Synthesis and Thermally Responsive Properties of Novel Pluronic F87/Polycaprolactone (PCL) Block Copolymers with Short PCL Blocks

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ABSTRACT: Polycaprolactone (PCL) was successfully grafted to both ends of Pluronic F87 block copolymers (PEO-PPO-PEO) to obtain novel amphiphilic PCL-F87-PCL block copolymers with short PCL blocks. The block composition and structure of PCL-F87-PCL block copolymers were studied by nuclear magnetic resonance (NMR), gel permeation chromatography (GPC), differential scanning calorimetric (DSC), and wide angle X-ray diffraction (WXRD) techniques. Several kinds of particles consisting of small micelles and medium and large aggregates were observed by laser light scattering (LLS) measurements because of the complicated structure of these copolymers. Importantly, PCL-F87-PCL block copolymers exhibit temperature-sensitive behavior similar to that found in Pluronic systems. Compared with Pluronics, the critical micellization temperature (CMT) values of PCL-F87-PCL block copolymers obtained from surface tension measurements are significantly lower due to the enhanced hydrophobicity of PCL segments. A fully reversible sol–gel transition was detected for the PCL-F87-PCL hydrogels. Preliminary results show that there is no burst release for hydrophobic model drug, 9-(methylaminomethyl) anthracene (MAMA), from PCL-F87-PCL hydrogel and the initial release rate is almost constant. This indicates that PCL-F87-PCL hydrogels possess attractive release profiles, which are beneficial for application in controlled release systems. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 100: 4163–4172, 2006

Key words: polycaprolactone; biocompatibility; controlled drug release; hydrogel; thermally responsive materials

INTRODUCTION

Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) block copolymer (PEO-PPO-PEO) (commercially available as Pluronics) is a macromolecular surfactant that can aggregate into micelles in aqueous solution.[1–10] It possesses excellent temperature-sensitive property because both PPO and PEO homopolymers have a lower critical solution temperature in water. Furthermore, the block copolymer has excellent biocompatibility and it is one of the very few synthetic polymeric materials that is approved by the US Food and Drug Administration for use as food additives and pharmaceutical ingredients.[1] Hence, they are potential candidates in biomedical applications such as drug delivery system, controlled release system, and gene therapy.[11–14]

However, the critical micellization concentration (CMC) and critical micellization temperature (CMT) of Pluronic block copolymers are reasonably high due to the weak hydrophobicity of PPO block, which limits their application in drug delivery system. To ensure that the hydrophobicity of Pluronic copolymers increases and their temperature-sensitive property is retained at the same time, hydrophobic polycaprolactone (PCL) chains were attached to both ends of F87 block copolymer to produce PCL-F87-PCL block copolymers. Since PCL is also a well-known biodegradable and biocompatible polyester, the resulting PCL-F87-PCL block copolymers have significant potential for application in the biomedical field such as drug delivery and controlled release systems. The aggregation, temperature sensitivity, and gelation behavior of PCL-F87-PCL block copolymers in water were studied by laser light scattering (LLS), surface tension, and rheological measurements. The release kinetics of hydrophobic model drug MAMA from PCL-F87-PCL hydrogel was examined.

EXPERIMENTAL

Materials

Pluronic F87 were kindly supplied by BASF Corp. (Mount Olive, New Jersey, US) and dried overnight under vacuum, prior to use. ε-Caprolactone (ε-CL)

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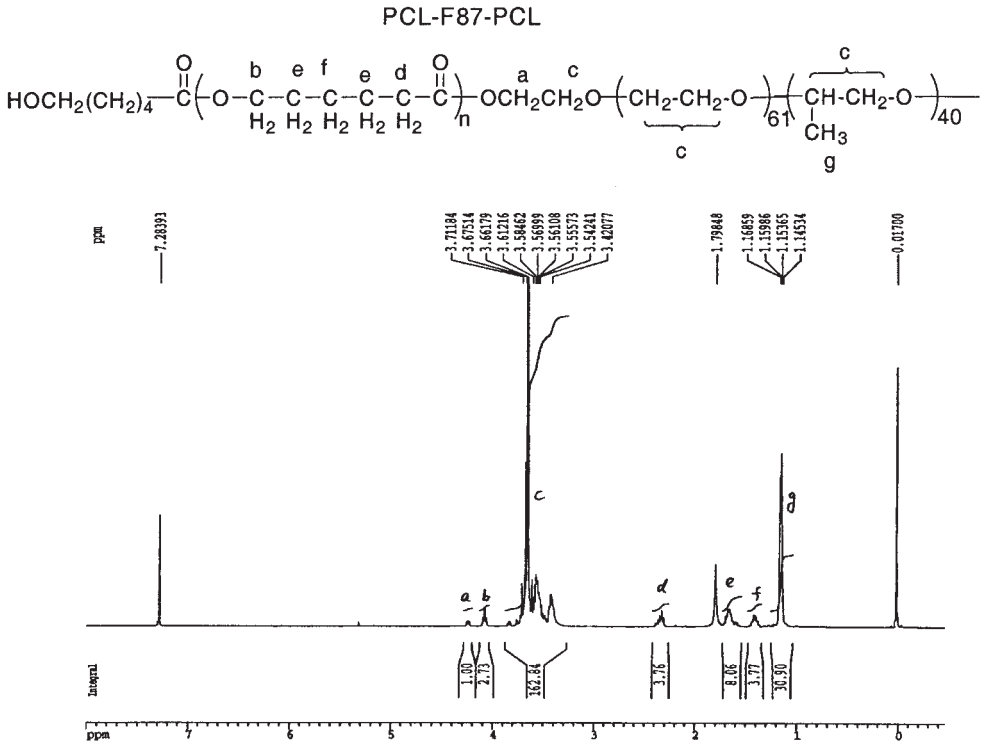

Figure 1 ^{1}H NMR spectrum of PCL_4-F87-PCL_4 ($CDCl_3$).

was purchased from Aldrich and dried over calcium hydride (CaH_2) under stirring at room temperature for 48 h and distilled under reduced pressure. The purified ε-CL was stored at room temperature under argon environment. Stannous octoate ($Sn(Oct)_2$) was purchased from Aldrich and used as received. Model drug 9-(methylaminomethyl)anthracene (MAMA) were purchased from Aldrich and used as received.

