Macromolecules

Volume 39, Number 9 May 2, 2006

Communications to the Editor

Preparation of Thermosensitive Diblock Copolymers Consisting of MPEG and Polyesters

Moon Suk Kim,[†,§] Hoon Hyun,[†,‡,§] Gilson Khang,[‡] and Hai Bang Lee*,[†]

Medicinal Science Division, Korea Research Institute of Chemical Technology, P.O. Box 107, Yuseong, Daejeon 305-600, Korea, and Department of Polymer/Nano Science and Technology, Chonbuk National University, 664-14, Duckjin, Jeonju 561-756, Korea

Received December 20, 2005
Revised Manuscript Received March 14, 2006

During the past decade, biodegradable thermogelling block copolymers that undergo a sol-to-gel transition with increasing temperature have been exploited in biomedical applications such as drug delivery and tissue engineering.[1,2] In particular, thermogelling block copolymers that are in the sol state at room temperature but the gel state at body temperature could potentially be injected into humans in the sol state, where they would then undergo a sol-to-gel transition in situ. Various block copolymers consisting of poly(ethylene glycol) (PEG) and biodegradable polyesters such as poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), or their copolyesters (PLGA) have been prepared as potential candidate biodegradable thermogelling polymers.[3−5]

It has been suggested that for a polymer in aqueous solution to undergo a sol-to-gel transition the polymer should contain both hydrophilic and hydrophobic parts and should contain segments capable of arranging into a crystalline structure.[6−9] Block copolymers consisting of PEG and polyesters form micelles in aqueous solution at room temperature and undergo a transition to a gel with increasing temperature; this transition has been attributed to aggregation of the micelles.[9−11] The behavior of these block copolymers is affected by the sizes of the polyester and PEG blocks. If the polyester block is too large, the polymer is insoluble in water. If, on the other hand, the PEG block is too large, micellar aggregation is restricted such that the block polymer aqueous solution does not undergo a sol-to-gel transition on heating from room temperature to body temperature and is still in the sol state at body temperature. These characteristics indicate that the balance of hydrophobicity and hydrophilicity within a block copolymer is critical to its thermal phase transition behavior in aqueous solution.

Many types of polyesters exhibit good biodegradability and biocompatibility. Poly(ϵ-caprolactone) (PCL) is an attractive biodegradable crystalline polyester[12] that can be easily prepared by ring-opening polymerization (ROP) of ϵ-caprolactone (CL). Recently, we prepared a methoxy poly(ethylene glycol) (MPEG)−PCL diblock copolymer via ROP of CL with MPEG as an initiator and showed that it undergoes a sol-to-gel transition with increasing temperature, making it a candidate thermosensitive material for biomedical applications.[7−9] Other candidate polyesters could potentially be synthesized by ROP of trimethylene carbonate (TMC) and 1,4-dioxan-2-one (DO) as well as LA or GA. Several polyester copolymers containing CL and TMC or CL and DO have been investigated for possible use in biomedical applications.[13−15] These copolymers have the advantage that their degradation does not result in an acid environment, unlike the degradation of PLLA and PLGA.

Random copolymerizations that enable control of the properties of copolymers of PCL and PTMC or PDO have been carried out with various metal initiating systems.[13−15] To our knowledge, however, the random copolymerization of TMC or DO with CL in the presence of MPEG as an initiator has never been performed using HCl as the monomer activator, despite the fact that HCl is a widely available commercial product that is easier to use than metal-based initiators such as stannous octoate.[16]

We hypothesized that MPEG−polyester copolymers may be suitable for use as thermosensitive materials in biomedical applications. Thus, in the present work we examined the dependence of the sol-to-gel transition temperature on the chemical composition of MPEG−polyester copolymers syn-

---

[*] Corresponding author: e-mail hblee@krict.re.kr; Tel 82-42-860-7220; Fax 82-42-860-7228.

[†] Korea Research Institute of Chemical Technology.

[‡] Chonbuk National University.

[§] Moon Suk Kim and Hoon Hyun contributed equally to this paper.

