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Synthesis, isothermal crystallization and micellization of mPEG–PCL diblock copolymers catalyzed by yttrium complex

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Abstract

Amphiphilic biodegradable mPEG–PCL diblock copolymers have been synthesized using rare earth catalyst: yttrium tris(2,6-di-*tert*-butyl-4-methylphenolate) [$Y(DBMP)_3$] in the presence of monomethoxy poly(ethylene glycol) (mPEG, $M_n = 5000$) as macro-initiator. The diblock architecture of the copolymers was thoroughly characterized by ^1H NMR, ^{13}C NMR and SEC. The molecular weights of mPEG–PCLs can be well controlled by adjusting the feeding molar ratio of ε-CL to mPEG. Thermal and crystallization behaviors of the diblock copolymers were investigated by DSC and POM (polarized optical microscope). The crystallization property of mPEG–PCL block copolymers depends on the length of PCL blocks. As the molecular weight of PCL block increased, the crystallization ability of mPEG block was visibly restrained. Aqueous micelles were prepared by dialysis method. The critical micelle concentration of the copolymers, which was determined to be 0.9–6.9 mg/L by fluorescence technique, increased with the decreasing of PCL block length. The particle sizes determined by DLS were 30–80 nm increasing with the PCL block length. TEM images showed that these micelles were regularly spherical in shape.

Keywords: Poly(ε-caprolactone); Poly(ethylene glycol); Yttrium complex

1. Introduction

In recent years, amphiphilic block copolymers with hydrophilic and hydrophobic blocks have been extensively studied in biotechnology and pharmaceutical fields for their ability to form polymeric micelle-like ''core-shell'' nanostructure in aqueous phase [1–4]. Hydrophobic blocks form the inner-core of the structure, which acts as a drug incorporation site, especially for hydrophobic drugs. Hydrophilic blocks form a hydrated outer shell which serves as a stabilizing interface between the hydrophobic core and the external medium. In most cases, the hydrophilic block of micelle forming copolymer refers to poly(ethylene glycol) (PEG) for its highly hydrophilic and biocompatible properties. Biodegradable aliphatic polyesters are widely studied as the hydrophobic blocks [5–8], among which poly(ε-caprolactone) (PCL) is one of the most attractive and promising hydrophobic blocks owing to its good biocompatibility, drug permeability, and nontoxicity.

mPEG–PCL diblock copolymers have been prepared by the ring-opening polymerization of ε-caprolactone (ε-CL) using mPEG as the macro-initiator with stannous octoate [$Sn(Oct)_2$] as the most conventional catalyst [9–12]. However, the activity of $Sn(Oct)_2$ is not very high leading to high polymerization temperature and long polymerization time. The exploring of new catalysts for mPEG–PCL synthesis never ends up. A few new catalysts such as calcium [13], aluminum [14] and bismuth [15] complexes have been developed. Rare earth complexes have been reported as a kind of efficient catalysts for the ring-opening polymerization of lactones, lactides and cyclocarbonates [16–21]. Recently, our group has developed a series of rare earth trisphenolats for ε-CL homopolymerization with high activity and good controllability preparing PCL with low toxicity [22,23].

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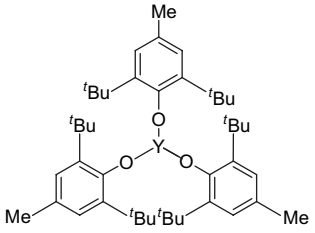


Scheme 1. Structure of $Y(DBMP)_3$.

In this work, yttrium tris(2,6-di-*tert*-butyl-4-methylphenolate) [$Y(DBMP)_3$] (Scheme 1) has been employed with mPEG as macro-initiator to prepare mPEG–PCL diblock copolymers under mild conditions. The diblock architectures of the copolymers were characterized by ^1H NMR, ^{13}C NMR and SEC analyses. The thermal and crystallization behaviors as well as the micellization characteristics of these diblock copolymers also have been investigated.

2. Experimental section

2.1. Materials

$Y(DBMP)_3$ and $PCL_{30,000}$ homo-polymer were synthesized as we previously reported [20]. ε-Caprolactone (Acros product) was dried over CaH_2 and distilled prior to use. mPEG ($M_n = 5000$) (Fluka product) was dried by an azeotropic distillation with dry toluene. Other reagents and solvents were purified by usual methods.

