Synthesis and Physicochemical Characterization of Amphiphilic Block Copolymer Self-Aggregates Formed by Poly(ethylene glycol)-*block*-Poly(ε-caprolactone)

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Received 4 December 2004; accepted 15 April 2005
DOI 10.1002/app.22979
Published online 19 January 2006 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Diblock copolymers with different poly(ε-caprolactone) (PCL) block lengths were synthesized by ring-opening polymerization of ε-caprolactone in the presence of monomethoxy poly(ethylene glycol) (mPEG-OH, MW 2000) as initiator. The self-aggregation behaviors and microscopic characteristics of the diblock copolymer self-aggregates, prepared by the diafiltration method, were investigated by using ^{1}H NMR, dynamic light scattering (DLS), and fluorescence spectroscopy. The PEG–PCL block copolymers formed the self-aggregate in an aqueous environment by intra- and/or intermolecular association between hydrophobic PCL chains. The critical aggregation concentrations of the block copolymer self-aggregate became lower with increasing hydrophobic PCL block length. On the other hand, reverse trends of mean hydrodynamic diameters were measured by DLS owing to the increasing bulkiness of the hydrophobic chains and hydrophobic interaction between the PCL microdomains. The partition equilibrium constants (K_v) of pyrene, measured by fluorescence spectroscopy, revealed that the inner core hydrophobicity of the nanoparticles increased with increasing PCL chain length. The aggregation number of PCL chain per one hydrophobic microdomain, investigated by the fluorescence quenching method using cetylpyridinium chloride as a quencher, revealed that 4–20 block copolymer chains were needed to form a hydrophobic microdomain, depending on PCL block length. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 99: 3520–3527, 2006

Key words: biodegradable; self-assembly; nanoparticles; diblock copolymer; critical aggregation concentration

INTRODUCTION

Polymeric amphiphiles containing hydrophilic and hydrophobic components have been extensively studied in biotechnology and pharmaceutical fields for their unique properties of micelle or micelle-like self-aggregate formation in aqueous milieu.[1–4] Because of the limited solubility of hydrophobic block in the aqueous environment and the hydrophobic interaction between the water-insoluble segments, the polymeric amphiphiles spontaneously form micelle or micelle-like self-aggregates via intra- and/or intermolecular segregation, mainly to achieve thermodynamic stability by minimizing interfacial free energy.[3,5]

In particular, polymeric micelles have been considered as one of the promising candidates for drug delivery systems owing more to the increment of drug concentration in an aqueous milieu than to the solubility limit of the hydrophobic free drug by partitioning the drugs into the hydrophobic core.[1,3–7] The hydrophilic corona, mostly composed of poly(ethylene glycol) (PEG), endowed the polymeric micelles with escape from nonspecific uptake by reticuloendothelial systems (RES). In the systemic circulation, the RES plays a crucial role for clearance of colloidal particle from the blood stream. Therefore, long systemic circulation can be achieved by introducing the PEG component into polymeric micelle systems.[8,9] Coupled with the long circulation effect, remarkably low critical micelle concentration is guaranteed to the polymeric micelle excellent stability owing to the rate of micelle dissociation slower than small molecular surfactant micelles during the systemic circulation. Furthermore, the enhanced permeation and retention effect at a tumor site gave the possibility of passive targeting of the polymeric micelles into tumor site.[10,11]

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Contract grant sponsors: Ministry of Education and Human Resources Development (MOE); Ministry of Commerce, Industry and Energy (MOCIE), Korea; (Project of the Industrial-Academic Cooperation Centered University).

Therefore, a number of studies have focused on the applications of polymeric micelles into cancer drug delivery systems.[8,10–14] As micelle forming materials, amphiphilic block copolymers,[4,6–9,11–13] hydrophobically modified water-soluble polymers,[15–17] and hydrophobized polysaccharides[3,14,18,19] have been extensively investigated.

In this study, we focused on the PEG–poly(ε-caprolactone) (PCL) diblock copolymer. The hydrophobic block of PCL is well-known as a biodegradable polyester with excellent biocompatibility and degradability. Furthermore, it is recently reported that the PEG–PCL block copolymer showed excellent potential for internalization into cellular cytoplasm by endocytosis.[20–22] Although a number of studies of PCL-based amphiphilic block copolymers have well documented the synthesis and characterization,[23–28] biodegradation,[29–31] and application for drug delivery systems,[32–34] the microscopic physicochemical properties of the diblock copolymers with different hydrophilic/hydrophobic balances still remain unclear. In this study, we synthesized PEG–PCL diblock copolymers that have different PCL lengths with the fixed PEG chain length (MW 2000 Da), investigating their self-aggregate formations and physicochemical properties of the formed self-aggregate.

