{12}$. The legend in the graph indicates molecular weight of constituting block.

compared with the copolymers of the lower molecular weight PLGA middle block.

The slight change in PLGA composition also caused the transition curve to shift (Figure 8). As the DLLA content in the PLGA block increased, thus increasing hydrophobicity of the block, the whole curve transferred to a lower concentration region. This result indicates that the nature of the middle hydrophobic block plays a critical role in gel formation.

It is very interesting to note that the PEG chain length adjusts the transition temperatures without altering the curve shape. The increase of 230 Da in PEG molecular weight vertically shifted the whole curve to a higher temperature by about 16 °C as demonstrated in Figure 9. This result suggests that the PEG length does not influence the CGC but strong modulation in CGT. The longer PEG has less tendency for phase mixing and requires higher temperatures for enough phase mixing and hydrophobic interaction for micelle packing and gelation. At elevated temperatures, PEG's become more hydrophobic, resulting in more phase mixing with PLGA.

From the information obtained by changing polymer composition and molecular weight of constituting blocks in this and our previous studies, it can be concluded that upper gel-to-sol transition is easily obtained in relatively wide range of molecular weight and hydrophobic block properties, but a full transition curve (combined upper and lower transition curves) is only realized in a delicate combination of each block length and hydrophobic block properties.[5] The hydrophobic block nature and its block length determined the CGC, whereas the PEG length is a key parameter for CGT. The fact that location of

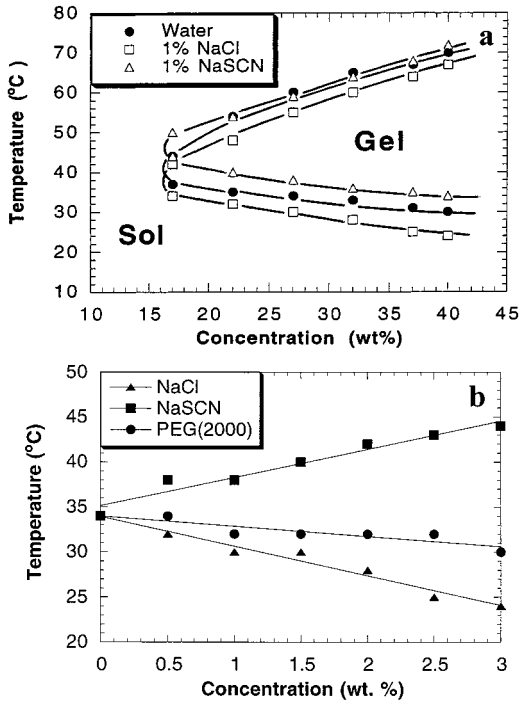

Figure 10. Additive effects on the phase transition of 27 wt % $EG_{12}-(L_{31}G_9)-EG_{12}$ triblock copolymer aqueous solutions: (a) salt effect; (b) concentration effects of NaCl, NaSCN, and PEG 2000.

the transition curve is very sensitive to the properties of the blocks and their length becomes a very convenient means for adjusting CGC and CGT for drug delivery applications as described in the Introduction.

Some salts are known as water structure making (NaCl) and water structure breaking (NaSCN). By adding the water structure making salt (NaCl), favorable ion−water interactions exclude the solutes (polymers) around the ion, resulting in a salt-out effect.[18] Therefore, such salts affect the phase transition behavior of the triblock copolymers. At a concentration of 1 wt %, NaCl caused the transition curve to shift to lower temperature without influencing CGC, while NaSCN showed an opposite result as shown in Figure 10a. The effect of concentration of each salt on sol-to-gel transition is presented in Figure 10b with the effect of PEG (MW 2000) as an additive. The degree of curve shift is linearly proportional to the salt concentration. Adding PEG to the solution lowered the curve in the transition temperature, but its effect was marginal.

The water structure making salt causes the precipitation of amphiphilic water-soluble polymers at high concentration. The salt mediates hydrogen bond interaction between water molecules and thus minimizes water−polymer hydrogen bonding. This apparently enhances the hydrophobic interaction between the micelles, resulting in a transition at lower temperature. The opposite effect is expected with a water structure breaking salt.

It is often discussed in the literature that the gelation temperature of Pluronic polymers is much influenced by PEG. This leads to variation of gelation temperature of unpurified Pluronics because the free PEG disturbs the Pluronic micelle packing. The free PEG makes the gelation of Pluronic polymers occur at higher temperature.[12] In this particular triblock copolymer system, free PEG additive resulted in the opposite shift of the transition curve; that is, free PEG lowered the transition

curve in temperature. This strongly suggests that free PEG might interact with micelles to enhance micelle packing rather than disturbing micelle−micelle interactions. The possible reason is that the free PEG interacts with the partially exposed PLGA core intermixed with PEG corona. This enhances the intermicellar interactions, acting as bridges between the micelles and thus leading to gelation at lower temperature.

IV. Conclusions

The PEG−PLGA−PEG triblock copolymer in aqueous solution is a free-flowing sol at room temperature and becomes a gel at body temperature. The gelation was investigated with a focus on mechanisms and structure−property relationship. These amphiphilic polymers form a micellar structure with a PLGA core and a PEG corona. As temperature increases, the PEG segments interact with the PLGA core, forming a new intermixed phase between core and shell. At low concentration, micelles grow and polymer−polymer attraction increases with increasing temperature.[11] This may lead to swollen micelles contacting each other at the sol-to-gel transition temperature above CGC. For a possible gelation mechanism, it is proposed that, with increased miscibility and increased interphase volume, the micelles start to contact, and the PEG chain in the corona interpenetrates between micelles or the intermixed phase hydrophobically interacts with each other, leading to solid micelle packing and preventing the gel from dissolution by dilution. The miscibility between the two blocks still increases with temperature even in the gel phase, leading to unusual turbidity changes with temperature dependency on degree of phase mixing. Structure−property relationships show that transition temperatures are sensitive to the block length of PEG−PLGA−PEG triblock copolymers. Increasing hydrophobicity of the polymer leads to decrease in CGC and CGT. Salt-out salt decreases the lower transition temperature while salt-in salt increases the sol-to-gel transition temperature. All of these finding suggest that the gelation is driven by hydrophobic forces.

The control of CGC and CGT is very important in drug delivery applications. It is shown that the structural parameters of polymers as well as additives can be used for fine-tuning of CGC and CGT for PEG−PLGA−PEG triblock copolymer aqueous solutions.

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