Synthesis of PCL-F87-PCL block copolymers

A 100-mL round-bottom flask with a stopcock was heated under vacuum to remove the moisture. After cooling to room temperature, argon was introduced into the flask. Then ε-CL (24 mmol) and F87 (1.5 mmol) were added and heated to 100°C under stirring to achieve a well-mixed molten phase. After the mixture was cooled, $Sn(Oct)_2$ (at 0.1 wt % of ε-CL) was added to the flask under argon environment and the vacuum-purge cycle was repeated three times. The mixture was degassed and heated to 140°C. After stirring for 16h, the reaction product was cooled to room temperature and subsequently dissolved with methylene chloride, precipitated twice in 10-fold volume of methanol, and once in 10-fold volume of diethyl ether. The polymer PCL_6-F87-PCL_6 was filtered and dried overnight under vacuum. A white powder with a 73% yield was obtained. ^{1}H NMR (400MHz, $CDCl_3$, TMS), δ (ppm): 1.15 (m, —OCH_2—$CH(CH_3)$—), 1.25–1.35 (m, —O—$(CH_2)_2$—CH_2—$(CH_2)_2$—CO—), 1.59–69 (m, —O—CH_2—CH_2—CH_2—CH_2—CH_2—CO—), 2.30–2.38 (m, —O—$(CH_2)_4$—CH_2—CO—), 3.35–3.8 5 (m, —OCH_2— CH_2— and —OCH_2—$CH(CH_3)$ —), 4.01–4.08 (m, —O—CH_2— $(CH_2)_4$—CO—). 4.21–4.28 (t, —CO—OCH_2—CH_2—) (Fig. 1). PCL-F87-PCL block copolymers with different block compositions were synthesized. They are designated as PCL_4-F87-PCL_4 and PCL_{11}-F87-PCL_{11}. For the nomenclature of the polymer "PCL_4-F87-PCL_4, PCL_6-F87-PCL_6 and PCL_{11}-F87-PCL_{11}," the numbers "4, 6, and 11" correspond to the number of repeating unit "CL" in PCL-F87-PCL block copolymers, respectively.

Sample preparation

The preparation of PCL-F87-PCL aggregates in water

The PCL-F87-PCL aggregates in aqueous solutions were prepared as follows: A sample of PCL-F87-PCL block copolymer (10 mg) was dissolved in 2 mL of tetrahydrofunan (THF). The PCL-F87-PCL solution was added drop-wise to 10 mL of distilled water under gentle stirring. THF was then removed under reduced pressure and the PCL-F87-PCL aggregates in water (0.1 wt %) were formed at the same time.

The preparation of PCL-F87-PCL hydrogels

The copolymers were first dissolved in acetone. A predetermined amount of distilled water was added

slowly into the polymer solutions in acetone under gentle stirring. After this, acetone was removed under reduced pressure. Then the hydrogels formed from copolymers were equilibrated for 2 days.

In vitro drug release of PCL-F87-PCL hydrogels

A certain amount of copolymer and hydrophobic model drug MAMA was first dissolved in acetone. A predetermined amount of distilled water was added slowly into the polymer solution under gentle stirring and acetone was removed under reduced pressure. Then the drug loaded hydrogels produced using the copolymers were equilibrated for two days. A predetermined amount of drug loaded hydrogel was introduced into a dialysis membrane (molecular weight cut-off, 8000 Da) and the sample was placed in a container filled with PBS solution. Then the container was placed in a shaking water bath for the drug release study. At predetermined time intervals, 2 mL of PBS solution outside the dialysis membrane was removed and measured at wavelength 254 nm, by ultraviolet spectrophotometer (HP UV, series 4) to determine the concentration of released drug. The solution was then returned to the system.

Characterization

Nuclear Magnetic Resonance (NMR) spectra were recorded at room temperature using a Bruker ACF-400 (400 MHz) Fourier Transform Spectrometer. Chemical shifts (δ) were given in ppm, using tetramethylsilane (TMS) as the internal reference. Gel permeation chromatography (GPC) of the copolymers was performed on an Agilent 1100 apparatus (Germany) equipped with a differential refractometer as the detector. Tetrahydrofuran (THF) was used as the mobile phase with a flow rate of 1.0 mL/min. Differential scanning calorimetric (DSC) thermograms were obtained using the modulated DSC 2920 (TA Instruments, Inc., New Castle, DE), and the scanning rate was set at 10°C/min. The sample (ca. 10 mg) was placed in an aluminum pan that was sealed using a sample pan crimper. The seal should be tight but not hermetic. The wide angle X-ray diffraction measurements (WXRD) were conducted using the Philips PW1830 powder diffractometer equipped with a Cu K_α radiation source. The X-ray diffractometer was operated at 20 kV and 10 mA. The CMT was measured using a Dataphysics DCAT-21 tensiometer. The rheological properties were studied by using a TA (Carrimed CSL 500) controlled stress rheometer. The geometry used is a rough steel plate with 2 cm diameter. Silicon oil was applied around the sample and plate to avoid the evaporation of solvent.

Laser light scattering

Static light scattering

Static light scattering (SLS) was used to measure and analyze the time–average scattered intensities. The method is often used to determine microscopic properties of particles such as the z-average radius of gyration (R_g), the weight–average molecular weight ($(\overline{M}_w)$), and the second virial coefficient (A_2) according to eq. (1):

$$\frac{KC}{R_\theta} = \frac{1}{M_w}\left[1 + \frac{16\pi^2 n^2 \langle R_g^2\rangle \sin^2\left(\frac{\theta}{2}\right)}{3\lambda^2}\right] + 2A_2C \qquad (1)$$

where, the Rayleigh ratio, $R_\theta = (I_s r^2/I_i \sin\theta)$; $4\pi^2 n^2(\partial n/\partial C)^2/(N_A\lambda^4)$; C, the concentration of the polymer solution; n, the refractive index of the solvent; θ, the angle of measurement; λ, the wavelength of laser light; N_A, the Avogadro's constant, and $(\partial n/\partial C)$, the refractive index increment of the polymer solution. A plot of (KC/R_θ) versus $[\sin^2(\theta/2) + kC]$ (where k is a plotting constant) can be used to determine the molecular parameters. By extrapolating the data to zero angles and concentrations, R_g and A_2 can be obtained from the slopes, respectively. A simultaneous extrapolation to zero angle and concentration yields an intercept, which is the inverse of the $\overline{M}_w$.