EXPERIMENTAL

Materials

Methoxy PEG (mPEG) with a molecular weight of 2000, ε-caprolactone, stannous 2-ethyl hexanoate (stannous octoate, SnOct), pyrene, and cetylpyridinium chloride (CPC) were purchased from Aldrich Chemical Co. The mPEG was purified by recrystallization from the dichloromethane/diethyl ether system, and ε-caprolactone was dried using CaH_2 and distilled under reduced pressure. All other chemicals and solvents were analytical and/or reagent grades and used without further purification.

Synthesis of PEG–PCL block copolymers

PEG–PCL diblock copolymers (PEGCLs) with different PCL block lengths were synthesized by ring-opening polymerization of ε-caprolactone in the presence of methoxy-PEG (mPEG-OH, MW 2000) as an initiator with a trace amount of stannous octoate (SnOct) as catalyst. The target molecular weights of PCL blocks were 1000, 2000, 3000, and 5000. Predetermined amounts of PEG and toluene/xylene cosolvent (12.5 mL toluene/g PEG, and 5 mL xylene/g PEG) were introduced into a flask, and moisture was removed by azeotropic drying with evaporation of a small part of the toluene at 120°C. After drying and cooling (~60°C), one drop of SnOct (~100 μL) and a predetermined amount of ε-caprolactone monomer were added. Then, the polymerization reaction was performed at 140°C for 24 h with vigorous stirring. After the reaction, the diblock copolymers were obtained by precipitating in excess amount of diethyl ether. The obtained copolymers were dried *in vacuo* for 48 h.

Characterization of PEG–PCL block copolymers

^1H nuclear magnetic resonance (^1H NMR) spectra of the diblock copolymers were recorded by using a Bruker spectrometer operating at 400 MHz using $CDCl_3$ as solvent. Chemical shifts (δ) were given in ppm using tetramethylsilane (TMS) as internal reference. Average molecular weights and their distribution in the copolymers were measured by gel permeation chromatography (Waters) using THF as an elution solvent.

Preparation of self-assembled nanoparticles

PEGCL self-aggregates were prepared by dissolving the copolymers in DMF (10 mg/mL), followed by dialysis against distilled water using dialysis membranes of 15,000 molecular weight cut-off at 20°C for 24 h. After the nanoparticles were formed, the solutions were filtered through a 0.8-μm pore-sized filter to remove large aggregates, and the copolymer nanoparticles were obtained by freeze-drying. Among the PEGCL copolymers, the PEGCL25 (PCL target MW of 5000) had a critical failure of re-suspension into water or buffer solutions with a significant loss during the filtration. Therefore, the PEGCL25 was withdrawn from further characterization.

Measurement of fluorescence spectroscopy (pyrene)

The pyrene solution in acetone ($6 \times 10^{-5} M$, prepared prior to use) was added to the deionized water to make a pyrene concentration of $1.2 \times 10^{-6} M$, and the acetone was removed at reduced pressure at 40°C for 2 h. This solution was mixed with block copolymer nanoparticle solutions to make a copolymer concentration from 2 to 1×10^{-5} mg/mL, resulting in a pyrene concentration of $6 \times 10^{-7} M$. Pyrene fluorescence spectra were obtained by using a spectrofluorophotometer (RF-5301PC, Shimadzu). The excitation and emission wavelengths were 339 and 390 nm, respectively.

The aggregation number of PCL block per one hydrophobic domain was determined by the steady-state fluorescence quenching method, with CPC as a pyrene fluorescence quencher.[35] In microheterogeneous systems such as aqueous micellar solution of amphiphilic block copolymers, the decrease in the probe fluorescence intensity is dependent upon the concentration of the quenching molecule in the system ([Q]). The

steady-state quenching data is widely accepted to fit in the quenching kinetics as follows[35]:

$$ln(I_0/I) = [Q]/[M] \quad (1)$$

where I_0 and I are the fluorescence intensity with the absence and presence of the quencher, [Q] is the concentration of the quencher, and [M] is the concentration of hydrophobic microdomains in the solution. Therefore, the number of hydrophobic group (PCL blocks in this system) in a hydrophobic microdomain (N_{PCL}) can be calculated by eq. (2).

$$N_{PCL} = [PCL_{block}]/[M] \quad (2)$$

Measurement of dynamic light scattering

The particle size and size distribution of PEGCL diblock copolymer self-aggregates were investigated on a dynamic light scattering (DLS) instrument. The DLS measurements were carried out using an ELS-8000 electrophoretic LS spectrophotometer (Otsuka Electronics Co., Japan) equipped with a He–Ne laser operating at 632.8 nm at 25°C and at a fixed scattering angle of 90°. Before measurement, the nanoparticles were re-dispersed in deionized water (1 mg/mL), sonicated for 30 s, and filtered through a 0.8-μm pore-sized filter. Measurements were carried out at a higher concentration of the critical aggregation concentration (cac) measured by fluorescence spectroscopy. The hydrodynamic diameters of the block copolymer nanoparticles were calculated by the Stokes-Einstein equation, and the polydispersity factors represented as μ_2/Γ^2 were evaluated with the cumulant method (μ_2; second cumulant of the decay function, Γ^2; average characteristic line width).[36,37]