2.2. Synthesis of mPEG–PCL diblock copolymers

The mPEG–PCL diblock copolymers were synthesized by the ring-opening polymerization of ε-CL using mPEG as the macro-initiator and $Y(DBMP)_3$ as the catalyst. All polymerizations were carried out in previously flamed 15-mL ampoules under dry argon atmosphere with Schlenk techniques. mPEG and $Y(DBMP)_3$ were dissolved in THF with certain molar ratio and kept in a water bath at 50 °C for aging 20 min before the ε-CL monomer was injected into the ampoule by a syringe. After the desired polymerization time, the copolymer was quenched by ethanol containing 5% hydrochloric acid (HCl), precipitated and washed by petroleum ether, and dried under vacuum to constant weight.

2.3. Characterization of mPEG–PCL diblock copolymers

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance DMX500 spectrometer in $CDCl_3$ with TMS as inner standard. Size-exclusion chromatographic (SEC) analyses were carried out on a Waters 208 apparatus with Waters 2410 RI detector in THF (1.5 mL/min) at 30 °C. The molecular weight was calibrated using polystyrene standards. Differential scanning calorimetry (DSC) curves were taken on a Perkin–Elmer Pyris 1 instrument. Each sample was heated from −30 °C to 100 °C (first heating run), held for 2 min to erase the thermal history, then cooled to −30 °C at 10 °C/min, and finally heated again to 100 °C (second heating run) at 10 °C/min. The samples used for polarized optical microscope (POM) measurement were prepared by casting three drops of a chloroform solution containing 1 wt% copolymer on a clean cover glass and then airing for 1 day at room temperature followed by drying under vacuum for 1 day. The morphology of particles was monitored with an Olympus BX51 POM equipped with a heating stage (Linksys css450).

2.4. Preparation of polymeric micelles

The aqueous micellar solutions were prepared by dialysis method. Briefly, the block copolymer (50 mg) was first dissolved in THF, a solvent for both PCL and mPEG blocks. Subsequently, doubly distilled water was added continuously at a rate of 1 drop every 5 s to the polymer/THF solutions (4 mL) with vigorous stirring until the water content reached about 50 wt%. The resulting solutions were transferred to dialysis tubes (MWCO: 14,000) and dialyzed against doubly distilled water for 48 h to remove the organic solvent.

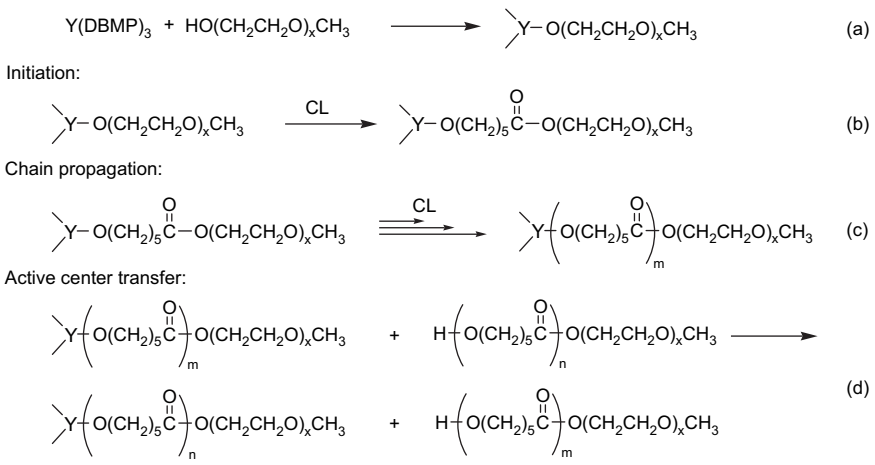
2.5. Characterization of micelles

The critical micelle concentration (CMC) was determined by fluorescence measurement using pyrene as a fluorescent probe. Fluorescence excitation spectra were recorded on HITACHI F-4500 fluorescence spectrometer at 390 nm emission

Table 1
mPEG–PCL diblock copolymers initiated by $mPEG_{5000}$ and $Y(DBMP)_3$[a]

Polymer	$\frac{[CL]}{[mPEG]}$	$\frac{[mPEG]}{[Y(DBMP)_3]}$	Conv (%)	$M_{n,cal}$[b] (kg/mol)	$M_{n,NMR}$[c] (kg/mol)	$M_{n,SEC}$[d] (kg/mol)	MWD[d]
$mPEG_{5000}$–PCL_{1900}	20	5	82.7	6.9	6.9	13.2	1.11
$mPEG_{5000}$–PCL_{3700}	37	5	85.1	8.7	8.5	–	–
$mPEG_{5000}$–PCL_{4900}	46	5	93	9.9	9.3	18.5	1.18
$mPEG_{5000}$–PCL_{5800}	55	5	93	10.8	10.1	–	–
$mPEG_{5000}$–PCL_{8500}	77	4.5	96.6	13.5	14.6	30.6	1.24
$mPEG_{5000}$–$PCL_{18,300}$	180	4.5	89.1	23.3	25.2	39.8	1.48