Dynamic light scattering

The frequency of scattered light fluctuates around the incident light because of the constant motion of the polymer molecules. Dynamic light scattering (DLS) measures the intensity fluctuations with time and correlates these fluctuations to the properties of the scattering objects. In general, the terms of correlation functions of dynamic variables are always used to describe the response of the scattering molecules to the incident light. From the expression,

$$\Gamma = Dq^2 \qquad (2)$$

the translational diffusion coefficients, D can be determined. Γ is the decay rate, which is the inverse of the relaxation time, τ, q the scattering vector ($q = (4\pi n \sin(\theta/2))/\lambda$), where θ is the scattering angle, n is the refractive index of the solution, and λ is the wavelength of the incident light. If the Stokes–Einstein equation is used, the apparent hydrodynamic radius, R_h, can be calculated using the following equation:

$$R_h = \frac{kT}{6\pi\eta D} \qquad (3)$$

TABLE I
Characteristics of PCL-F87-PCL Block Copolymers

Sample	$\bar{M}_n$ (NMR)[a]	$\bar{M}_n/\bar{M}_w$ (GPC)	$\bar{M}_w$[b]	Yield (%)
PCL_4-F87-PCL_4	8,610	1.04	8,950	75
PCL_6-F87-PCL_6	9,070	1.06	9,610	73
PCL_{11}-F87-PCL_{11}	10,210	1.08	11,030	70

[a] Determined by the integration ratio of the peak at 2.32 ppm (—O— $(CH_2)_4$—CH_2—CO— group in PCL block) and the peak at 1.15 ppm (—OCH_2—CH(CH_3)— group in Pluronic F87 block) in the ^{1}H NMR spectrum.
[b] $\bar{M}_w = \bar{M}_n$ (NMR) × [$\bar{M}_n/\bar{M}_w$ (GPC)].

where, k, is the Boltzmann constant; T, the absolute temperature; and η, the solvent viscosity.

A Brookhaven BIS200 laser scattering system was used to perform the static and dynamic light scattering experiments. The light source is a power adjustable vertically polarized 350 mW argon ion laser with a wavelength of 488 nm. The inverse Laplace transform of REPES supplied with the GENDIST software package was used to analyze the time correlation function (TCF), and the probability of reject was set to 0.5.

RESULTS AND DISCUSSION

Synthesis and characterization

The block copolymers PCL-F87-PCL were synthesized by ring opening polymerization of the monomer ε-Caprolactone, using Pluronic copolymer F87 as the initiator and stannous octoate ($Sn(Oct)_2$) as the catalyst, where the reaction mechanism is that of co-ordination polymerization.[15,16] The polymer composition, structure, and molecular weight were characterized by NMR and GPC techniques. A ^{1}H NMR spectrum of PCL_4-F87-PCL_4 in $CDCl_3$ is shown in Figure 1. The small peak at 4.23 ppm belongs to the methylene protons of the PCL-CO—OCH_2—CH_2—O-F87 group, which indicates the formation of the PCL_4-F87-PCL_4 block copolymer. From the intensity ratio of —CO—OCH_2—CH_2— (δ 4.25 ppm) and —OCH_2—CH(CH_3)— (δ 1.15 ppm), we confirmed that PCL blocks were attached to both ends of Pluronic F87. The polymerization degree (DP,k) of PCL in PCL_k-F87-PCL_k copolymers was calculated from the peak intensity ratio of methylene protons of PCL (—O— $(CH_2)_4$—CH_2—CO— : δ = 2.32 ppm) and methyl protons of F87 (—OCH_2—CH(CH_3)—: δ = 1.15 ppm). The number–average molecular weight ($\bar{M}_n$) of the PCL_n-F87-PCL_n copolymer was obtained by using the following expression:

$$\bar{M}_n = \bar{M}_n(\text{F87}) + 114n \quad (4)$$

The calculated weight contents of PCL in PCL_4-F87-PCL_4, PCL_6-F87-PCL_6, and PCL_{11}-F87-PCL_{11} block copolymers are shown in Table I.

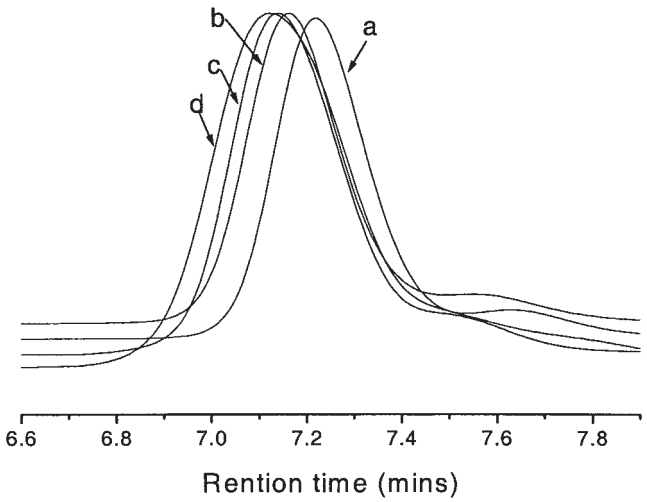

Figure 2 GPC traces of (a) F87, (b) PCL_4-F87-PCL_4, (c) PCL_6-F87-PCL_6, and (d) PCL_{11}-F87-PCL_{11}.

GPC traces of PCL-F87-PCL block copolymer and Pluronic F87 are shown in Figure 2. The molecular weight distribution ($\bar{M}_w/\bar{M}_n$) of PCL_4-F87-PCL_4, PCL_6-F87-PCL_6, and PCL_{11}-F87-PCL_{11} block copolymers were determined by GPC and summarized in Table I. It is evident that GPC curves of PCL-F87-PCL block copolymers shift to left with the molecular weight of copolymers increasing. Also, the resulting PCL-F87-PCL copolymers are very pure as shown by the narrow and single symmetrical peaks.