The shapes of the nanoparticles were also characterized by DLS (Malvern Instrument LTD., Series 4700) with an argon ion laser system at 488 nm with a digital autocorrelator. The scattering angle varied from 30° to 150° at the constant temperature of 25°C.[18,19,37] The PEGCL block copolymer concentrations of the samples were fixed at 1 mg/mL in deionized water.

RESULTS AND DISCUSSION

Synthesis and characterization of PEG–PCL diblock copolymers

The block copolymers of PEG–PCL (PEGCLs) with different hydrophobic PCL block lengths were synthesized by ring-opening polymerization as shown in Figure 1. To make sure the ring-opening polymerization of ε-caprolactone occurred, the synthesized copolymers were investigated by ^{1}H NMR spectroscopy. Typical ^{1}H NMR spectrum of the PEGCL block copolymer (PEGCL21) is illustrated in Figure 2(B). The chemical shifts of the PEGCL copolymers are as followed. PEGCL21 ^{1}H NMR ($CDCl_3$, ppm, TMS): 3.27 ppm (**a** in Fig. 2, s, CH_3—O in PEG end), 3.54 ppm (**b**, s, —CH_2CH_2—O in PEG), 4.11 ppm (**c**, t, CH_2 CH_2—OCO— in PEG end), 2.20 ppm (**d**, t, OCOCH_2 $(CH_2)_4$ in PCL), 1.54 ppm (**e**, m, $OCOCH_2CH_2CH_2$ CH_2CH_2 in PCL), 1.28 ppm (**f**, m, $OCOCH_2CH_2$ $CH_2CH_2CH_2$ in PCL), 3.96 ppm (**g**, t, $OCOCH_2CH_2$ $CH_2CH_2CH_2$ in PCL), and 3.44 ppm (**h**, t, $OCOCH_2$ $CH_2CH_2CH_2CH_2$OH in PCL end). The number average molecular weights of PEGCLs and PCL block lengths were calculated from the integration data of ^{1}H NMR spectra ($DP_{PCL} = g/c + 1$, $M_{nPCL} = DP_{PCL} \times$ 114.14, and $M_n = M_{nPCL} + 2000$). The results are summarized in Table I.

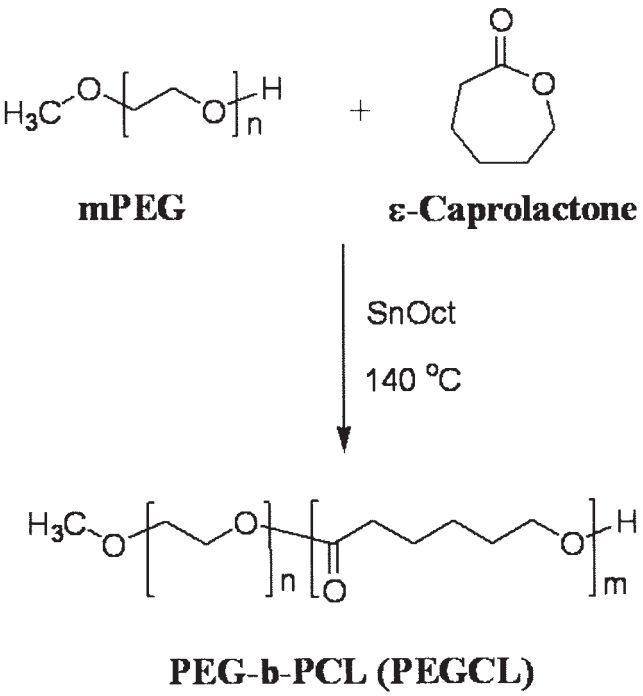

Figure 1 Synthetic scheme for mPEG-*b*-PCL diblock copolymers.

The average molecular weights and polydispersity indexes (PDIs) of the PEGCLs were also measured by GPC using THF as an elution solvent and monodisperse poly(styrene) as standards. The GPC results and chromatograms clearly show the formation of diblock copolymer by increasing MW and shifting chromatograms to a high MW range with increasing PCL length (chromatograms not shown). The PEGCLs show narrow molecular distributions with PDI values around 1.23–1.46. The GPC results are listed in Table I.