[a] Conditions: 50 °C in THF for 3 h except $mPEG_{5000}$–$PCL_{18,300}$ reacting for 12 h.
[b] Calculated from the feeding molar ratio and conversion, $M_{n,cal} = \frac{[CL]\times 114\times Conv.}{[mPEG]} + M_{n,mPEG}$.
[c] Measured by ^1H NMR spectra, $M_{n,NMR} = \frac{I^k/2\times 114}{(I^a+I^b+I^c+I^d+I^e)/4\times 44} \times M_{n,mPEG} + M_{n,mPEG}$.
[d] Measured by SEC analyses.



Scheme 2. Synthesis of mPEG–PCL catalyzed by $Y(DBMP)_3$.

wavelength and 2.5 nm slit width. Sample solutions for fluorescence investigation were described previously [24], and the concentration of the aqueous solutions ranged from 1.0×10^{-7} to 2 g/L. The pyrene concentration in the solution was chosen to be 6.0×10^{-7} M.

The hydrodynamic diameter and size distribution of micelles were determined by dynamic light scattering (DLS) at 90° angle to the incident beam and at 25 °C on a Brookhaven 90 Plus particle size analyzer. All micellar solutions had a final polymer concentration of 2 g/L and were filtered through 0.45 μm filters.

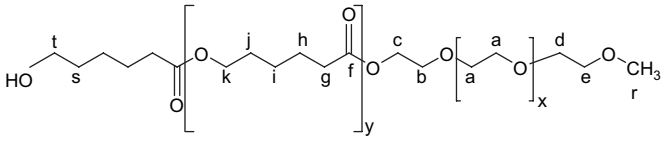
TEM images were obtained using JEM-1230 operating at an acceleration voltage of 60 kV. A drop of 2 g/L micellar solution was placed onto a copper grid with carbon film and dried before measurement. All grids were finally negatively stained by 2 wt% phosphotungstic acid.

3. Results and discussion

3.1. Synthesis and characterization of mPEG–PCL diblock copolymers

Six mPEG–PCL diblock copolymers with different hydrophobic PCL block lengths have been synthesized by adjusting the feeding molar ratio of ε-CL to mPEG in the presence of $Y(DBMP)_3$ as shown in Table 1. $Y(DBMP)_3$ and mPEG reacted in THF for 20 min to form an *in situ* active center (bond of Y–O, Scheme 2a), which initiates the ring-opening polymerization of ε-CL (Scheme 2b and 2c). Less amount of $Y(DBMP)_3$ molecules co-worked with large amount of mPEG molecules by the active center transfer reaction as Scheme 2d shows.

Typical ^{1}H NMR and ^{13}C NMR spectra of mPEG–PCL block copolymer $mPEG_{5000}$–PCL_{4900} are illustrated in Figs.



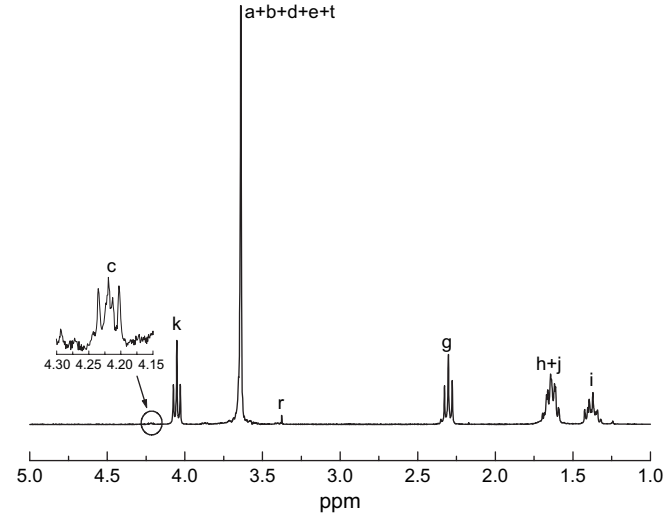


Fig. 1. ^{1}H NMR spectrum of $mPEG_{5000}$–PCL_{4900} in $CDCl_3$.

