Synthesis and Evaluation of a Star Amphiphilic Block Copolymer from Poly(ε-caprolactone) and Poly(ethylene oxide) as Load and Release Carriers for Guest Molecules

Guohua Jiang,[1,2] Hao Xu[1,2]

[1]*Key Laboratory of Advanced Textile Materials and Manufacturing Technology (ATMT), Ministry of Education, Zhejiang Sci-Tech University, Hangzhou 310018, People's Republic of China*
[2]*Department of Materials Engineering, College of Materials and Textile, Zhejiang Sci-Tech University, Hangzhou 310018, People's Republic of China*

Received 16 July 2009; accepted 27 February 2010
DOI 10.1002/app.32364
Published online 3 June 2010 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: The use of polymeric materials as the carrier in the controlled release of guest molecules has become an important research area in the polymeric materials science, because of their advantages of the safety, efficacy and patient convenience. One of them, star amphiphilic polymer can self-assemble into supermolecular structure (polymer micelles) by the balance of hydrophilic and hydrophobic interaction. In this study, star amphiphilic copolymer consisting of hydrophobic and biodegradable poly(ε-caprolactone) (PCL) and hydrophilic poly(ethylene oxide) (PEO) blocks were synthesized by two-step ring-opening polymerization. The resultant polymer was characterizated by FTIR, ^{1}H-NMR, and DSC to determine its chemical structure. The morpholoy of the polymer micelles was analyzed by TEM. Using star-PCL-*b*-PEO as carriers and congo red as model guest molecules, the encapsulation and release properties were investigated by UV–visable analysis. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 118: 1372–1379, 2010

Key words: ring-opening polymerization; star polymers; drug delivery systems

INTRODUCTION

Polymeric micelles formed by amphiphilic copolymers demonstrate a series of attractive properties as promising colloidal carriers for targeting poorly water-soluble and amphiphilic drugs and genes to tumor sites, such as high-stability both *in vitro* and *in vivo*, and good biocompatibility.[1] Polymeric micelles are small in size (<200 nm) and can solubilize hydrophobic drugs, genes or proteins in their inner cores through hydrophobic interaction, electrostatic interaction and hydrogen bonding, and so forth, when exposing their hydrophilic shells to the external environment. This effectively protects the enclosed bioactive compounds against degradation and enables them to exhibit prolonged activity in the systemic circulation by avoiding the scavenging of the reticuloendothelial systems.[2–5] Indeed, much attention has been paid to the self-assembly and morphological transformation of traditional amphiphilic copolymers in aqueous solution. It has been well established that amphiphilic block copolymers can self-assemble in aqueous solution into a variety of morphological structures including spheres, rods, lamellae, vesicles, and large compound micelles or vesicles.[6] However, the formation of polymeric micelles is thermodynamically favorable only above the critical micelle concentration (CMC) of the amphiphilic molecules. When the concentration drops below the CMC, the micellar structure becomes unstable and dissociates into free chains. Such thermodynamic instability of the micelles below the CMC is one of the major concerns for their *in vivo* drug delivery application. Once the micelles are introduced into the bloodstream, they are subjected to severe dilution and become thermodynamically unstable, when below the CMC. The disruption of micellar structures leads to the burst release of entrapped drugs, which may cause serious

Correspondence to: G. Jiang (polymer_jiang@hotmail.com).
Contract grant sponsor: National Natural Science Foundation of China; contract grant number: 20604024.
Contract grant sponsor: Scientific Research Foundation of Zhejiang Sci-Tech University; contract grant number: 0901808-Y.
Contract grant sponsor: Training Foundation for the Excellent Young Talents by the Key Laboratory of Advanced Textile Materials and Manufacturing Technology (ATMT), Ministry of Education; contract grant number: 2008QN10.
Contract grant sponsor: Program for Changjiang Scholars and Innovative Research Team in University; contract grant number: PCSIRT: 0654.

© 2010 Wiley Periodicals, Inc.

toxicity problems because of the potentially large fluctuations in drug concentrations.[7]

The problem associated with the self-assembled multimolecular polymeric micelles can be potentially overcome by developing an amphiphilic miktoarm star polymers that has a hydrophobic inner core and a hydrophilic outer arms. Miktoarm star polymers typically refer to star polymers with three or more arms, and at least two of which are of different monomer types.[8–11] In recent years, ever-increasing attention has been paid to the synthesis of ABC miktoarm star terpolymers because of their intriguing properties both in solution and solid states.[12–14] As a branched nanoscale material, star polymers with well-defined structure and multiple arms/functionalities have potential applications in drug delivery, coatings, and lithography.[15] This new type of molecule was capable of encapsulating a hydrophobic or hydropholic model drug in liquid media. A series of star block copolymers with the number of arms ranging from 3 to 8 has also been synthesized.[16–18] The arms were composed with block copolymer with polyethylene glycol (PEG) as the inner hydrophilic block and poly(ε-caprolactone) (PCL) as the outer hydrophobic block. The application of this type of copolymer as an injectable drug delivery system was reported.[19] Kim et al.[20] describe the synthesis and solution properties of PEG-*b*-PTMC star block copolymers via ring-opening polymerization (ROP) of trimethylene carbonate monomer initiated at the hydroxyl end group of the core PEG. The amphiphilic PEG-*b*-PTMC star block copolymers formed spherical micelles with a core-shell structure in an aqueous phase. Wang et al.[21] star-shaped amphiphilic block copolymers on the basis of hydrophobic polysulfides [poly(propylene sulfide), PPS] and hydrophilic polyethers [polyethylene glycol, PEG]. In a water environment, these polymers aggregate in the form of submicron carriers that, because of the sensitivity to oxidation reactions typical of PPS, can be used for responsive drug delivery.