Self aggregation of PEG–PCL diblock copolymers

The amphiphilic PEGCLs with hydrophilic PEG blocks and hydrophobic PCL blocks can self-associate

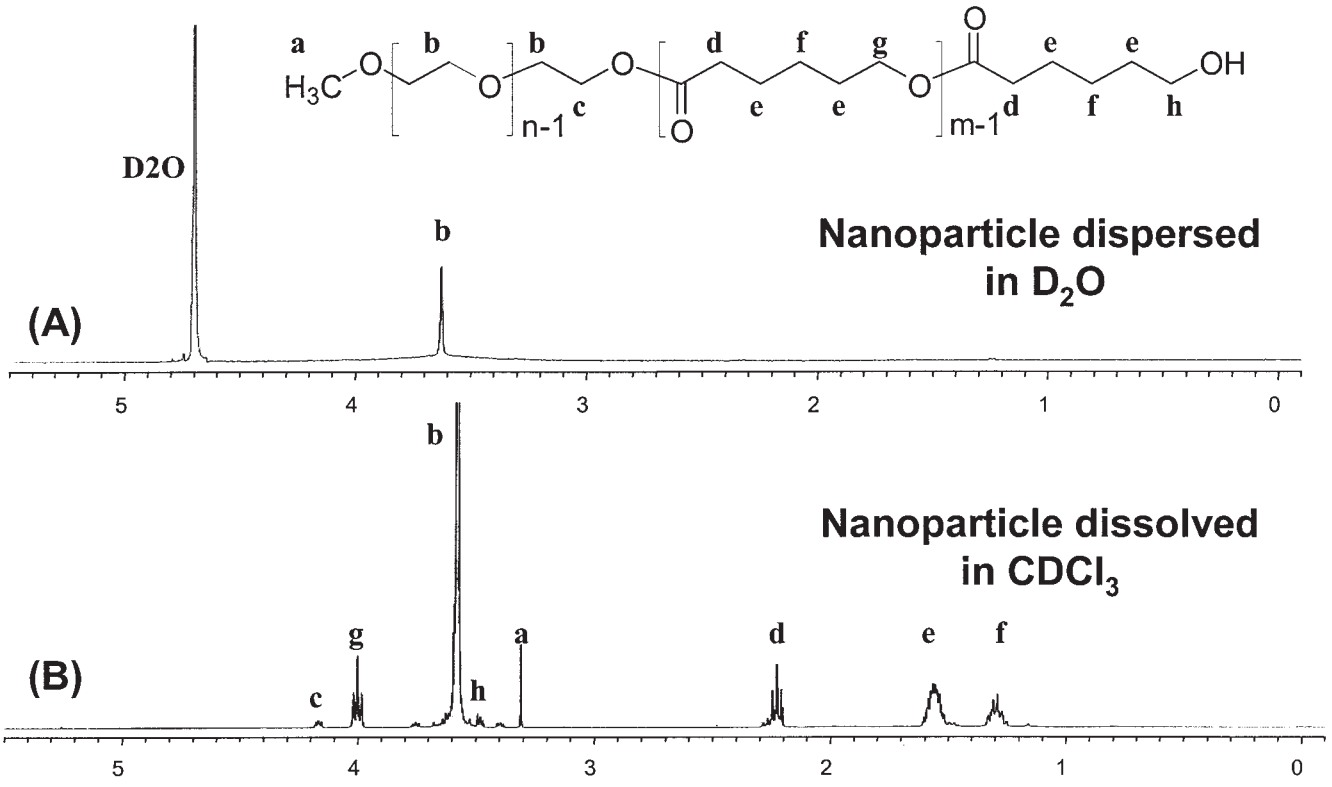

Figure 2 ^{1}H NMR spectra of PEGCL21 in (A) D_2O and (B) $CDCl_3$ at 25°C and peak assignment of the synthesized copolymer.

to form micelle-like self-aggregates in an aqueous environment. The formation of the hydrophobic PCL domain of the PEGCLs in an aqueous environment can easily be verified by ^{1}H NMR spectra with different NMR locking solvents of D_2O and $CDCl_3$. The results, demonstrated in Figure 2, show that in $CDCl_3$, a nonselective solvent for the PEGCL copolymers, the completed structural resolution of PEG and PCL blocks were observed. However, in D_2O, only the PEG signals were detected, which mainly originated from the selective hydration of exterior hydrophilic PEG corona through hydrogen bond formation with D_2O. The results clearly revealed that the PCL blocks in PEGCLs were self-aggregated into a hydrophobic domain and remained in a solid and/or semisolid state, which resulted in the disappearance of PCL peaks with D_2O. Similar trends of ^{1}H NMR spectra are consistent with other amphiphilic block copolymer systems and hydrophobized polysaccharides.[3,6,38]

The mean diameters of PEGCL copolymer nanoparticles, prepared by the dialysis method and measured by the DLS technique, were in the range of 50–300 nm (Table II, Fig. 3). The particle size increased as the PCL block length increased. The increase of particle size, with increasing PCL block length, originated mainly from the increase of hydrophobic property by the longer hydrophobic PCL chain in the aqueous milieu. Furthermore, the fairly low polydispersity factors (μ_2/Γ,[2] 0.19–0.21), estimated by the cumulant method, suggest that the nanoparticles showed a narrow size distribution.