Thermal properties

Thermal characteristics of PCL-F87-PCL block copolymers were studied by DSC. Figure 3 shows the DSC

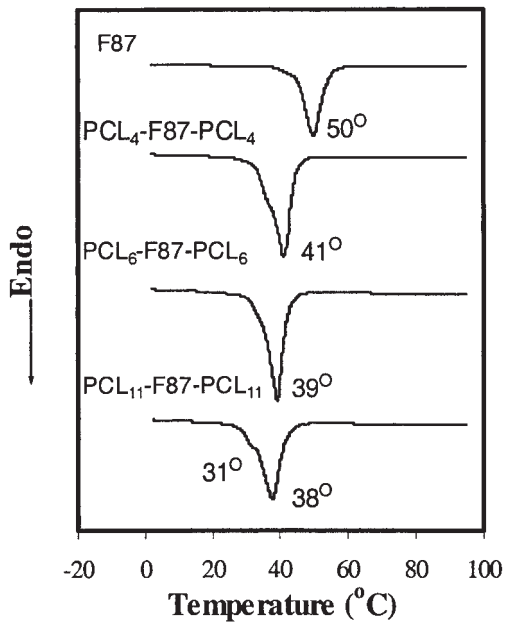

Figure 3 DSC results of PCL-F87-PCL block copolymers.

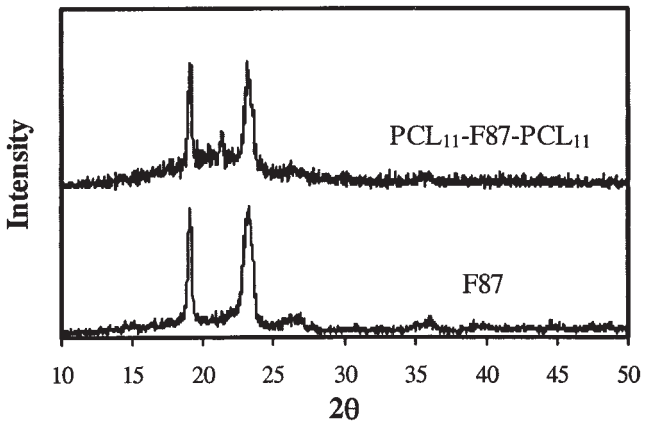

Figure 4 Wide angle X-ray diffraction pattern of PCL_{11}-F87-PCL_{11} and F87 block copolymers.

results of F87 and PCL-F87-PCL block copolymers. To remove the influence of thermal history, all the DSC curves shown in Figure 3 were obtained at the second heating run. There is only one endothermic peak for F87 at 50°C, which is the melting temperature (T_m) of F87. For PCL_4-F87-PCL_4 and PCL_6-F87-PCL_6 block copolymers, there is still one endothermic peak and their T_m values are 41 and 39°C, respectively. PCL is a known semicrytalline polymer (T_m = 55°C),[17] however, there is no melting peak of PCL block for PCL_4-F87-PCL_4 and PCL_6-F87-PCL_6. This could be because PCL blocks in PCL_4-F87-PCL_4 and PCL_6-F87-PCL_6 block copolymers are not long enough to form crystalline structure. However, there are two endothermic peaks for PCL_{11}-F87-PCL_{11} at 31 and 38°C, respectively, and the main peak at 38°C is the melting peak of F87 block in PCL_{11}-F87-PCL_{11}. The small shoulder peak is the melting peak of PCL blocks, indicating that the PCL blocks in PCL_{11}-F87-PCL_{11} are long enough to form crystalline structure. The crystallizability of PCL_{11}-F87-PCL_{11} was confirmed by WXRD pattern shown in Figure 4. Pluronic F87 shows two characteristic crystalline peaks at 2θ = 19.1 and 23.2°. The other two small peaks at 2θ = 20.5 and 21.4° belong to the crystalline PCL blocks. It is shown that T_m of F87 block in PCL_4-F87-PCL_4, PCL_6-F87-PCL_6, and PCL_{11}-F87-PCL_{11} block copolymers decreases with increasing block content of PCL. This should be related to the degree of crystallinity of F87 block in the three block copolymers. The crystallinity of F87 block in PCL-F87-PCL block copolymers decreases with increasing PCL block length, which lowers T_m.

The aggregation behaviors of PCL-F87-PCL aqueous solutions were examined by static and dynamic light scattering measurements. The concentration used in the LLS experiments is equal to or lower than 0.1 wt %, which is in the dilute solution regime. The behavior of individual particles can be characterized at this concentration.[18] Figure 5 shows the relaxation time distribution functions of PCL_4-F87-PCL_4, PCL_6-F87-PCL_6, and PCL_{11}-F87-PCL_{11} block copolymers in aqueous solutions obtained at different scattering angles. Two relaxation peaks were detected for PCL_4-F87-PCL_4 and PCL_6-F87-PCL_6 block copolymers with varying angles. The relaxation time distribution functions of PCL_{11}-F87-PCL_{11} block copolymer are more complicated, exhibiting three peaks. The relaxation time of each peak shifts to lower value with increasing angles.

Whether the relaxation time peak corresponds to true particles is dependent on the observation of q^2 dependence of Γ (the reciprocal of peak relaxation