In this article, we describe the synthesis and micellar characterization of a novel amphiphilic three-arm star polymer. The core of this star polymer is a 1,1,1-tris(hydroxymethyl)propane (TMP), the inner block in the arm is lipophilic PCL, and the outer block in the arm is hydrophilic PEG. First, a star-PCL polymer was synthesized using the TMP as the initiator for ROP of ε-caprolactone. A PEG polymer was then attached to the terminal group of PCL by ROP of ethylene oxide (EO). In this star polymer, the arms consist of polymers that are biocompatible and biodegradable. The star structure of the polymers was confirmed by several physicochemical methods. To establish this system as a suitable drug carrier, a water-soluble dye (Congo Red) as the corresponding guest molecule for load and release experiments were carried out.

EXPERIMENTAL

Materials

Tetrahydrofuran (THF, 99%) was dried by refluxing over sodium and distilled under nitrogen before use. The ε-caprolactone (ε-CL, 99%; Acros) was dried over CaH_2, distilled under reduced pressure, and stored under a nitrogen atmosphere. The TMP (99%) and EO (99%) were obtained from Acros (Geel, Belgium) and used without further purification. Tin(II) 2-ethylhexanoate ($Sn(Oct)_2$, 98%) purchased from East China Chemical (Shanghai, China) and used as received. Other reagents were purchased from Shanghai Chemical Reagent and used as received.

Synthetic of PCL (2, star-PCL) by ROP

Polymerization of ε-CL was initiated with TMP using a catalytic amount of $Sn(Oct)_2$. Typically, $Sn(Oct)_2$ (0.5 wt % ε-CL) was accurately weighed and placed in a dried glass flask. After 0.133 g (1 mmol) of TMP and various predetermined amounts of ε-CL (15.4 g, 135 mmol for PCL-1, 20.0 g, 175 mmol for PCL-2, and 30.0 g, 263 mmol for PCL-3) had been added and mixed to homogeneity, the flask was exhausted under vacuum for degassing and purged 3 times with dry nitrogen. The polymerization was carried out at 120°C for 18 h. The resultant polymer was then dissolved in THF and precipitated in cold methanol.[22] The polymer (star-PCL) was determined by ^{1}H-NMR and GPC. ^{1}H-NMR ($CDCl_3$, ppm): 1.10–1.65 (—C***H***$_3$, —CC***H***$_2$CH$_3$, —C***H***$_2$ CH$_2$COO, —C***H***$_2$CH$_2$CH$_2$COO, and —C***H***$_2$CH$_2$ CH$_2$CH$_2$COO), 2.10–2.40 (—C***H***$_2$COO), 3.90–4.10 (—COOC***H***$_2$—).

Synthetic of poly(ε-caprolactone)-b-poly(ethyl oxide) (3, star-PCL-*b*-PEO)

The attachment of poly(ethyl oxide) (PEO) onto star-PCL was carried out by cationic polymerization of EO directly initiated by $BF_3{\cdot}OEt_2$. The polymerization was carried out at under a dry nitrogen atmosphere in a three-necked round-bottomed flask with a PTEE stirrer and a funnel. The reaction temperature was controlled at 0°C. Before carrying out the reaction, 1 g of PCL was added into the flask, and then the system was degassed using nitrogen for at least 15 min. A suitable amount of catalyst ($\sim$ 0.2 mL), CH_2Cl_2 (20 mL), and EO (5 mL) were added via syringe to the reactor and funnel, respectively. The reaction vessel was placed in an ice-salt bath and monomer (0.1 mole) was rapidly introduced through the funnel. The reaction temperature was gradually increased from –10 to 4°C and after 24 h the polymerization was quenched with ammonia water. The products were precipitated in ethyl ether and dried

in a vacuum oven over night at 50°C. The polymer (star-PCL-*b*-PEO) was determined by ^{1}H-NMR and GPC. ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.10–1.65 (—C***H***$_3$, —CC***H***$_2$CH$_3$, —C***H***$_2$CH$_2$COO, —C***H***$_2$CH$_2$CH$_2$COO, and —C***H***$_2$CH$_2$CH$_2$CH$_2$COO), 2.10–2.40 (—C***H***$_2$COO), 3.63–3.73 (—C***H***$_2$OH, —C***H***$_2$CH$_2$OH), 3.90–4.10 (—COOC***H***$_2$—).