The PEGCL block copolymers formed stable and unimodal nanoparticles in the concentration ranges of

TABLE I
Characterizations of PEGCL Block Copolymers

Samples	PEG MW	PCL MW[a]	PCL MW[b]	PCL wt %[b]	Mn[b]	Mn[c]	PDI[c]
PEGCL21[d]	2000	1000	890	30.1	2890	3160	1.23
PEGCL22	2000	2000	1910	48.8	3910	4840	1.37
PEGCL23	2000	3000	2780	58.2	4780	6100	1.42
PEGCL25	2000	5000	3950	66.4	5950	7570	1.46

[a] Theoretical PCL MW based on feed ratio.
[b] Calculated from ^{1}H NMR data.
[c] Number average MW and polydispersity index measured by GPC.
[d] PEGCL21 is PEG2K-*block*-PCL1K.

TABLE II
Characterization of PEGCL Self-Aggregates by DLS and Fluorescence Probe Method

Samples	x_{PCL}[a]	CAC (mg/L)	K_v (10^{-5})[b]	N_{PCL}	d (nm)[d]	μ/Γ^2[e]
PEGCL21	0.301	5.95	3.89	19.12	49.7	0.21
PEGCL22	0.488	2.06	5.35	7.05	192.3	0.19
PEGCL23	0.582	0.83	6.07	4.53	266.2	0.15

[a] PCL weight fraction calculated from ^{1}H NMR data.
[b] Binding equilibrium constant of pyrene in water in the presence of PEGCL nanoparticles.
[c] Aggregation number of PCL blocks per one hydrophobic microdomain.
[d] Mean diameter in water measured by DLS.
[e] Polydispersity factor estimated by cumulant method.

0.1–5 mg/mL without interparticle aggregations. As shown in Figure 4, the independence of the particle size of PEGCL nanoparticles suggested a stable nanoparticle formation with negligible interparticle aggregation. Further increase of the polymer concentration (>5 mg/mL) resulted in the large particle formation owing to the interparticle aggregation, with a tendency for increased interparticle aggregation by higher PCL block length. The PEGCL nanoparticles (1 mg/mL) also showed superior long term stabilities, maintaining their size and size distribution in aqueous environment at 37°C up to 1 week, without any PCL chain length dependencies.

The shapes of PEGCL nanoparticles, in an aqueous environment, were investigated in a DLS study by adopting different scattering angles. In the case of spherical particles, there is no angular dependence of the translational diffusion coefficient (D).[18,19,37,39] As shown in Figure 5, the PEGCL nanoparticles showed

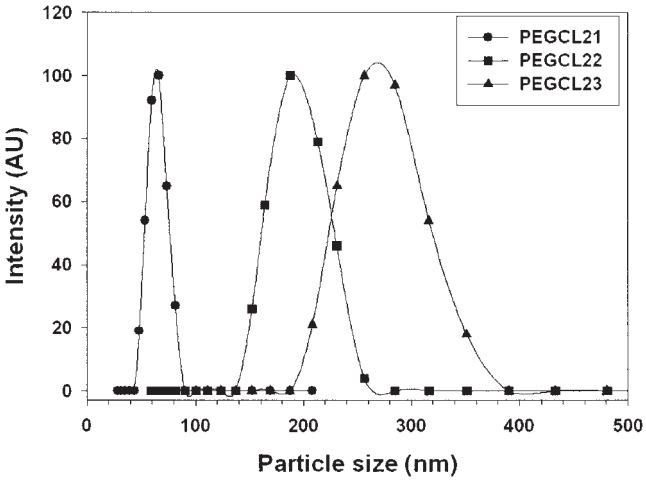

Figure 3 Distribution of PEGCL nanoparticles in aqueous environment (intensity average particle size, [PEGCL] = 1.0 mg/mL, θ = 90°, λ = 632.8 nm, and T = 25°C). (●) PEGCL21, (■) PEGCL22, and (▲) PEGCL23.