10.1021/ma052713d CCC: $33.50 © 2006 American Chemical Society

Table 1. Synthesis of MPEG−Polyester Diblock Copolymers[a]

no.[b]	polyester	$M_{n,NMR}$[c] MPEG−polyester	M_w/M_n[d]
$E_{17}C_{24}$	100/0 (PCL)	750−2490	1.14
$E_{17}C_{23}T_1$	95/5 (PCL/PTMC)	750−2300/120	1.14
$E_{17}C_{23}D_1$	95/5 (PCL/PDO)	750−2320/130	1.19
$E_{17}C_{23}L_1$	95/5 (PCL/PLLA)	750−2380/120	1.17
$E_{17}C_{22}T_2$	89/11 (PCL/PTMC)	750−2200/280	1.26
$E_{17}C_{19}T_5$	78/22 (PCL/PTMC)	750−2130/600	1.25
$E_{17}C_{18}T_6$	75/25 (PCL/PTMC)	750−1900/650	1.19
$E_{17}T_{24}$	0/100 (PTMC)	750−2400	1.13

[a] MPEG = 750 (M_w/M_n = 1.09). [b] Numbers represent the unit of each segment and E, C, T, L, and D represent MPEG, PCL, PTMC, PLLA, and PDO. [c] Determined by ^{1}H NMR. [d] Measured by gel permeation chromatography (based on standard polystyrene).

thesized by random copolymerization of TMC or DO with CL in the presence of HCl, with MPEG as the initiator.

MPEG−polyester diblock copolymers [(MPEG-*b*-PCL, MPEG-*b*-(PCL-*co*-PTMC), and MPEG-*b*-(PCL-*co*-PDO)] were synthesized via the random copolymerization of TMC or DO with CL as the monomer using the terminal alcohol of MPEG (M_n, 750 g/mol) as an initiator in the presence of HCl. For comparison, the copolymerization of LA and CL with MPEG [MPEG-*b*-(PCL-*co*-PLLA)] was also performed in the presence of stannous octoate. The MPEG−polyester diblock copolymers obtained, all of which had similar M_n values, are summarized in Table 1.

By using HCl as the monomer activator, we were able to prepare large quantities of copolymers, it was easy to purify the residual products, and the PCL and PTMC or PDO designed with MPEG could be prepared with a narrow molecular weight distribution and a controlled block composition. The compositions of all of the copolymers were verified by ^{1}H NMR spectroscopy and were found to be in good agreement with the predicted compositions (Figure 1); this demonstrated that the monomers were randomly incorporated into the copolymers.[17]

The hydrophobicity of the segments within a copolymer, as well as the overall crystallinity of the copolymer, may be important determinants of the sol−gel transition behavior of MPEG−polyester copolymers. We investigated their properties in the bulk state using DSC and XRD. DSC analysis indicated that the diblock copolymers exhibit glass transition temperatures at around −60 °C. In addition, the thermograms of all diblock copolymers showed two exothermic peaks, which were assigned to crystallization of the MPEG blocks and the polyester blocks, respectively.[18] Introduction of PTMC, PDO, or PLLA into the PCL segments caused a lowering of the crystallization enthalpies of the polyester block segments in the diblock copolymers, likely due to phase mixing between polyester blocks. The degree of crystallinity of the MPEG−PCL block copolymer in the bulk state was estimated to be 36% by XRD analysis. However, the degree of crystallinity decreased to 27% with the inclusion of PTMC, PDO, or PLLA into the PCL segments.[19] Moreover, as the amount of PTMC was further increased, the crystallinity gradually decreased to 15%. This indicates that as the crystalline domains of polyester blocks decrease in size, the interactions between hydrophobic blocks in the block copolymer are weakened. These characteristics mean that MPEG−polyester diblock copolymers with different crystallinities can be designed by adjusting the amount of PTMC, PDO, or PLLA in the PCL segments.

To examine the phase transitions of the synthesized diblock copolymers in aqueous solution as a function of temperature, 20 wt % aqueous solutions of the diblock copolymers were prepared by dissolution in deionized water at 80 °C. The polymer solutions formed translucent sols at room temperature.