Preparation of star-PCL-*b*-PEO micelles

The THF solution of the block copolymer was added dropwise into doubly distilled water with agitation, and then the THF was removed by evaporating under reduced pressure at 25°C for 2 h. Pyrene solution in acetone (0.1 mg/mL) was added to doubly distilled water to give a pyrene concentration of 0.25 mg/L, and then the acetone was removed with a water aspirator pump for 8 h. These two solutions and doubly distilled water were mixed to achieve the copolymer concentration from 1 g/L to 0.01 mg/L, whereas the pyrene concentration was kept constant at 6×10^{-7} mol/L. The samples were ultrasonited for 15 min, heated at 50°C for 1 h and cooled to room temperature overnight to equilibrate the pyrene in water and micelles.[23] In each measurement, 2 mL of star-PCL-*b*-PEO dispersion containing 6×10^{-7} mol/L of pyrene were placed in a 1.0 × 1.0 cm square quartz cell. The excitation wavelength (λ_{ex}) was set at 339 nm for emission spectra measurement, and the detection wavelength (λ_{em}) was set at 390 nm for excitation spectra measurement. Steady-state fluorescence spectra as a function of copolymer concentration were recorded on a PerkinElmer LS50 B luminescence spectrometer with a scanning rate of 20 nm/min.

Encapsulation and release of dye using star-PCL-*b*-PEO as carriers

The congo red aqueous solution with the concentration at 0.0019 g/mL was added into the star-PCL-*b*-PEO/CH_2Cl_2 solution with concentration at 0.03 g/mL. The mixture was stirred at a speed 150 rounds/min. After phase transfer equilibrium of congo red is reached, the dye-loaded complexes were facilely obtained by removing the aqueous layer and organic solvent. The separated dye-loaded complexes and dried under a vacuum at 60°C for 12 h were used for the release of dye-loaded complexes without any further management. About 3 mg of dye-loaded complexes were added into 5 mL SBF and the rotating speed and temperature of shaking table were controlled at 80 r/min and 37°C, respectively. The amount of release congo red in the aqueous solution was analyzed by UV–vis spectrometer. Through the comparison working curve, the concentration of congo red was calculated. The release concentration of congo red with [$c = A/(\varepsilon \times d)$], where ε are the molar absorptivity of congo red in an aqueous solution, whereas d were defined as thickness of sample pool ($\varepsilon_{\lambda max} = 45{,}000\ \mathrm{L\,mol^{-1}\,cm^{-1}}$, $\lambda_{max} = 498$ nm).[24]

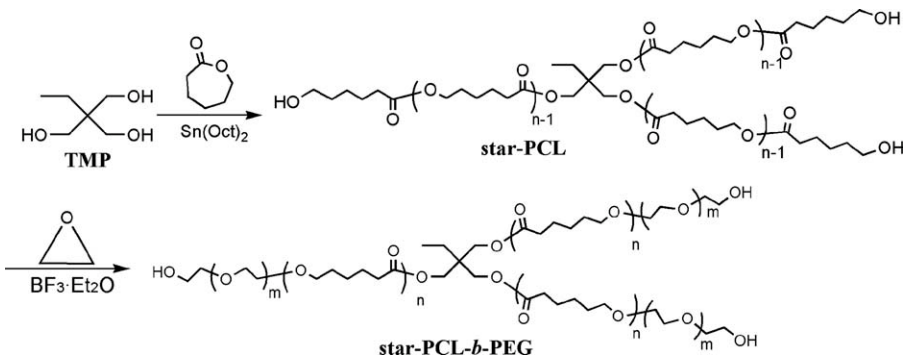
Measurments

^{1}H-NMR spectra were recorded with an AVANCE DMX-500 NMR spectrometer by using tetramethylsilane as internal standard at room temperature. The gel permeation chromatography (GPC) measurements were carried out on a Waters 201 with a μ-styragel column and THF as an eluent, and the molecular weight was calibrated with standard polystyrene. Infrared spectra were recorded on Jasco IR-700 infrared spectrophotometer. Differential scanning calorimetry (DSC) was carried out on a DS822 with a heating rate of 10°C/min from 30 to 200°C under nitrogen atmosphere, relative to indium standards. Transmission electron micrographs were obtained on a JEOL model 1200EX instrument operated at an accelerating voltage at 160 kV. Size distribution of micelles was measured by dynamic light scattering (DLS) with avertically polarized He-Nelaser(DAWNEOS, Wyatttechnology). The scattering angle was fixed at 90°, and the measurement was carried out with constant temperature at 25°C. Before the measurement, the samples were filltered using 0.45 μm PTFE membrane fillters to eliminate dust particles. UV measurements of encapsulation and release of dye using star-PCL-*b*-PEO as carriers were performed on a Lambda 900 spectrometer (Waltham, MA) with synthetic body fluids as solvent at 37°C.

RESULTS AND DISCUSSION

Synthesis of star-PCL-*b*-PEO copolymers

The amphiphilic three-arm star polymers with lipophilic PCL as the inner block in the arm and hydrophilic PEO as the outer block were involved in this study. The synthesis of the star amphiphilic polymer was carried out as outlined in Scheme 1. The $Sn(Oct)_2$ catalyst was added in a concentration of 1/200 relative to the amount of initiating hydroxyl groups, which is the optimum catalyst amount reported in the literature.[15] The reaction was carried out in neat ε-caprolactone at 115°C for 20 h. In this way, the polymerization was well-controlled, and the molecular weight of each arm in the product was determined by the monomer/initiator ratio. The star-PCL product was obtained in quantitative yield. Three star-PCL samples with M_n = 15,250, 20,050, and 31,250 g/mol were synthesized. Because there are three initiator sites in a TMP molecule, star-PCL samples have three PCL chains. Each PCL chain has



Scheme 1 Reaction scheme for synthesis of star-PCL-*b*-PEO copolymers.