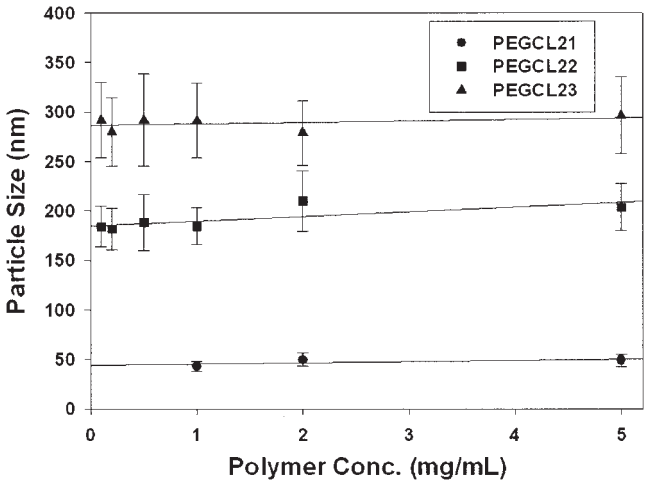

Figure 4 Concentration-dependent particle sizes of PEGCL nanoparticles in water. Data represents mean ± standard deviations (n = 3). (●) PEGCL21, (■) PEGCL22, and (▲) PEGCL23.

linear relationships between the relaxation rates (Γ) and the square of the scattering vector (K) according to:

$$\Gamma = DK^2 \tag{3}$$

$$K = 4\pi n_o \sin(\theta/2)/\lambda_0 \tag{4}$$

where n_0 is the solvent refractive index, λ_0 is the wavelength of incident light *in vacuo*, and θ is the scattering angle. The linear relationship due to the consistent translational diffusion coefficient with various detection angles, caused by undetectable rota-

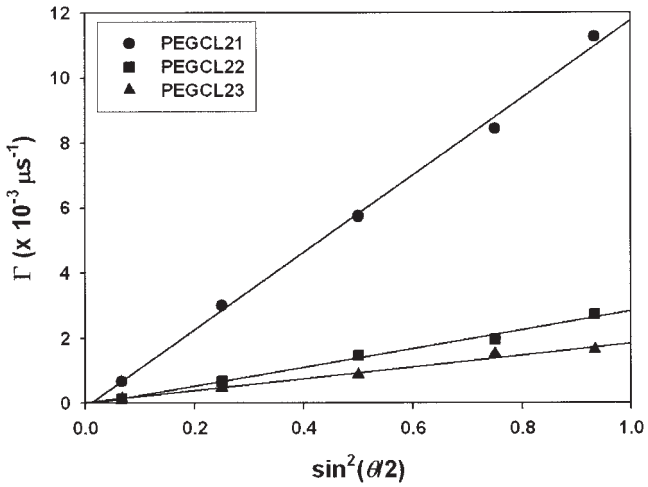

Figure 5 Relationship between relaxation rate (Γ) versus scattering angle ($\sin^2(\theta/2)$) at 25°C ([PEGCL] = 1.0 mg/mL). The regression lines indicate the best fit to the data according to eq. (3). (●) PEGCL21, (■) PEGCL22, and (▲) PEGCL23.

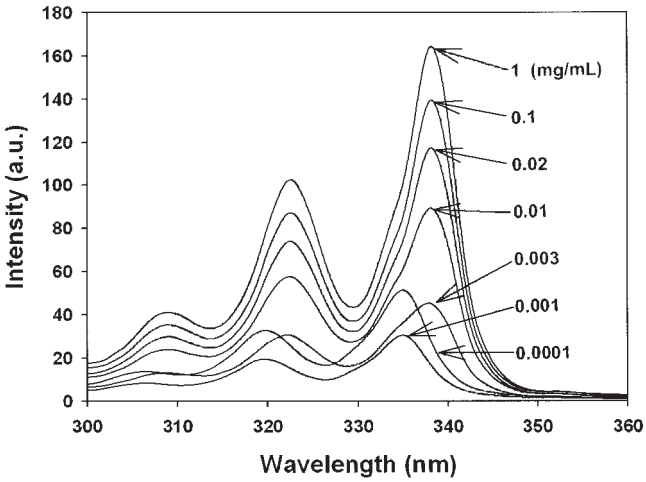

Figure 6 Pyrene excitation spectra ([Py] = $6.0 \times 10^{-7}M$) in PEGCL self-aggregates aqueous solutions (emission wavelength was 390 nm).

tional motion, indicated that the PEGCL nanoparticles in aqueous milieu are spherical.[37] Furthermore, the decreasing diffusion coefficients with increasing PCL block lengths indicated that particle size of the nanoparticles increased with increasing the hydrophobic PCL block.