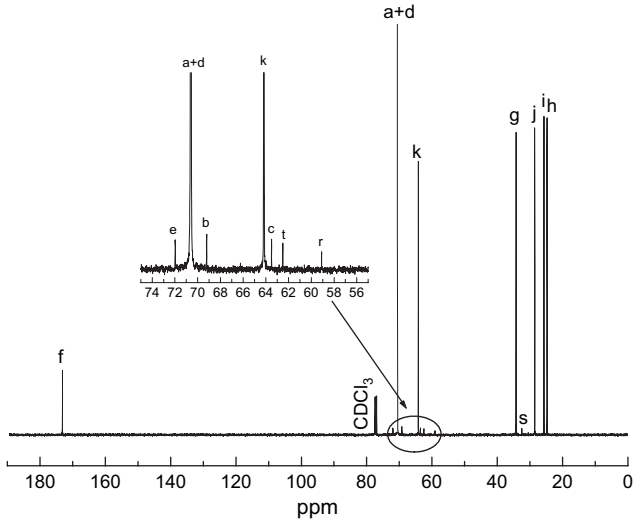


Fig. 2. ^{13}C NMR spectrum of $mPEG_{5000}$–PCL_{4900} in $CDCl_3$.

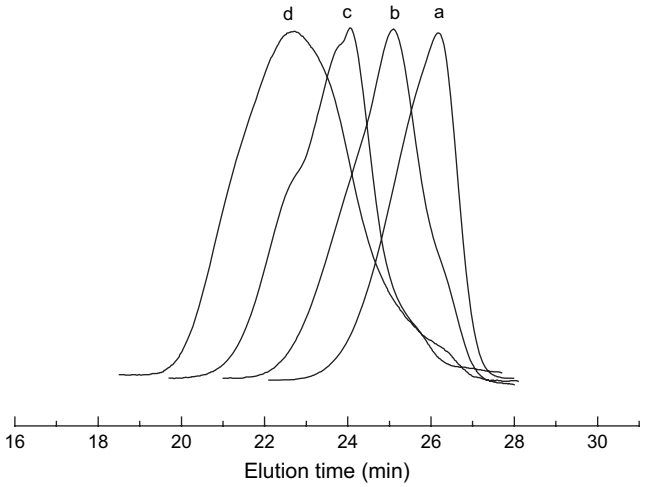


Fig. 3. SEC patterns of (a) $mPEG_{5000}$–PCL_{1900}; (b) $mPEG_{5000}$–PCL_{4900}; (c) $mPEG_{5000}$–PCL_{8500} and (d) $mPEG_{5000}$–$PCL_{18,300}$.

1 and 2, respectively. The small peak at around 4.2 ppm (multiplet) in the ^{1}H NMR spectrum as well as the signal at 63.5 ppm in the ^{13}C NMR spectrum is the characteristic signal of the last $-CH_2-$ group in mPEG segments next to the $-COO-$ group of PCL block, which clearly demonstrates that the neighboring blocks are connected through an ester linkage. The molecular weights of the diblock copolymers determined by end group ^{1}H NMR analysis are in good agreement with the values calculated from the monomer over initiator molar ratio and the monomer conversion, which indicates the active center transfer reaction between Y–O active center and hydroxyl end group (Scheme 2d) is essential for controlling products' molecular weights. Fig. 3 shows the SEC patterns of a series of mPEG–PCL copolymers, in which the molecular weight increased with the increasing feeding molar ratio of ε-CL to mPEG, and the molecular weight distributions of the copolymers are narrow confirming the diblock structure.

Table 2
Melting and crystallizing characteristics of the mPEG–PCL diblock copolymers

Polymer	$T_{c,mPEG}$[a] (°C)	$T_{c,PCL}$[a] (°C)	$\Delta H_{c,mPEG}$[b] (J/g)	$\Delta H_{c,PCL}$[b] (J/g)	$T_{m,mPEG}$[c] (°C)	$T_{m,PCL}$[c] (°C)
$mPEG_{5000}$–PCL_{1900}	32.2	2.1	155.4	11.6	56.4	47.5
$mPEG_{5000}$–PCL_{3700}	29.7	20.6	144.1	28.7	55.4	
$mPEG_{5000}$–PCL_{4900}	28.6	23.5	–[d]		53.1	
$mPEG_{5000}$–PCL_{5800}	20.3	27.9	–[d]		52.4	
$mPEG_{5000}$–PCL_{8500}	22.5	29.3	75.1	46.2	44.9	52.2
$mPEG_{5000}$–$PCL_{18,300}$	12.3	27.6	63.4	63.3	41.9	54.0

[a] Crystallization points of mPEG and PCL block.
[b] Exothermic enthalpies of mPEG and PCL block, calibrated by the wt% of each block in the copolymers from ^{1}H NMR data.
[c] Melting points of mPEG and PCL block.
[d] The melting peaks of PCL and PEG block are superposed, and cannot be separated.