44, 58, or 91 monomer units in three samples, respectively. M_n (GPC) are slightly higher than M_n (NMR). This phenomenon can be ascribed to the structure of resultant polymers because of their different hydrodynamic volumes compared with linear polymer having the same molecular weight.[25]

The next step was to introduce hydrophilic PEO into the star-PCL polymer. The attachment of PEO on star-PCL was carried out by cationic polymerization of EO directly initiated by $BF_3{\cdot}OEt_2$. The hydroxyl terminal groups of the star-PCL polymer was used as initiator sites to react with EO to produce the desired final star-PCL-*b*-PEO. The advantages of this method are that, reactions are conducted under very mild conditions, and the product is formed in high-yield. The yield of the final star-PCL-*b*-PEO polymer was >90%.

Characterization of star copolymers

The molecular weights of the synthesized polymers were determined by SEC and are summarized in Table I. As can be seen, the polydispersity of these star polymers was sufficiently narrow ($M_w/M_n <$ 1.23). Comparison with the elution profiles for star-PCL and star-PCL-*b*-PEO samples revealed that peak of star-PCL-*b*-PEO shifted toward higher molecular weight after attaching the PEO blocks (Fig. 1).

The FTIR spectrum of the star-PCL has a band characteristic for the ester carbonyl at 1730 cm^{-1} and a band for hydroxyl from 3500 to 3000 cm^{-1}.[26] There is only one hydroxyl group per PCL chain, so the intensity of the hydroxyl band was low, reflecting the low-content of —OH in the sample. In the IR spectrum of star-PCL-*b*-PEO, the relatively intensity of —OH band has decreased, confirming the conjugation of PCL and PEO blocks. A stronger band at 1100 cm^{-1} for C—O—C appeared, consistent with the addition of PEO ether units (Fig. 2). Spectroscopic measurements also confirmed the structures of the star polymer products.

In the ^{1}H-NMR spectrum of star-PCL, three major resonances attributed to the repeat unit of PCL $[—O—CH_2—(CH_2)_3—CH_2—CO—]_n$ are observed: the triplet peak at 4.07 ppm is assigned to methylene protons in the $—OCH_2—$ group; the triplet at 2.32 ppm is assigned to methylene protons adjacent to the carbonyl group; and the $—(CH_2)_3—$ protons are

TABLE I
The Molecular Characteristics of Synthesized Hyperbranched Polyols Grafted with Poly (ε-caprolactone)

Sample	M_n[a] g/mol	PDI[a] M_w/M_n	M_n[b] g/mol	M_n[c] g/mol	PDI[c] M_w/M_n	$m : n$	Coversion[d] (%)	Radium[e] (nm)
$PCL1_n$-*b*-PEO_m-1				25,130	1.20	225 : 134	92.5	12.5
$PCL1_n$-*b*-PEO_m-2	15,250	1.20	14,860	30,570	1.21	348 : 134	92.6	12.9
$PCL1_n$-*b*-PEO_m-3				45,680	1.16	692 : 134	95.3	15.8
$PCL2_n$-*b*-PEO_m-4				30,050	1.20	227 : 176	92.6	15.6
$PCL2_n$-*b*-PEO_m-5	20,050	1.18	19,720	40,130	1.22	456 : 176	90.9	18.7
$PCL2_n$-*b*-PEO_m-6				45,150	1.18	570 : 176	95.4	19.4
$PCL3_n$-*b*-PEO_m-7				50,160	1.19	429 : 274	95.3	20.8
$PCL3_n$-*b*-PEO_m-8	31,250	1.21	30,840	60,240	1.18	659 : 274	93.5	22.5
$PCL3_n$-*b*-PEO_m-9				80,550	1.23	1120 : 274	94.5	32.1

[a] M_n of star-PCL polymers obtained from GPC method.
[b] M_n of star-PCL polymers obtained from NMR method by comparing the integral area of methyl of TMP at 0.9 ppm and methylene of PCL at 2.20 ppm.
[c] M_n of star-PCL-*b*-PEO copolymers obtained from GPC method.
[d] The yield of the final star-PCL-*b*-PEO copolymer.
[e] Calibrated against DLS results.

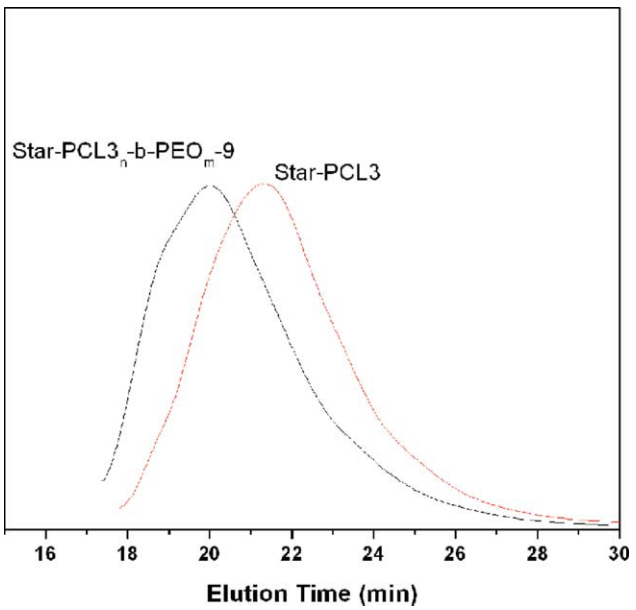


Figure 1 GPC curves of star-PCL3 and star-PCL3$_n$-*b*-PEO$_m$-9 samples. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