Viscosity measurements were employed to study the phase transitions of the diblock copolymer solutions as a function of temperature. This approach is based on the hypothesis that sol-to-gel and gel-to-sol transitions involve the formation and destruction of a structured network, respectively, and hence will be accompanied by a substantial change in the viscosity. We chose to identify the sol-to-gel transition by analyzing the temperature dependence of the viscosity rather than by the test-tube inversion method that has been used previously[3−8] because the former provides more reproducible and quantitative results.

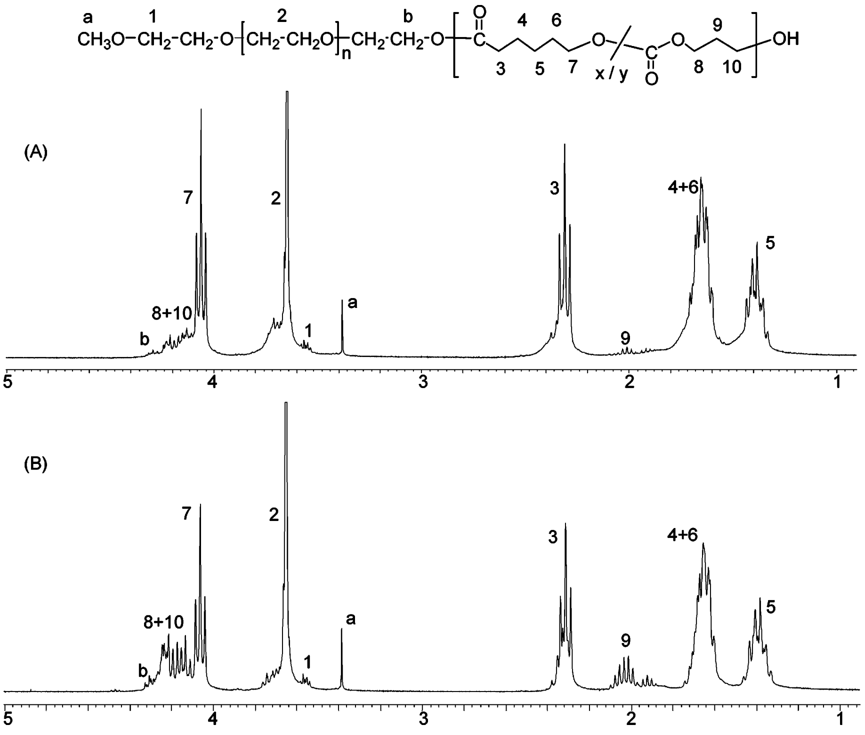

Figure 1. ^{1}H NMR spectra of (A) $E_{17}C_{23}T_1$ and (B) $E_{17}C_{18}T_6$ in $CDCl_3$.