To investigate the self-aggregation behavior of PEGCL block copolymers in an aqueous milieu, pyrene was used as a fluorescence probe. When exposed to a polymeric micelle aqueous solution, pyrene molecules preferably participated in the hydrophobic microdomains of micelles rather than the aqueous phase. Combined with strong fluorescence illumination of pyrene in a nonpolar environment, the localization showed different photo-physical characteristics depending on the concentration of micelle forming materials.[3,40,41] Therefore, to investigate the cac, the self-aggregation behaviors of the PEGCL copolymers in an aqueous phase were investigated by using fluorescence excitation spectra of the copolymer solutions, with various concentrations, in the presence of $6.0 \times 10^{-7}M$ pyrene, and the results are illustrated in Figure 6. At a low concentration ($c <$ cac), there were small or negligible changes in total fluorescence intensity and a shift of (0,0) band at 335 nm. As the concentration increased, a remarkable increase of the total fluorescence intensity and a red shift of the (0,0) band from 335 to 338 nm were observed. Figure 7 shows the intensity ratio (I_{338}/I_{335}) of the pyrene excitation spectra versus the logarithm of the PEGCL concentrations. On the basis of the intensity ratio data, the cac values of PEGCLs were calculated by the crossover point at low concentration ranges. The cac values of PEGCL block copolymers were in the range of 0.83–5.95 mg/L (Table II). The cac values obtained from pyrene emission spectra showed similar trends (data not shown). The cac values of PEGCLs were similar to the reported values of amphiphilic block copolymers such as PEG–PLA, poly(2-ethyl-2-oxazoline)–PCL, and PVP–PCL block copolymers.[23,27,40]

Characteristics of PEG–PCL self-aggregates

To determine the microscopic character of the inner core of the PEGCL self-aggregates, we investigated the hydrophobic nature of the interior microdomain of PEGCL block copolymer self-aggregates. The hydrophobic natures of the self-aggregate with different PCL block lengths were investigated by estimating the pyrene equilibrium constant (K_v), which resulted from the localization of pyrene between aqueous and hydrophobic microdomain.[41] Assuming a simplified equilibrium state, the molar ratio of pyrene in the micellar phase to the water phase can be expressed with the following equation:

$$[Py]_m/[\mathrm{Py}]_w = K_v V_m / V_w \tag{5}$$

where V_m and V_w are the micellar and water phase volumes, respectively. In the micellar association sensitive case, the eq. (5) can be expressed as

$$[Py]_m/[\mathrm{Py}]_w = K_v x_{\mathrm{PCL}}(c\text{-cac})/1000\rho_{\mathrm{PCL}} \tag{6}$$

where x_{PCL} is the weight fraction of PCL block, c is the concentration of the PEGCLs, and ρ_{PCL} is the density of the inner core of self-aggregates. ρ_{PCL} was assumed the bulk density of PCL (1.073–1.146 in Aldrich catalogue, used the average value of 1.10). In the intermediate range of PEGCL concentration, the $[\mathrm{Py}]_m/[\mathrm{Py}]_w$ values can be calculated by:

$$[Py]_m/[\mathrm{Py}]_w = (F - F_{\min})/(F_{\max} - F) \tag{7}$$

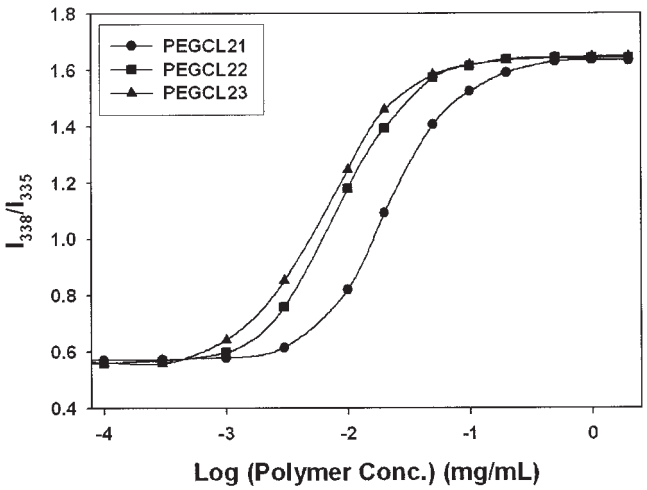

Figure 7 Intensity ratio (I_{338}/I_{335}) from pyrene excitation spectra as a function of PEGCL concentration in H_2O.

where F_{max} and F_{min} are the intensity ratio (I_{338}/I_{335}) at high and low polymer concentration ranges, and F is the intensity ratio in the intermediate concentration range. Therefore, the equilibrium constant (K_v) values of pyrene in aqueous PEGCL micelle suspensions can be easily calculated from the slopes of $(F - F_{min})/(F_{max} - F)$ versus polymer concentration graph (Fig. 8). As summarized in Table II, the K_v values were in the range of $3.89-6.07 \times 10^5$. Increasing the K_v values, by increasing the PCL block length, revealed that the hydrophobicity of the inner-core of the self-aggregate was increased as the PCL block increased. Compared to the PEGCL diblock copolymers, the amphiphilic copolymers, such as PEG–PLLA, poly(2-ethyl-2-oxazoline)–PCL, and PVP–PCL block copolymers, showed similar K_v values ($1-6 \times 10^5$), depending on the hydrophilic–hydrophobic balance.[23,40] On the other hand, the hydrophobized polysaccharides, such as glycochitosan–colanic acid conjugates and pullulan–cholesterol conjugates, showed K_v values higher than that of PEGCLs owing to the difficulty of hydrophobic aggregation among the randomly distributed hydrophobic moieties in large polysaccharide molecules.[3,42]