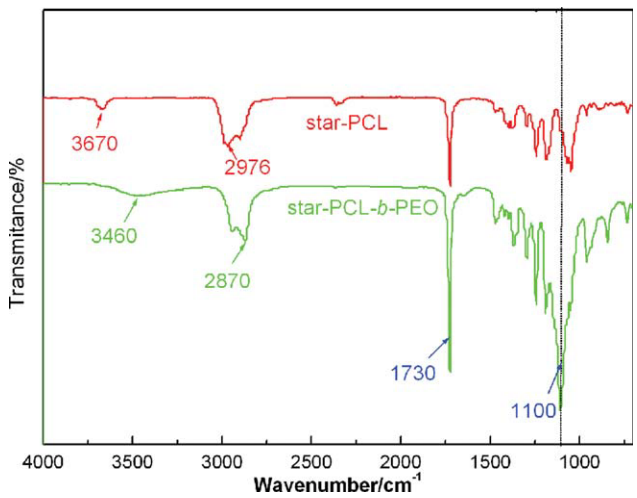


Figure 2 FTIR spectra of star-PCL (Sample 1) and star-PCL-*b*-PEO copolymer (Sample 1). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

shown as a multiple peak from 1.9 to 1.1 ppm.[15] In the ^{1}H-NMR spectrum of star-PCL-*b*-PEO, in addition to the peaks from PCL blocks, the single peak at 3.65 ppm is observed because of the methylene protons in PEO blocks (Fig. 3).[27] The integrated peak area ratio of PEO and PCL for the purified star-PCL-*b*-PEO sample is consistent with the expected structure.

The thermal behavior of the synthesized copolymers was investigated using DSC. As shown in Figure 4, some crystallinity of both the PEO and PCL blocks remains in the copolymer. The presence of two peaks indicates micphase separation. The lower of the peak at 44°C is identified with PEO domains. The T_m of a PCL homopolymer was reported to be 50°C,[28] and thus the second-higher peaks in the DSC curves at 49.8°C are identified with the PCL domains. As crystallization of PEO is affected by the presence of PCL, the T_m of PEO is expected to decrease from the homopolymer value in copolymer.[29,30]

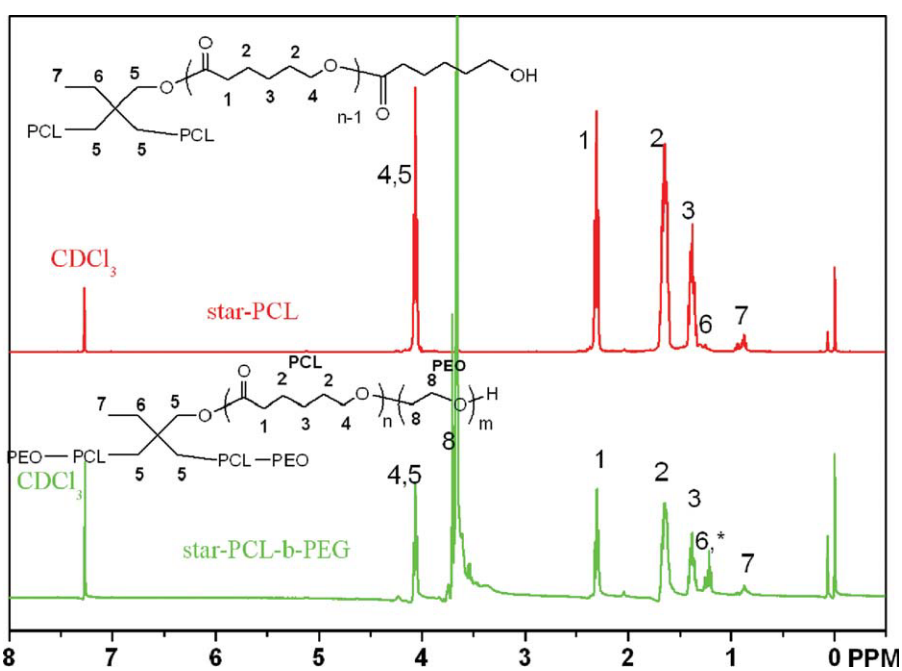


Figure 3 ^{1}H-NMR spectra of star-PCL (Sample 1) and star-PCL-*b*-PEO copolymer (Sample 1). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