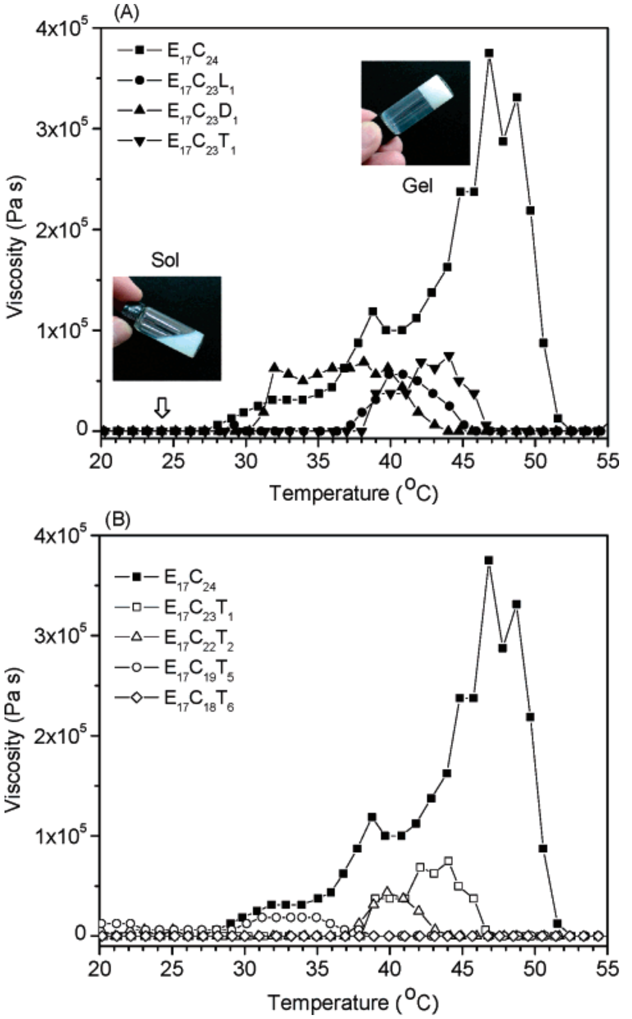

Figure 2. Viscosity vs temperature curves for different diblock copolymers: (A) (■) $E_{17}C_{24}$, (●) $E_{17}C_{23}L_1$, (▲) $E_{17}C_{23}D_1$, and (▼) $E_{17}C_{23}T_1$; (B) (■) $E_{17}C_{24}$, (□) $E_{17}C_{23}T_1$, (△) $E_{17}C_{22}T_2$, (○) $E_{17}C_{19}T_5$, and (◇) $E_{17}C_{18}T_6$ at 20 wt % concentration.

We measured the viscosities of the diblock copolymer solutions from 6 to 70 °C in increments of 1 °C. Figure 2 shows the viscosity as a function of temperature for a variety of diblock copolymer solutions. At low temperatures, the diblock copolymer solution viscosities are zero, indicating they are in a sol state in which the diblock copolymers are homogeneously dissolved in the water. At intermediate temperatures, the solution viscosity increases to a sharp maximum and then drops rapidly, indicative of the formation and disruption of a gel state. At higher temperatures, the solution viscosity returns to zero. The shapes of the phase transition curves are similar for all diblock copolymer solutions except for the diblock copolymer with 75% PCL content or lower, which did not show a transition; however, introduction of the polyester segments causes the gel state of the solution to have a lower viscosity and to be stable over a narrower temperature range, suggesting that the hydrophobic segment affects the phase transition behavior.

Figure 2A shows the viscosity vs temperature curves for 20 wt % aqueous solutions of diblock copolymers with different polyesters of 5% content in the PCL segment. The MPEG−PCL diblock copolymer [$E_{17}C_{24}$] solution was a gel between 28 and 52 °C and showed a maximum viscosity of 380 kPa•s. The maximum viscosities of the MPEG-*b*-(PCL-*co*-PTMC) [$E_{17}C_{23}T_1$], MPEG-*b*-(PCL-*co*-PDO) [$E_{17}C_{23}D_1$], and MPEG-*b*-(PCL-*co*-PLLA) [$E_{17}C_{23}L_1$] gels were 75, 68, and 56 kPa•s, respectively. Introduction of different polyester segments into the diblock copolymer led to a shift in the onset temperature of gelation and caused the gel state to be stable over a slightly narrower temperature range than was observed for $E_{17}C_{24}$, which contains the greatest amount of PCL hydrophobic block segments.

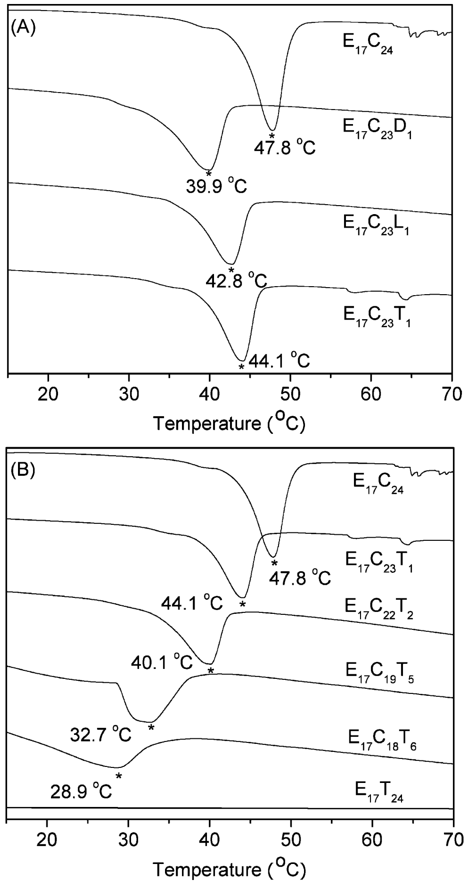

Figure 3. DSC profiles for 20 wt % aqueous solution of diblock copolymers.