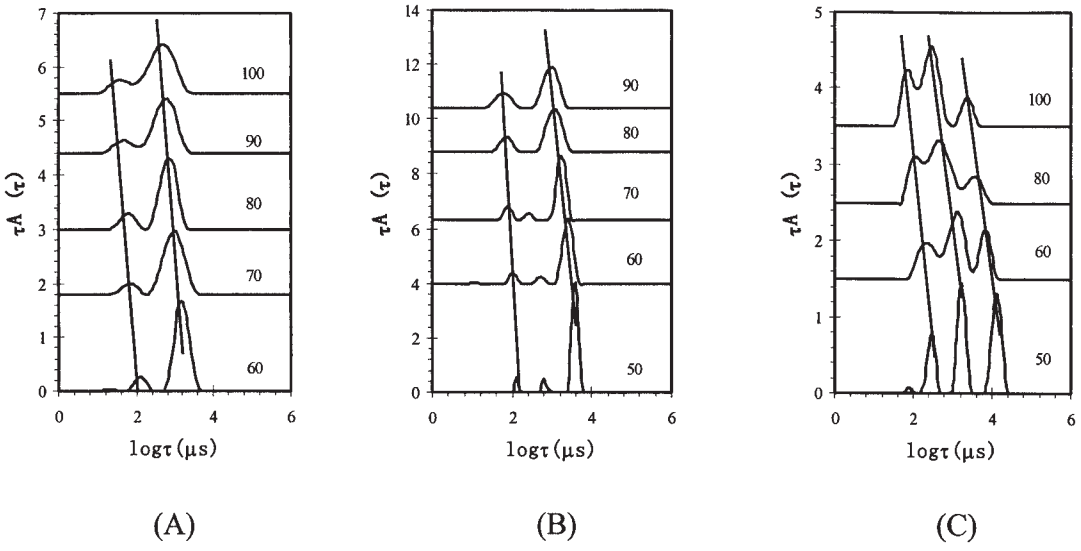

Figure 5 Relaxation time distribution functions of PCL_4-F87-PCL_4 (A, 0.1 wt %), PCL_6-F87-PCL_6 (B, 0.15 wt %), and PCL_{11}-F87-PCL_{11} (C, 0.1 wt %) block copolymers in aqueous solutions at different scattering angles.

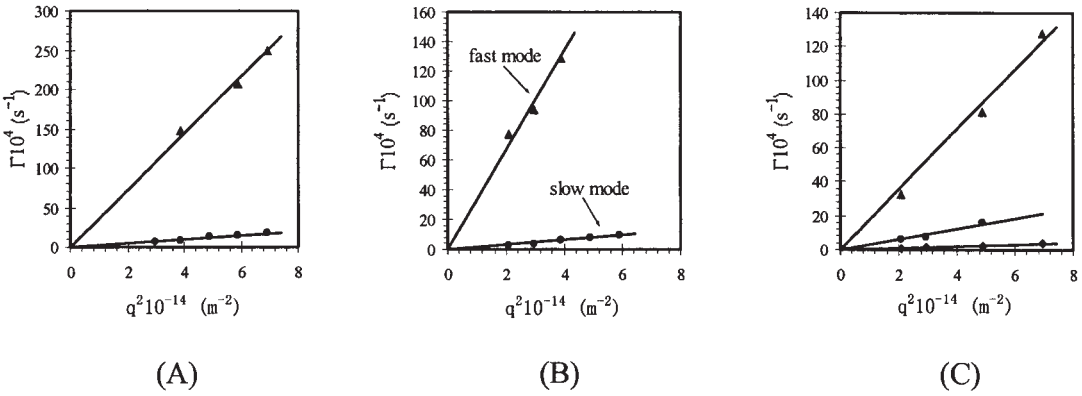

Figure 6 Plots of Γ versus q^2 for PCL_4-F87-PCL_4 (A, 0.1 wt %), PCL_6-F87-PCL_6 (B, 0.15 wt %), and PCL_{11}-F87-PCL_{11} (C, 0.1 wt %) block copolymers in aqueous solution.

time). Hence, the parameter, Γ was plotted as a function of q^2 for PCL_4-F87-PCL_4, PCL_6-F87-PCL_6, and PCL_{11}-F87-PCL_{11} block copolymers (see Fig. 6) and good q^2 dependence of Γ was observed for all the relaxation peaks, indicating that these relaxation time peaks are attributed to true particles. The R_h values of PCL_4-F87-PCL_4 aggregates were determined to be 6.8, 97 nm, while PCL_6-F87-PCL_6 contains aggregates with size of 7.3 and 156 nm. For PCL_4-F87-PCL_4 and PCL_6-F87-PCL_6 block copolymers, the small particle is micelles, whose size is similar to that of Pluronic F87 micelles. The large particles observed are believed to possess rather complex structure. For PCL_{11}-F87-PCL_{11} block copolymer, three kinds of particles are produced, whose R_h values are 14, 80.5, and 454 nm, respectively. Such complicated aggregation behavior in water has also been observed for PLA-F87-PLA block copolymers with short PLA blocks, which was analyzed and discussed in a previous publication.[19] It is believed that there are two reasons for PCL-F87-PCL showing complex aggregation behavior: first, the short PCL blocks on both ends; second, the existence of another hydrophobic block PPO in the middle of PCL-F87-PCL block copolymers. Although the hydrophobicity of PCL is stronger than that of PPO, the block length of PCL is much shorter than that of PPO. Thus, the hydrophobicity of PPO and PCL blocks competes and controls the aggregation behavior of PCL-F87-PCL block copolymers, resulting in the complicated aggregation behavior. There is also a small peak at several scattering angles, as evident from Figure 5. The Γ of the peaks are not q^2 dependent, thus, these peaks do not correspond to true particles. They may be induced by the internal vibrational modes of the particles.

The R_g, $\bar{M}_w$ and aggregation number of PCL_4-F87-PCL_4, PCL_6-F87-PCL_6, and PCL_{11}-F87-PCL_{11} aggregates were studied by SLS and are summarized in Table II. It is shown that the aggregation number ($N_{aggregation}$) increases with increasing PCL block length because the aggregates formed become bigger and more complex with increasing PCL block length. The R_g values of the three polymers are large and there is no obvious trend. The effect of concentration of PCL_4-F87-PCL_4 aqueous solutions on the particle size was studied by DLS and the results are shown in Figure 7. The relaxation time peak remains constant at all concentrations for PCL_4-F87-PCL_4, indicating that the aggregation mechanism of the polymer is based on the closed association model.