3.2. Thermal and crystallization behaviors

The crystallization and melting behaviors of the mPEG–PCL diblock copolymers were investigated by DSC as shown in Fig. 4. There are two exothermic peaks during the cooling process of all diblock copolymers due to the fact that two different blocks crystallized, respectively. However, in the heating process, only one endothermic peak was detected in $mPEG_{5000}$–PCL_{3700}, $mPEG_{5000}$–PCL_{4900} and $mPEG_{5000}$–PCL_{5800} and owning to the close T_m of the PCL and mPEG blocks with similar length. And the other three samples with too long or too short PCL block show two endothermic peaks. All of the melting and crystallization data are summarized in Table 2. The T_c, T_m and ΔH_c of PCL block all increased with the increasing of the length of PCL block. Nevertheless, the T_c, T_m and ΔH_c of $mPEG_{5000}$ block all decreased with the increasing of PCL length, which suggests that the crystallization ability of mPEG blocks was obviously reduced by increasing PCL block length in the diblock copolymers.

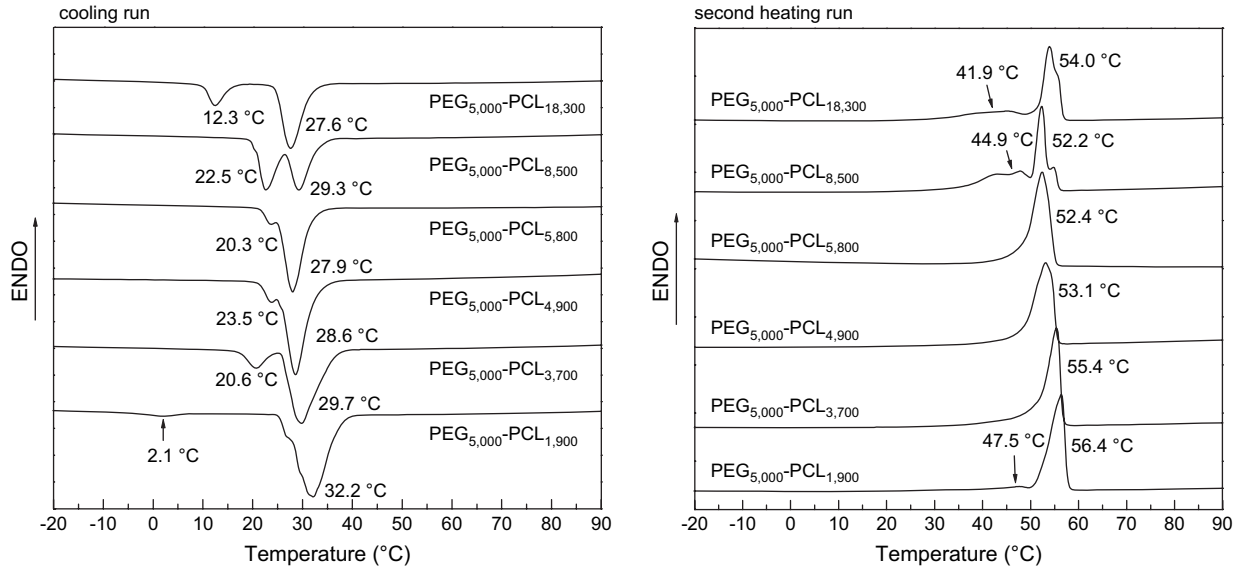


Fig. 4. DSC curves of mPEG–PCLs with cooling and heating rate of 10 °C/min.