To understand the sol-to-gel phase transitions, we investigated the crystallinities of the diblock copolymers in aqueous solution using DSC and XRD. In the DSC thermograms (Figure 3A), 20 wt % solutions of the diblock copolymers each exhibited one exothermic peak at around 40−50 °C due to the phase mixing between the polyesters. Introduction of PTMC, PDO, or PLLA into the PCL segment caused the crystallization enthalpy of the polyester block segment in the diblock copolymers to decrease from 13 to 8 J/g, probably due to phase mixing between the PCL and polyester blocks in aqueous medium. In the XRD analysis, all of the diblock copolymers in aqueous solution showed peaks assignable to crystalline regions of polyester blocks, with the fraction of polyester blocks contained within these crystalline regions decreasing with the inclusion of PTMC, PDO, or PLLA into the PCL segments.[20,21] The DSC and XRD data thus indicate that the diblock copolymers are organized into crystalline domains even when dissolved in aqueous medium. Moreover, the lower degree of crystallinity of the polyester-containing diblock copolymers $E_{17}C_{23}D_1$, $E_{17}C_{23}L_1$, and $E_{17}C_{23}T_1$ compared with $E_{17}C_{24}$ likely means that these diblock copolymers have weaker hydrophobic interactions between their chains and thus form gels with lower viscosities over a narrower temperature range.

When heated, $E_{17}C_{23}T_1$ changed from a sol to a gel at around 37 °C (i.e., body temperature), indicating that copolymers with this composition may be promising candidate materials for biomedical applications. To further explore these copolymers, we compared the phase transition behaviors of copolymers with varying amounts of PTMC in the PCL segment. Figure 2B presents the viscosity vs temperature curves for a 20 wt % aqueous solution of diblock copolymers with different amounts of PTMC in the PCL segment. The diblock copolymer solutions with PCL:PTMC ratios of 4:1 or higher showed sol-to-gel phase transitions, whereas the diblock copolymer $E_{17}C_{18}T_6$ remained in the sol state over the entire temperature range considered, presumably due to the good solubility of this copolymer. As the amount of PTMC in the PCL segment was increased, the maximum viscosity of the gel state gradually decreased from 380 to 14 kPa•s, and the gelation range shifted to lower temperature.

Figure 3B shows the DSC thermograms for the diblock copolymer solutions with different PTMC contents. The crystallization enthalpy of copolymers gradually decreased from 13 to 1 J/g with increasing PTMC content. No crystallization peak was observed in thermogram for the MPEG−PTMC block copolymer solution. XRD analysis of the $E_{17}C_{24}$ diblock copolymer solutions showed peaks assignable to crystalline regions of PCL blocks.[20,21] As PTMC segments were increasingly included into the PCL blocks, the degree of crystallinity gradually decreased. The observed behavior is consistent with introduction of the PTMC segments creating a more hydrophilic environment around the PCL block, leading to a decrease in the onset temperature of gelation and a lowering of the gel viscosity. These observations indicate that the crystallinity of these diblock copolymers in aqueous solution is critical to their thermal phase transition behavior.