Critical micellization temperature

The CMT of PCL-F87-PCL aqueous solutions was examined by surface tension measurement. For PCL-F87-PCL block copolymers, the CMT of PCL_4-F87-PCL_4 and PCL_6-F87-PCL_6 was observed, while that of

TABLE II
Laser Light Scattering Results of PCL-F87-PCL Block Copolymers in Aqueous Solutions at Room Temperature

Sample	R_h (nm) Small	Middle	Large	R_g (nm)	$\bar{M}_w$ (aggregates)	$N_{aggregation}$ [a]
PCL_4-F87-PCL_4	6.8	97		156	8.3×10^5	90
PCL_6-F87-PCL_6	7.3	156		117	2.4×10^6	250
PCL_{11}-F87-PCL_{11}	14	80	454	139	6.9×10^7	6240

a $N_{aggregation} = \bar{M}_w$ (aggregates)/ $\bar{M}_w$ (polymer), where $\bar{M}_w$ (polymer) is given in Table 1.

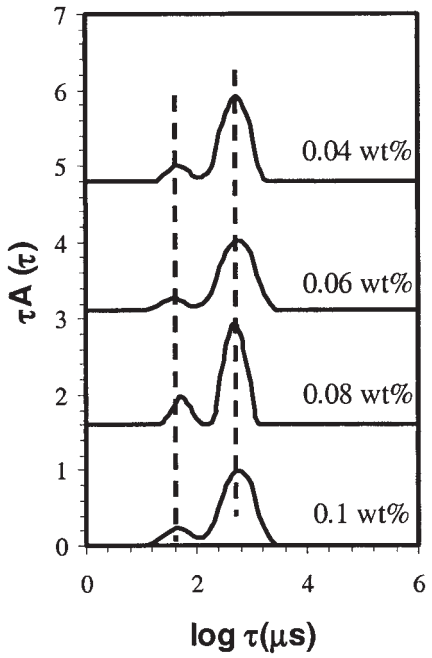

Figure 7 Relaxation time distribution functions of PCL_4-F87-PCL_4 in aqueous solutions with different concentrations at constant scattering angle of 90°.

PCL_{11}-F87-PCL_{11} was not detected. This indicates that the PCL block length in PCL_{11}-F87-PCL_{11} is sufficiently long to negate the temperature-sensitive property of F87 block copolymer, which is corroborated by DSC results discussed previously. There is no crystal structure of PCL blocks formed in PCL_4-F87-PCL_4 and PCL_6-F87-PCL_6, while crystalline PCL domain was observed in PCL_{11}-F87-PCL_{11}. Figures 8 and 9 show the surface tension of PCL_4-F87-PCL_4 and PCL_6-F87-PCL_6 aqueous as a function of temperature at different polymer concentrations respectively. As expected, the critical micellization temperature of PCL_4-F87-PCL_4 and PCL_6-F87-PCL_6 is much lower than that of F87 because of the higher hydrophobicity of PCL-F87-PCL, which is favorable for their applications in controlled release systems.[20] The CMT of PCL_4-F87-PCL_4 and PCL_6-F87-PCL_6 block copolymers was plotted as a function of polymer concentration as shown in Figure 10, where it decreases with increasing concentration. It is also observed that the CMT of PCL_6-F87-PCL_6 is lower than that of PCL_4-F87-PCL_4, at similar concentration due to the more hydrophobic PCL_6-F87-PCL_6 block copolymer. Therefore, PCL_6-F87-PCL_6 block copolymer is easier to aggregate at the same concentration than PCL_4-F87-PCL_4. In addition, the temperature-sensitive property of PCL-F87-PCL block copolymers is significantly more pronounced than Pluronic block copolymers, where it decreases much faster with increasing concentration and this was also observed by Bromberg and coworkers.[21] Such behavior is attrib-

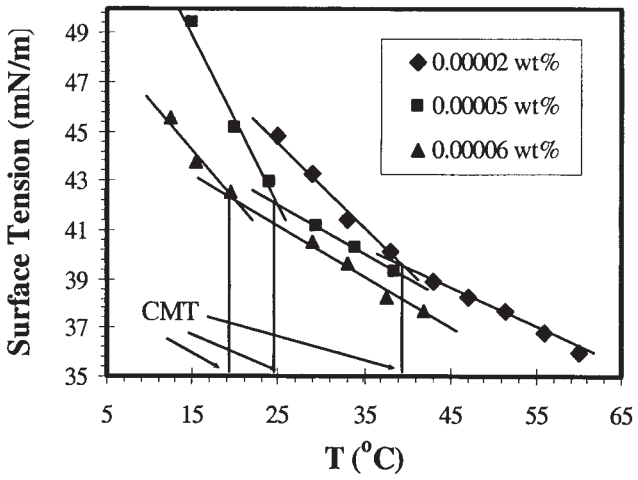

Figure 9 Surface tension as a function of temperature for PCL_6-F87-PCL_6 block copolymer at different concentrations.

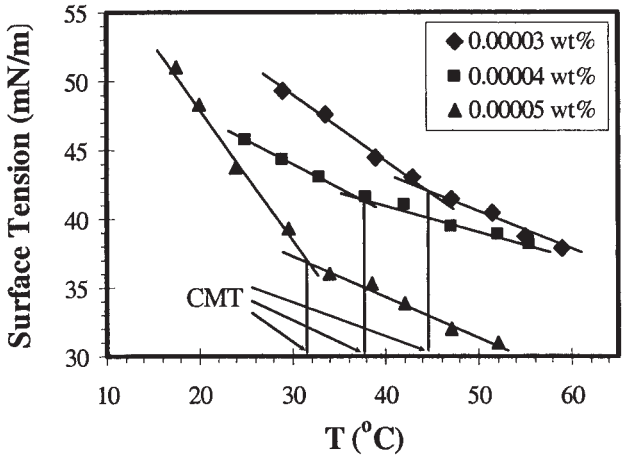

Figure 8 Surface tension as a function of temperature for PCL_4-F87-PCL_4 block copolymer at different concentrations.