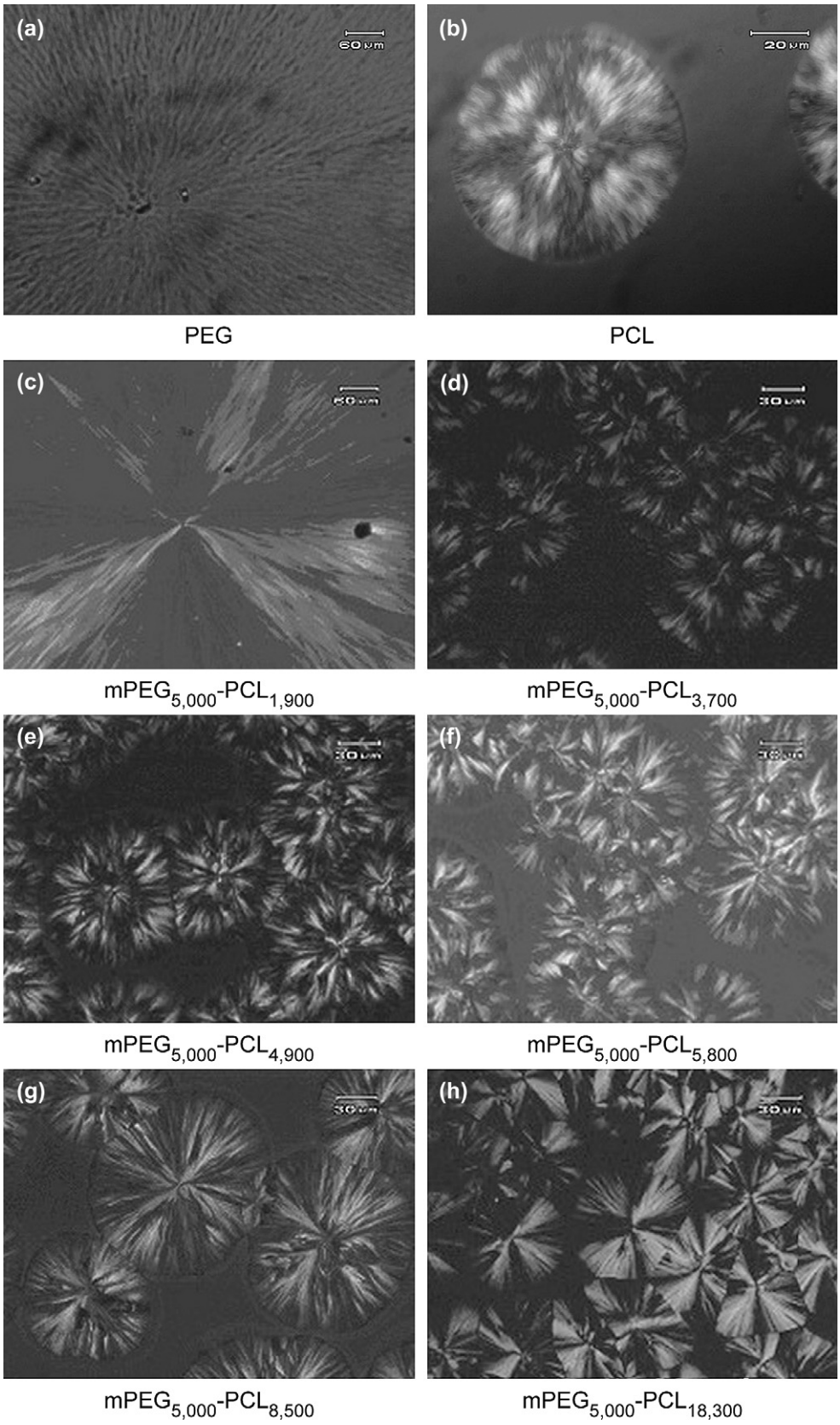


Fig. 5. POM micrographs of spherulites of mPEG–PCLs isothermal crystallized at 45 °C for about 20 min.

Fig. 5 shows the POM micrographs of the diblock copolymers with fixed mPEG block length and various PCL block lengths isothermally crystallized at 45 °C, as well as that of $mPEG_{5000}$ and $PCL_{30,000}$ homopolymers as comparisons. The spherulite of mPEG homopolymer (Fig. 5a) is larger and grows faster than that of PCL homopolymer (Fig. 5b). Among all of the diblock copolymers, only $mPEG_{5000}$–PCL_{1900} (Fig. 5c) shows spherulite morphology similar to that of mPEG homopolymer, and the other five samples (Fig. 5d–h) show similar spherulite patterns to that of PCL homopolymer. It is supposed that the crystallization abilities of mPEG blocks were visibly restrained by the PCL blocks besides them when the molecular weight of PCL block reaches 3700. In that case, PCL block crystallized first fixing the total morphology of the crystalline region with typical PCL spherulite. The result of POM micrographs matches the DSC data quite well.

3.3. Micellization behaviors

In order to evaluate CMC values of mPEG–PCL diblock copolymers with different PCL block lengths in aqueous solution, the fluorescence technique has been used and pyrene was chosen as a probe. As reported by Wilhelm et al. [24], pyrene will preferentially partition into hydrophobic microdomains with a concurrent change in the molecule's photophysical properties. In the excitation spectra a sharp rise in intensity ratio of peaks at 338 and 333 nm of pyrene indicates the on-set of micellization (CMC) for block copolymers. Fig. 6 plots the ratio of intensities (I_{338}/I_{333}) vs. logarithmic concentration (log C) of the diblock copolymer. At lower concentrations this ratio takes the characteristic value of pyrene in water, and at higher concentrations it takes the value of pyrene entirely in the hydrophobic environment afforded by the micelle core. The CMC was determined from the crossover point at the low concentration range.