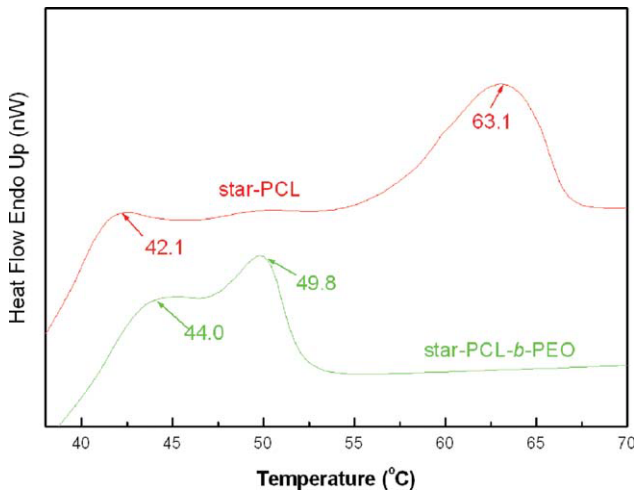


Figure 4 DSC curves of star-PCL (Sample 1) and star-PCL-*b*-PEO copolymer (Sample 1). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The star-PCL-*b*-PEO copolymer does not dissolve directly in water because of the hydrophobicity of the polycaprolactone core-forming block. For this reason, a dialysis method was employed to prepare polymeric micelles. The polymer was first dissolved in THF, which is a good solvent for both PCL and PEO segments, and micellization was induced by the dropwise addition of water followed by dialysis. The micelle size distribution of a polymer solution with a concentration of $\sim$ 12 mg/mL was determined by DLS and is shown in Table I. The mean size of star-PCL-*b*-PEO copolymers ranged from 12.1 to 32.1 nm, indicating the existence of unimolecular micelle structures of the star-PCL-*b*-PEO copolymers in aqueous solution. The size of the unimolecular micelles increase as PCL content increses. The higher PCL content might produce unimolecular micelles with thicker cores. Micelle morphology was investigated from TEM in Figure 5. It is evident that the polymer micelles were dispersed as spherical micelles with a diameter of $\sim$ 20 nm.

Encapsulation and release of guest molecules in star-PCL-*b*-PEO copolymer micelles

Information about the onset of micellization of star-PCL-*b*-PEO is drived from steady-state fluorescent prob studies.[23] Pyrene was chosen as the fluorescent probe because of its photophysical property. It was known that pyrene, as a fluorescene probe, shows little fluorescence when it was inaggregation state and shows strong fluorescence when it was separated molecularly. The hydrophobic environment is also favorable to improve the fluorescent intensity of pyrene. In the CMC measurements, keeping a relatively high-concentration of pyrene is to make sure that, the pyrene is in its aggregation state in pure water. So, under this condition, if the concentration of the pyrene was kept same, the fluorescence intensity would be improved greatly, when the micelle existed in the solution because the pyrene molecules can be separated because of the fact that, they entered into the hydrophobic core of micelles. The solutions were kept at room temperature for 24 h to reach the equilibrated solubilization of pyrene in the aqueous phase. Emission was carried at 390 nm, and excitation spectra were recorded ranging from 240 to 360 nm. Both excitation and emission bandwidths were 10 nm. From the pyrene excitation spectra, the intensities at 336.4 and 333 nm were analyzed as a function of the polymer concentrations. A CMC value ($\sim$ 10.7 mg/L) was determined from the intersection of the tangent to the curve at the inflection with the horizontal tangent through the points at low-concentration (Fig. 6).

The solubilization of dyes in dilute solutions of star-PCL-*b*-PEO copolymers is probably the result of incorporation of the dye in the PCL region of the intact star copolymer molecules. Therefore, this observation can be confirmed the existence of a "unimolecular micelle." Star-PCL-*b*-PEO copolymers have a unimolecular micelle structure, which offers the ability of transferring guest molecules between two immiscible liquid phases. We use star-PCL-*b*-PEO copolymers as carrier to demonstrate the encapsulation behaviors for guest molecules. As shown in the picture inset in Figure 6, the aqueous phase containing congo red dye and organic phase containing star-PCL-*b*-PEO were separated in the

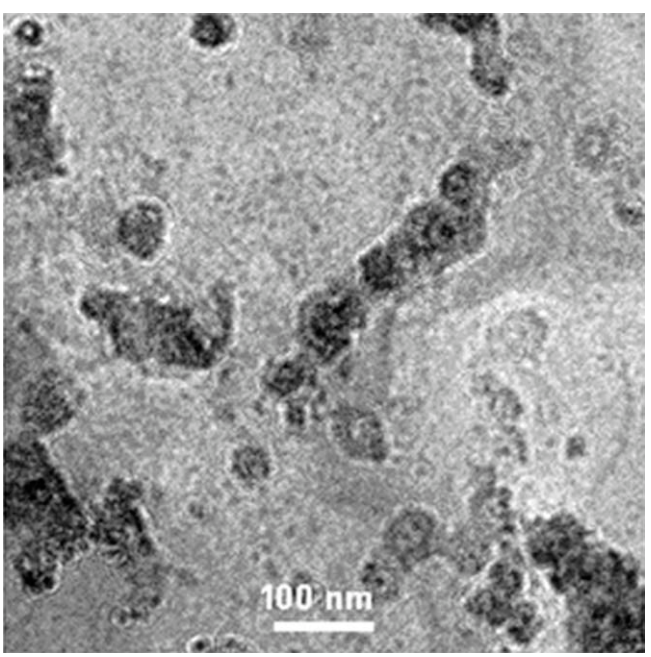


Figure 5 TEM image star-PCL-*b*-PEO copolymer micelles (Sample 5).