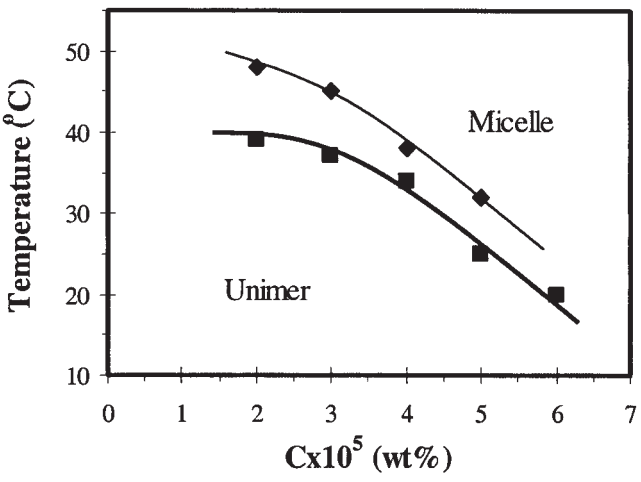

Figure 10 The CMT–CMC boundary of PCL_4-F87-PCL_4 (◆) and PCL_6-F87-PCL_6 (■) block copolymers.

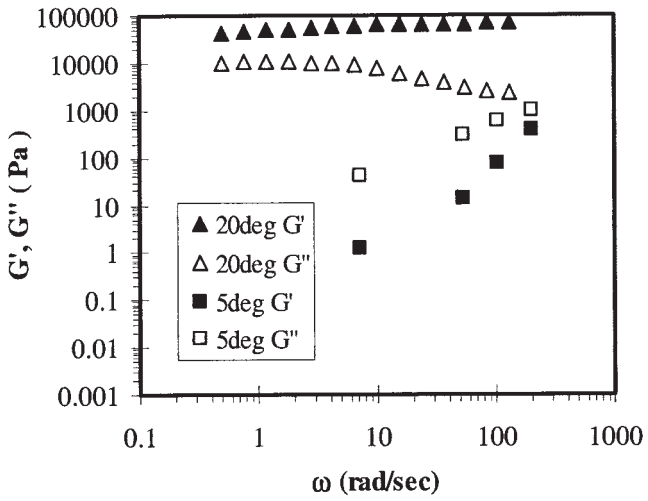

Figure 11 G′ and G″ of PCL_4-F87-PCL_4 (44 wt %) as a function of ω at 5 and 20°C.

uted to the hydrophobic PCL block, which alters the hydrophile–lipophile balance (HLB) and promotes the micellization of PCL-F87-PCL block copolymers.

Critical gelation temperature

The critical gelation temperature (CGT) of PCL-F87-PCL hydrogels was studied by rheological measurements. Rheological method is the most convenient technique for studying gel properties.[22–24] The viscoelastic properties, such as $G'$and G'' were measured as a function of ω to verify whether PCL-F87-PCL block copolymers do form gels. Figure 11 shows the plots of G' and G'' of PCL_4-F87-PCL_4 (44 wt %) block copolymers versus ω at two temperatures. It is evident from Figure 11 that G' is smaller than G'' and not independent of ω at 5°C, where the system exists as a sol. However, when the temperature was increased to 20°C, G' increased by three orders of magnitude, and G' is larger than G'' and is independent of ω, indicating that a gel was formed.

The effect of temperature on the gelation of PCL-F87-PCL block copolymers was studied. G' of PCL_4-F87-PCL_4 sample was plotted as a function of temperature at different concentrations as shown in Figure 12. It is evident that the G' values of PCL_4-F87-PCL_4 increase by about three orders of magnitude for the transition from sol to gel. Also, the thermoreversible sol–gel transition for PCL_4-F87-PCL_4 is very sensitive, which is similar to that observed for Pluronic block copolymers. More interestingly, both sol–gel transition at lower temperature and gel–sol transition at higher temperature were observed for PCL_6-F87-PCL_6, which is similar to that of F127 gel. For PCL_{11}-F87-PCL_{11}, it forms gels above a critical polymer concentration, but its gelation behavior is not thermoreversible. This means the temperature-sensitive property of Pluronic F87 is destroyed when relatively longer hydrophobic chains are attached onto both ends of F87 block copolymer, a result that is consistent with the temperature-sensitive behavior of PCL_{11}-F87-PCL_{11} copolymer in aqueous solutions. These results are interesting in that it provides a strong fundamental basis in the development of chemically modified Pluronic systems for various biomedical applications. High concentration is also required for the gelation of PCL-F87-PCL block copolymers, similar to Pluronics. Therefore, the mechanism of gelation for PCL-F87-PCL could be similar to that of Pluronic, namely attributed to close packed micellar mechanism.

Figure 13 shows the relationship between G' and polymer concentration for PCL-F87-PCL hydrogels. G' for both F87 and PCL-F87-PCL hydrogels increases with concentration, indicating that PCL-F87-PCL hydrogels become stronger when the concentration is higher. The CGT of PCL-F87-PCL hydrogels was plotted against the concentration as shown in Figure 14. The temperature sensitivity of PCL-F87-PCL hydrogels is also more dramatic than that of F87 gel, similar to the temperature-sensitive property of PCL-F87-PCL aqueous solutions. It is shown that the CGT of PCL_4-F87-PCL_4 hydrogel is lower than that of F87 at concentration exceeding 35 wt %. Furthermore, PCL-F87-PCL hydrogels is more hydrophobic than F87 gels, indicating that the former maybe able to deliver more hydrophobic drugs.

The drug release behavior of PCL-F87-PCL hydrogels loaded with hydrophobic model drug MAMA in PBS (pH 7.4, 0.01*M*) aqueous solution was monitored at two temperatures, 25 and 37°C by UV spectrophotometer. The release behavior of MAMA (0.004 wt %)

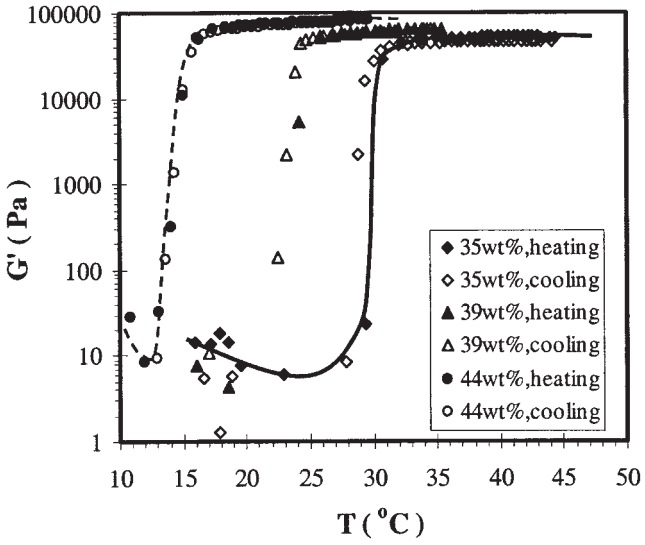

Figure 12 G′ of PCL_4-F87-PCL_4 as a function of temperature at different concentrations (35, 39, and 44 wt %).