In conclusion, we successfully prepared a series of MPEG−polyester diblock copolymers by ring-opening random copolymerization of TMC or DO and CL in the presence of HCl with MPEG as the initiator. All of the copolymers formed a sol at room temperature when prepared as 20 wt % aqueous solutions. As the temperature was increased above room temperature, a sol-to-gel transition, manifesting as an increase in viscosity, was observed for all copolymers except for the diblock copolymer with a large PTMC content in the PCL segment ($E_{17}C_{18}T_6$). The sol-to-gel phase transition temperature was found to depend on the type and amount of polyester segment introduced into the copolymer. In addition, the maximum viscosity of the copolymer solution decreased with decreasing degree of crystallinity of the diblock copolymer, which depended on the type and amount of polyester segment introduced into the PCL segment. XRD and DSC analyses revealed that even in aqueous solution the diblock copolymer solutions exhibited crystalline domains that favored the formation of a gel due to the hydrophobic interactions between the hydrophobic polyester blocks. The present results therefore confirm that the MPEG−polyester diblock copolymer solutions exhibit a sol-to-gel transition as a function of temperature, indicating that aqueous solutions of these copolymers could be utilized as thermosensitive materials.

Acknowledgment. This work was supported by a grant from KMOHW (Grant A050082).

Supporting Information Available: ^{1}H NMR spectra, DSC and XRD in bulk and aqueous medium, and the thermal properties of all of the diblock copolymers. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Griffith, L. G.; Naughton, G. *Science* **2002**, *295*, 1009.
(2) Petka, W. A.; Harden, J. L.; McGrath, K. P.; Wirtz, D.; Tirrell, D. A. *Science* **1998**, *281*, 389.
(3) Jeong, B.; Bae, Y. H.; Kim, S. W. *Macromolecules* **1999**, *32*, 7064.
(4) Jeong, B.; Bae, Y. H.; Lee, D. S.; Kim, S. W. *Nature (London)* **1997**, *388*, 860.
(5) Jeong, B.; Bae, Y. H.; Kim, S. W. *J. Biomed. Mater. Res.* **2000**, *50*, 171.
(6) Jeong, B.; Wang, L.; Gutowska, A. *Chem. Commun.* **2001**, *16*, 1516.
(7) Kim, M. S.; Seo, K. S.; Khang, G.; Cho, S. H.; Lee, H. B. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 5784.
(8) Kim, M. S.; Seo, K. S.; Khang, G.; Cho, S. H.; Lee, H. B. *J. Biomed. Mater. Res.* **200**4, *70A*, 154.
(9) Kim, M. S.; Hyun, H.; Cho, Y. H.; Seo, K. S.; Jang, W. Y.; Kim, S. K.; Khang, G.; Lee, H. B. *Polym. Bull. (Berlin)* **2005**, *55*, 149.
(10) Yang, Z.; Pickard, S.; Deng, N.; Barlow, R. J.; Attwood, D.; Booth, C. *Macromolecules* **1994**, *27*, 2371.
(11) Lee, D. S.; Shim, M. S.; Kim, S. W.; Lee, H. Park, I. Chang, T. *Macromol. Rapid Commun.* **2001**, *22*, 587.
(12) Pitt, C. Poly(caprolactone) and its copolymer. In Chasin, M., Langer, R., Eds.; *Biodegradable Polymers as Drug Delivery System*; Marcel Dekker: New York, 1990; pp 71−120.
(13) Matsuo, J.; Sanda, F.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **1997**, *35*, 1357.
(14) Shibasaki, Y.; Sanda, F.; Endo, T. *Macromolecules* **2000**, *33*, 3590.
(15) Hu, Y.; Zhu, K. *J. Polym. Degrad. Stab.* **2004**, *85*, 705.
(16) Ould-Ouali, L.; Noppe, M.; Langlois, X.; Willems, B.; Te Riele, P.; Timmerman, P.; Brewster, M. E.; Arien, A.; Preat, V. *J. Controlled Release* **2005**, *102*, 657.
(17) ^{1}H NMR spectra of diblock copolymers are illustrated in the Supporting Information (Figures S1 and S2).
(18) Thermal properties of the all diblock copolymers in bulk state are summarized in the Supporting Information (Table S1).
(19) XRD of the diblock copolymers in bulk state are illustrated in the Supporting Information (Figure S3).
(20) XRD of the diblock copolymers in an aqueous medium are illustrated in the Supporting Information (Figure S4).
(21) Thermal properties of the all diblock copolymers in an aqueous medium are summarized in the Supporting Information (Table S2).

MA052713D