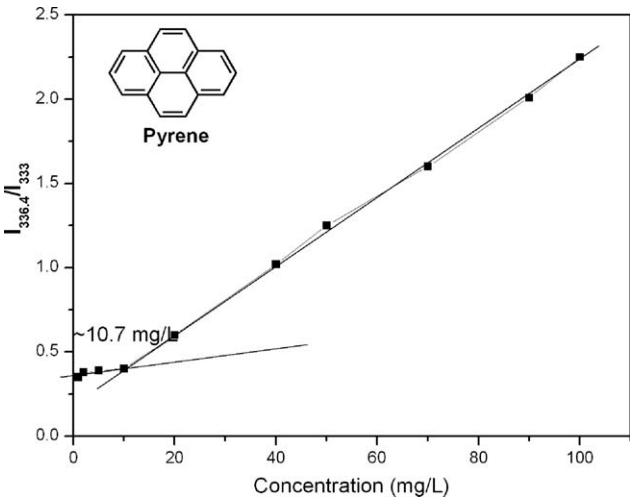


Figure 6 Dependence of intensity ratio $I_{336.4}/I_{333}$ (from pyrene excitation spectra) as a function of star-PCL-*b*-PEO concentration (Sample 1). ([Py] = 6.0×10^{-7} M, λ_{em} = 390 nm, T = 37°C).

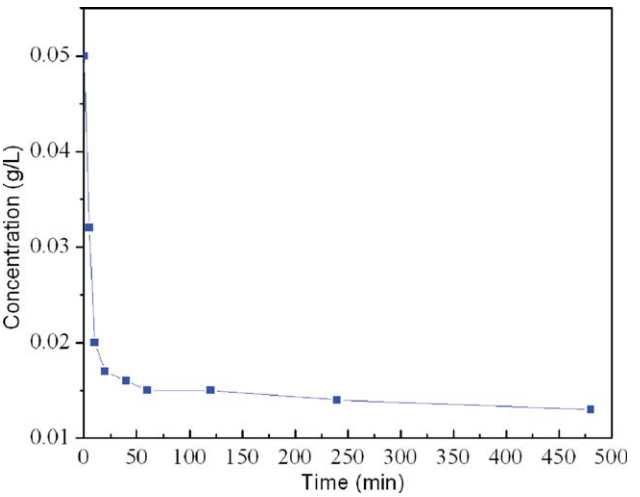


Figure 7 Influence of the time on the transfer performance of congo red using star-PCL-*b*-PEO (Sample 5) as the transfer agent. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

vial. As the time proceed, the vial was stirred at a speed 150 rounds/min, the colorless chloroform became red. As suggested by its intense red color, congo red has important spectrophotometric properties. Indeed, its UV–visible absorption spectrum shows a characteristic, intense peak around 498 nm in aqueous solution, at low-dye concentration. Because the congo red aqueous solution showed characteristic in UV–vis spectra, the concentration of congo red in the aqueous solution could be determined with a UV–vis spectrometer.

First, the influence of the time on the transfer performance of congo red was investigated. star-PCL-*b*-PEO was dissolved in CH_2Cl_2 to concentration of 0.03 g/mL, and the solution was feed into a small vial. Then, congo red aqueous solutions with the concentration at 0.002 g/mL was added into the vial. The aqueous phase containing congo red dye and organic phase containing star-PCL-*b*-PEO were observed. The characteristic absorbance at 486 nm decreased gradually as increasing the proceeding time. Meanwhile, the organic phase changed gradually from colorless to red during this step. The influence of the transfer time on the concentration of congo red in aqueous layer for the this systems is depicted in Figure 7. The concentration of congo red in aqueous layer decrease quickly in first 30 min. After 1 h, the concentration of congo red in aqueous layer is almost not changed, which indicated the phase transfer equilibrium of congo red is reached.

Dye-loaded complexes were facilely obtained after removing the aqueous layer and organic solvent. The separated dye-loaded complexes, dried under a vacuum at 60°C for 12 h, were used for the release of dye-loaded complexes without any further management. About 3 mg dye-loaded complexes were immersed into 5 mL SBF with different pH values. The mixture was shaken at a speed 150 rounds/min at 37°C. The amount of released congo red in the aqueous solution was analyzed by UV–vis spectrometer. Through the comparison with various absorption intensity as working curve, the concentration of congo red was calculated. As shown in Figure 8, the influence of the release time on the concentration of loaded dye increased gradually. When increasing pH of solution, fewer congo red molecules could be released into the solution. After 5 h, the concentration of congo red in solution is almost not changed, which indicated the release equilibrium of congo red is reached. However, the lower pH solution the more of congo red can be released. The possible

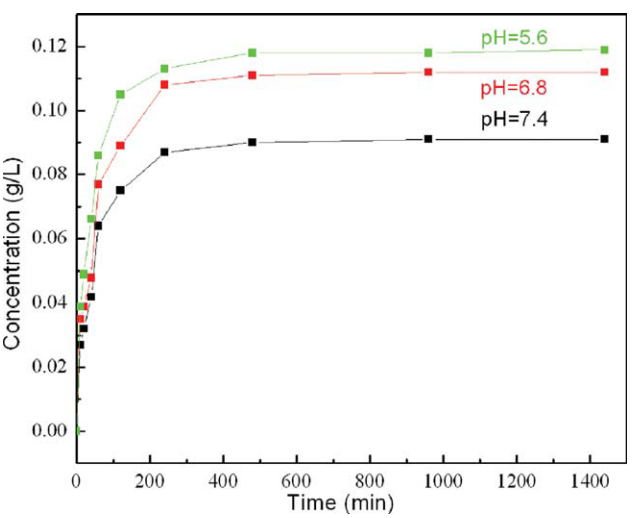


Figure 8 Influence of the pH value of the aqueous layer on the transfer percentage of congo red. [Color figures can be viewed in the online issue, which is available at www.interscience.wiley.com.]