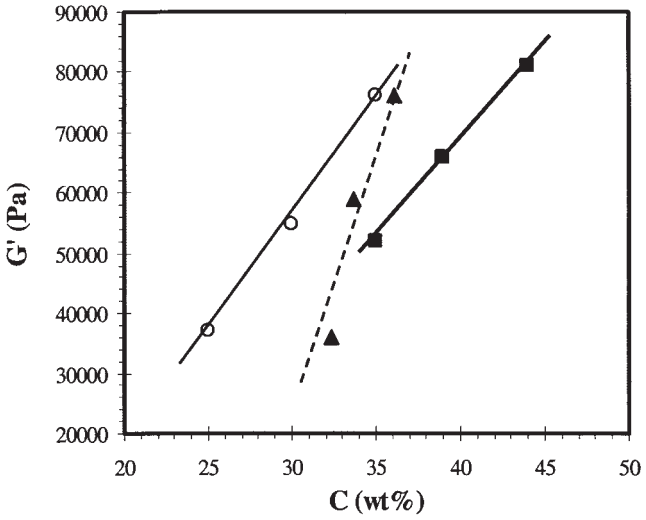

Figure 13 G′ of F87 (○), PCL_4-F87-PCL_4 (■) and PCL_6-F87-PCL_6 (▲) hydrogels as a function of concentration.

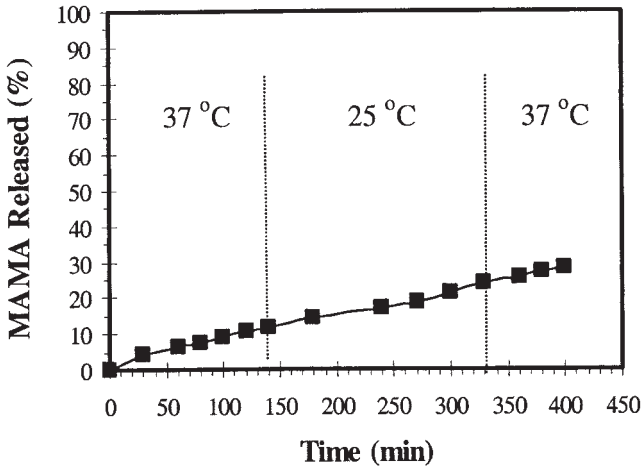

Figure 15 The release behavior of MAMA (0.003 wt %) loaded in PCL_4-F87-PCL_4 (35 wt %) samples in PBS aqueous solutions at 25 and 37°C.

loaded in PCL_4-F87-PCL_4 (35 wt %) is shown in Figure 15. The purpose in preparing the PCL_4-F87-PCL_4 sample at 35 wt % is to ensure that the PCL_4-F87-PCL_4 is a gel at 37°C, and a sol at 25°C. Thus, the effect of sol–gel transition on the drug release behavior can be studied. It is interesting that no burst release was observed for MAMA in PCL_4-F87-PCL_4 sample. The release rate is almost constant at the initial release stage, which is similar to Pluronic and other types of gels.[25,26] It is shown in Figure 15 that only 25% of MAMA was released after 6 h. This finding indicates that PCL_4-F87-PCL_4 hydrogel could be an attractive system for controlled release applications. There is not much difference between the release rate of MAMA from PCL_4-F87-PCL_4 sol at 25°C and its gel at 37°C, which suggests that the diffusion of hydrophobic drug from gels is not a strong function of the viscosity since the viscosity of PCL_4-F87-PCL_4 gel is much larger than that of its sol, which is in agreement with the results for F127 gel obtained by Moore and coworkers.[25] Further study on the drug release kinetics of PCL-F87-PCL hydrogels is in progress.

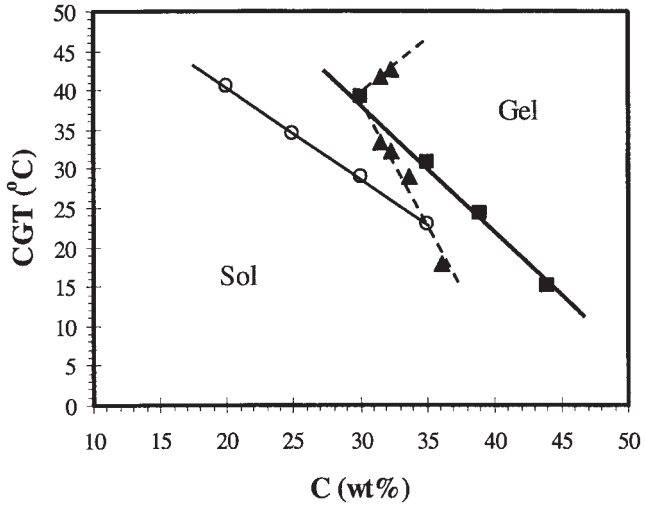

Figure 14 CGT of F87 (○), PCL_4-F87-PCL_4 (■) and PCL_6-F87-PCL_6 (▲) hydrogels as a function of concentration.

CONCLUSIONS

Short hydrophobic PCL chains have been successfully attached to both ends of Pluronic F87 to obtain PCL-F87-PCL block copolymers. The aggregation behavior of PCL-F87-PCL aqueous solutions is complex because of their complicated chemical structure. Several kinds of particles (micelles, large aggregates, and larger aggregates) are formed in such systems. Importantly, PCL-F87-PCL block copolymers also show the temperature sensitivity in water, which is similar to Pluronic block copolymers. For PCL-F87-PCL hydrogels, an excellent sol–gel transition is also observed by rheological measurements. The initial constant and slow release of hydrophobic model drug from PCL-F87-PCL hydrogel was observed, which is favorable for their application in controlled release systems.

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