To determine the aggregation number of PCL chains in a hydrophobic microdomain, self-aggregates were investigated by using a fluorescence quenching method with various quencher concentrations.[35] As shown in Figure 9, the $\ln(I_0/I)$ versus CPC concentration plots showed linear relationships, and the aggregation numbers of PEGCLs can be calculated using the slope of the straight line of eq. (2). The numbers of PCL blocks (aggregation numbers) to form a hydrophobic microdomain were in the range of 4–20, depending on the PCL block lengths, as summarized in Table II. The results revealed that the copolymers with longer hydrophobic PCL blocks (PEGCL23, $N_{PCL} = 4.53$) required a relatively smaller number of PCL blocks to form a hydrophobic microdomain than did the block copolymer with shorter PCL block (PEGCL21, $N_{PCL} = 19.12$). In comparison with the particle size and hydrophobicity data represented by the K_v values, the copolymers with short PCL blocks (PEGCL21) may form a nanoparticle with one or a few of hydrophobic microdomains, while the copolymer with relatively longer PCL blocks needed intermicrodomain interactions such as hydrophobic interaction in an aqueous environment to form nanoparticles.[7,18]

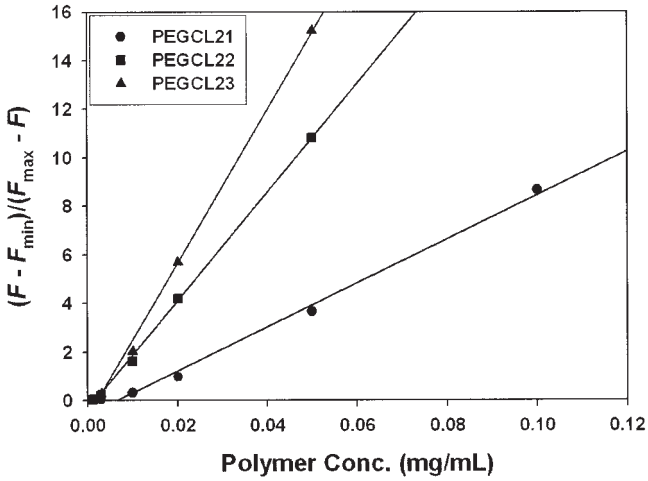

Figure 8 Plot of $(F - F_{min})/(F_{max} - F)$ versus polymer concentration. Solid lines indicate the best fit to the data according to eqs. (6) and (7). (●) PEGCL21, (■) PEGCL22, and (▲) PEGCL23.

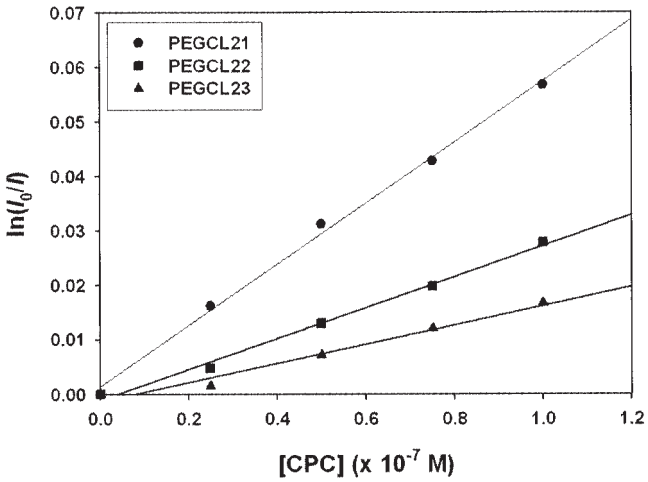

Figure 9 $\ln(I_0/I)$ of pyrene fluorescence intensity as a function of CPC concentration in PEGCL nanoparticle solutions. [PEGCLs] = 0.1 mg/mL, [Py] = 6.0×10^{-7} *M*. (●) PEGCL21, (■) PEGCL22, and (▲) PEGCL23.

CONCLUSIONS

The present study demonstrated the synthesis and self-aggregation behavior of PEG–PCL diblock copolymer in an aqueous environment. Applying various technical procedures such as ^{1}H NMR, DLS, and fluorescence spectroscopy, we found that the physicochemical characteristics of PEG–PCL block copolymer self-aggregates are closely related to the hydrophobic/hydrophilic balance, resulting from different PCL block lengths. These findings open the possibility of introducing the PEGCL self-aggregates into various biomedical fields such as drug delivery and imaging.

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