reason of this phenomenon is the degradation of PCL. Because of the biocompatibility of the PCL and PEO blocks, and the biodegradability of the PCL arms, these well-defined multi-arm star copolymers are attractive materials for biomedical applications.[31]

CONCLUSION

In conclusion, star amphiphilic polymer consisting of hydrophobic and biodegradable PCL and hydrophilic PEO blocks was synthesized by two-step ring-opening polymerization. The resultant polymer was characterizated by FTIR, ^{1}H-NMR, and DSC to determine its chemical structure. The morpholoy of the polymer micelles was analyzed by TEM. Using star-PCL-*b*-PEO as carriers and congo red as model molecules, the encapsulation and release properties were investigated by UV–visable analysis. Thus, this copolymer system should be an attractive candidate for drug-delivery system in aqueous media and could provide the phase-transfer carriers between water and organic media.

References

1. Wei, H.; Zhang, X.-Z.; Chen, W.-Q.; Cheng, S.-X.; Zhuo, R.-X. J Biomed Mater Res 2007, 83, 980.
2. Kwon, G. S.; Forrest, M. L. Drug Dev Res 2006, 67, 15.
3. Onaca, O.; Enea, R.; Hughes, D. W.; Meier, W. Macromol Biosci 2009, 9, 129.
4. Zhang, J.; Ma, P. X. Angew Chem Int Ed Engl 2009, 48, 964.
5. Haag, R. Angew Chem Int Ed Engl 2004, 43, 278.
6. Ge, Z.; Liu, S. Macromol Rapid Commun 2009, 30, 1523.
7. Prabaharan, M.; Grailer, J. J.; Pilla, S.; Steeber, D. A.; Gong, S. Biomaterials 2009, 30, 3009.
8. Hirao, A.; Matsuo, A.; Morifuji, K.; Tokuda, Y.; Hayashi, M. Polym Adv Technol 2001, 12, 680.
9. Irvine, D. J.; Mayes, A. M.; Satija, S. K.; Barker, J. G.; Sofia-Allgor, S. J.; Griffith, L. G. J Biomed Mater Res 1998, 40, 498.
10. Qiu, S.; Huang, H.; Dai, X.-H.; Zhou, W.; Dong, C.-M. J Polym Sci Part A: Polym Chem 2009, 47, 2009.
11. Dai, X.-H.; Dong, C.-M. J Polym Sci Part A: Polym Chem 2008, 46, 817.
12. Stiriba, S.-E.; Kautz, H.; Frey, H. J Am Chem Soc 2002, 124, 9698.
13. Gao, H.; Matyjaszewski, K. Macromolecules 2007, 40, 399.
14. Gao, H.; Ohno, S.; Matyjaszewski, K. J Am Chem Soc 2006, 128, 15111.
15. Wang, F.; Bronich, T. K.; Kabanov, A. V.; Rauh, R. D.; Roovers, J. Bioconjugate Chem 2005, 16, 397.
16. Keys, K. B.; Andreopoulos, F. M.; Peppas, N. A. Macromolecules 1998, 31, 8149.
17. Georgiou, T. K.; Vamvakaki, M.; Phylactou, L. A.; Patrickios, C. S. Biomacromolecules 2005, 6, 2990.
18. Park, S. Y.; Han, B. R.; Na, K. M.; Han, D. K.; Kim, S. C. Macromolecules 2003, 36, 4115.
19. Jeong, B.; Choi, Y. K.; Bae, Y. H.; Zentner, G.; Kim, S. W. J Controlled Release 1999, 62, 109.
20. Kim, B. S.; Oh, J. M.; Cho, J. S.; Lee, S. H.; Lee, B.; Khang, G.; Lee, H. B.; Kim., M. S. J Appl Polym Sci 2009, 111, 1706.
21. Wang, L.; Kilcher, G.; Tirelli, N. Macromol Biosci 2007, 7, 987.
22. Jiang, G.; Chen, W.; Wang, Z. Macromolecules: An Indian J 2007, 3, 8.
23. Li, Y. Y.; Zhang, X. Z.; Zhu, J. L.; Cheng, H.; Cheng, S. X.; Zhuo, R. X. Nanotechnology 2007, 18, 215605.
24. Cho, S.; Allcock, H. R. Macromolecules 2007, 40, 3115.
25. Jiang, G.; Wang, L.; Chen, T.; Yu, H. Polymer 2005, 46, 81.
26. Du, J.; Chen, Y. Macromolecules 2004, 37, 3588.
27. Hua, C.; Peng, S.-M.; Dong, C.-M. Macromolecules 2008, 41, 6686.
28. Kang, J.; Beers, K. J. Biomacromolecules 2006, 7, 453.
29. Jiang, S.; He, C.; Men, Y.; Chen, X.; An, L.; Funari, S. S.; Chan, C.-M. Eur Phys J E Soft Matter 2008, 27, 357.
30. Gan, Z.; Zhang, J.; Jiang, B. J Appl Polym Sci 1997, 63, 1793.
31. Gottschalk, C.; Wolf, F.; Frey, H. Macromol Chem Phys 2007, 208, 1657.