As shown in Table 3, the CMC values of mPEG–PCL block copolymers are in the range of 0.9–6.9 mg/L, increasing

Table 3
Micellar characteristics of the mPEG–PCL block copolymers

Samples	CMC (mg/L)	Particle size[a] (nm)
$mPEG_{5000}$–PCL_{1900}	6.9	30.1 ± 8.9
$mPEG_{5000}$–PCL_{4900}	3.7	31.7 ± 8.8
$mPEG_{5000}$–PCL_{8500}	1.8	33.6 ± 8.1
$mPEG_{5000}$–$PCL_{18,300}$	0.9	72.1 ± 12.6

[a] Number-average mean diameters by dynamic light scattering (DLS).

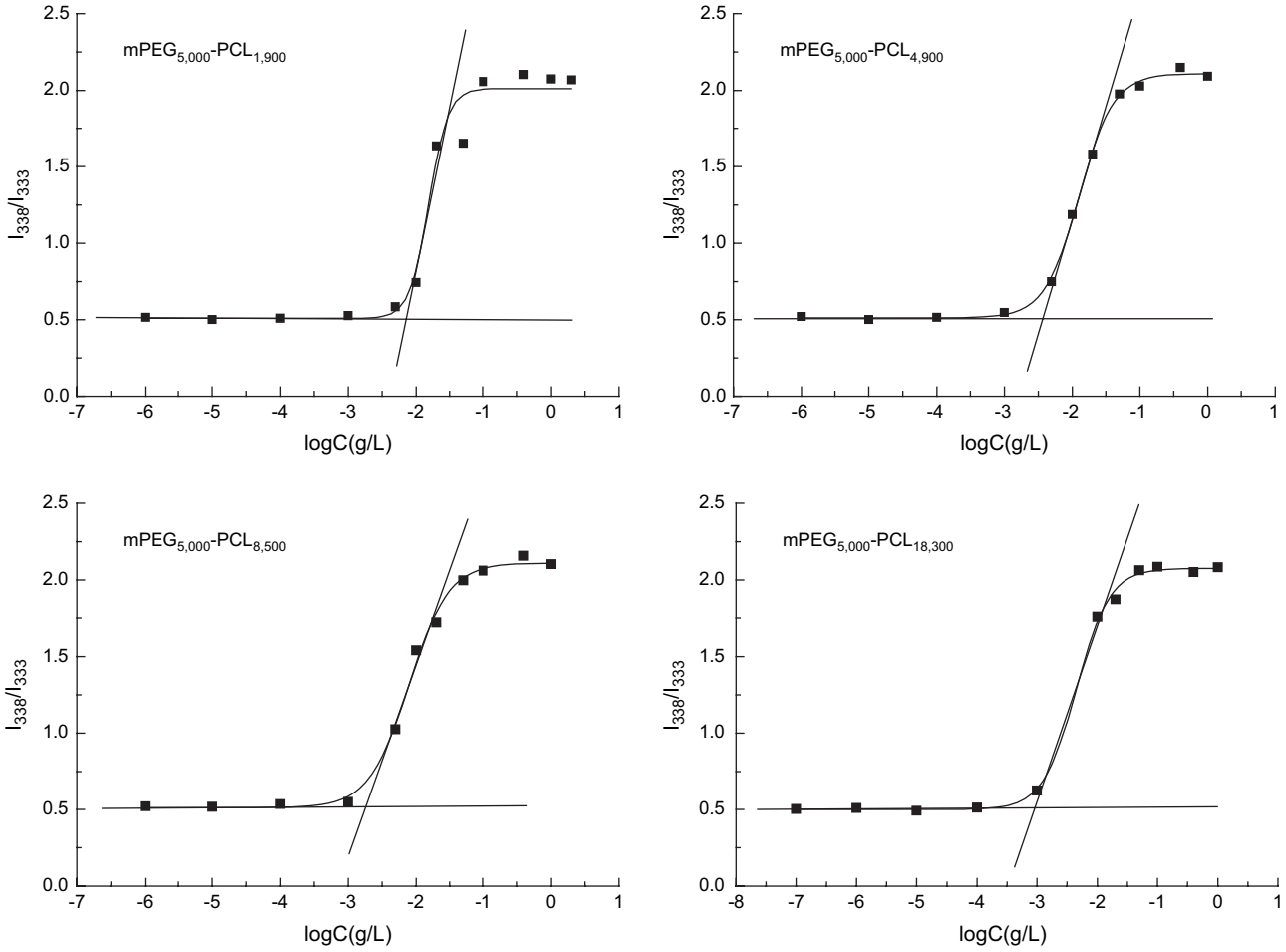


Fig. 6. Plots of fluorescence intensity ratio I_{338}/I_{333} from pyrene excitation spectra vs. log C for mPEG–PCL diblock copolymers with different PCL length.

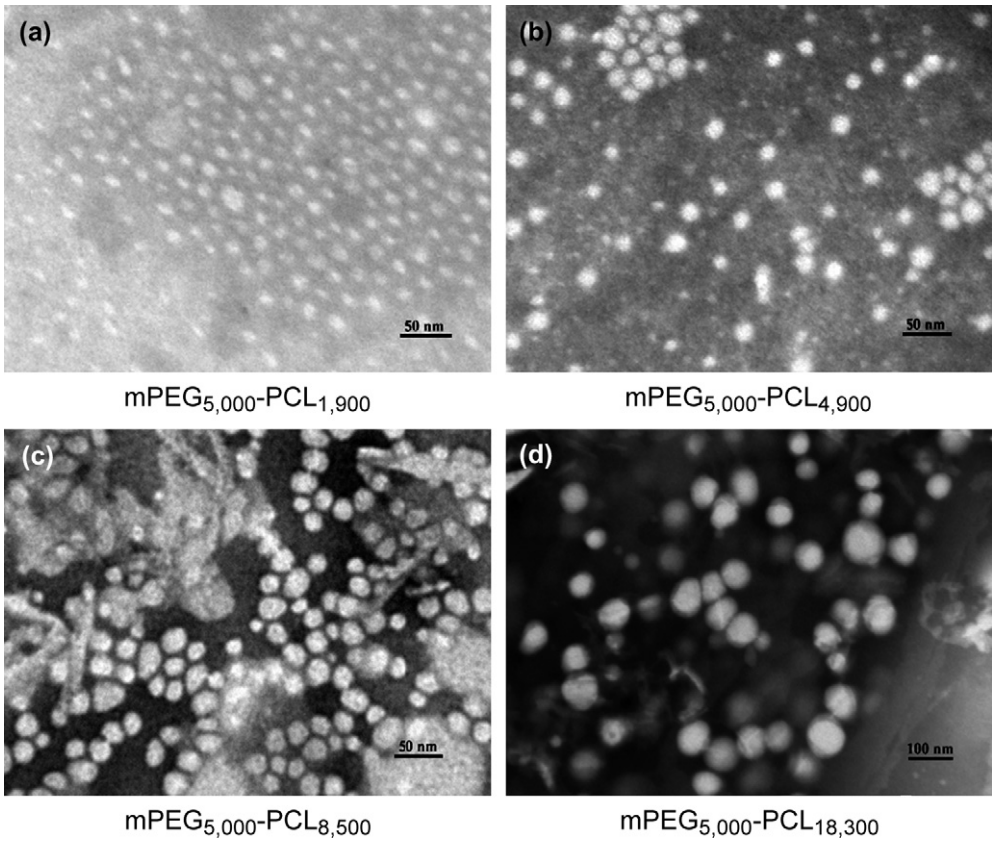


Fig. 7. TEM micrography of spherical micelles from mPEG–PCL block copolymers.

as the length of hydrophobic PCL block decreases. The CMC values of mPEG–PCL diblock copolymers are much lower than low molecular surfactants, e.g. 2.3 g/L for sodium dodecyl sulfate in water indicating that the mPEG–PCL diblock copolymers are easy to form micelles.

The particle sizes of mPEG–PCL micelles were measured by means of DLS method. As shown in Table 3, the number average mean diameters of micelles were in the range of 30–80 nm. The micelle diameters increased as the increasing of hydrophobic PCL block length, which originated mainly from the increase of hydrophobic property by the longer hydrophobic PCL chain in the aqueous phase. Morphology of mPEG–PCL micelles was observed by TEM (Fig. 7) showing spherical in shape. It is worth to note that the size values estimated by TEM are similar to those obtained from the DLS measurements (Table 3), and the size-changing trend in TEM images is in good agreement with DLS data.

4. Conclusion

In this study, mPEG–PCL diblock copolymers have been synthesized successfully using $Y(DBMP)_3$ as catalyst. Molecular weights of the diblock copolymers can be well controlled by adjusting the molar ratio of [ε-CL]/[mPEG] and coincide with the theoretical values. The crystallization properties of the copolymers depend on the length of PCL block according to DSC and POM analyses. The micellization behaviors of mPEG–PCL in aqueous phase were also studied. CMC values of the diblock copolymers are generally quite low, which indicates the potential application of these copolymers as drug delivery carriers. DLS and TEM showed the micelles were spherical in shape with narrow distribution.

Acknowledgements

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