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Facile Synthesis and Micellization of Biodegradable Poly(decamethylene succinate)-*graft*-Poly(ethylene glycol)

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ABSTRACT: In this article, we report the facile one-pot synthesis of poly(decamethylene succinate) (PDS) with multiple hydroxyl groups by direct polycondensation with malic acid (MA) as the functional monomer and dysprosium triflate as the chemoselective catalyst at 80°C. The secondary hydroxyl groups of malic units were inactive during the polycondensation process. The density of hydroxyl groups of the copolymer could be well-controlled by the molar ratio of succinic acid and MA in the feed. These hydroxylated PDSs were grafted by poly(ethylene glycol) (PEG) through a simple esterification reaction; this resulted in amphiphilic PDS-*g*-PEG copolymers, which could undergo micellization in aqueous media to form nanosized aggregates with diverse morphologies and diameters. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 000: 000–000, 2012

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INTRODUCTION

Graft polymers have attracted considerable interest on account of their unique molecular architecture, relatively easy synthesis, and potential industrial applications.[1–3] Generally, there have been three main strategies adopted for the preparation of graft polymers: grafting through, grafting from, and grafting onto.[4] Both the grafting-onto and grafting-from methods involve first the synthesis of a multifunctional polymeric backbone. Functional vinyl monomers, such as 2-hydroxyethyl methacrylate,[5–7] vinyl alcohol,[8,9] chloromethylstyrene,[10,11] and their derivatives, have been widely investigated for the preparation of multifunctional polymeric backbones by controlled/living radical polymerization. Nevertheless, these polymeric backbones are nonbiodegradable, which may restrain their further application.

Aliphatic polyesters and polycarbonates are important biomaterials that contribute to the biodegradability, biocompatibility, and nontoxicity of graft copolymers. Various functional cyclic esters[12–15] and carbonates[16–19] have been synthesized and polymerized to prepare multifunctional polyesters and polycarbonates by ring-opening polymerization. Then, polymeric side chains can be grafted from or grafted onto the backbone to give well-defined biodegradable graft copolymers. Nevertheless, the synthesis of functional cyclic monomers always involves multistep reactions and lead to a low yield and high cost. The polycondensation of aliphatic diols and dicarboxylic acids is another important strategy for synthesizing biodegradable polyesters. The use of diols or dicarboxylic acids with additional functional groups for polycondensation is supposed as an efficient method for preparing multifunctional polyesters facilely on a large scale. However, the polycondensation of diols and dicarboxylic acids are generally performed at high temperatures (>250°C), under which the functional groups should be destroyed by side reactions. Recently, Takasu and coworkers[20,21] reported a regioselective catalyst, scandium triflate, for the direct polycondensation of functional diols and dicarboxylic acid having secondary hydroxyl groups under moderate temperature; these could prevent the esterification of secondary hydroxyl groups and prepare linear multifunctional polyesters within one step. However, scandium is excruciatingly expensive because of its relative rarity, and this may prevent it from being used in industry applications. Rare earth elements show similar chemicophysical properties because of their similar configuration of extranuclear electron. In this study, dysprosium triflate [$Dy(OTf)_3$], a much cheaper rare earth triflate, was used as a catalyst for the chemoselective polycondensation of succinic acid (SA), malic acid (MA), and decamethylene glycol (DG) at

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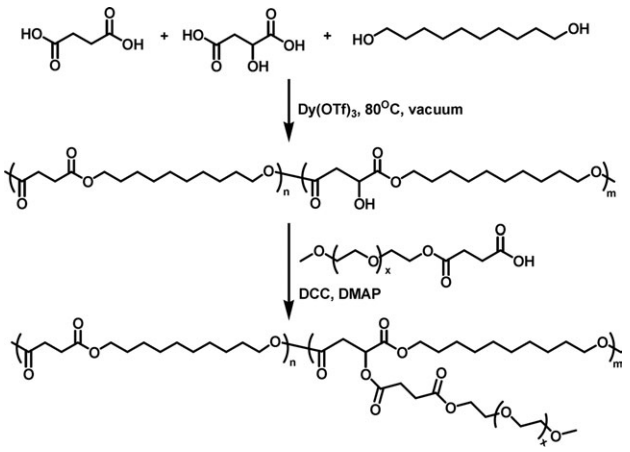

Scheme 1. Synthetic route of PSD-*g*-PEG.

80°C. This resulted in high-molecular-weight poly(decamethylene succinate) (PDS) with multiple hydroxyl groups (Scheme 1). The density of hydroxyl groups could be controlled well by the feeding molar ratio of SA to MA.

Poly(ethylene glycol) (PEG) is an FDA-approved polymer that has been widely investigated in materials science and biotechnology because of its stability, biocompatibility, water solubility, nontoxicity, rapid clearance from the body, and lack of immunogenicity.[22–24] Amphiphilic polymers containing PEG segments can undergo self-assembly in water to form micelles with hydrophilic PEG shells and have potential applications in drug and gene delivery.[25–32] Here, the PEGylation of hydroxylated poly (decamethylene succinate) (PDSOH) was carried out by simple esterification with monocarboxyl-terminated methoxy poly(ethylene glycol) (mPEG-COOH) to give well-defined PDS-*g*-PEG amphiphilic graft copolymers (Scheme 1). These polymeric amphiphiles could be self-organized into nanosized micelles in aqueous media with diverse morphologies and diameters, which were dependent on the grafting density of the PEG side chains.

EXPERIMENTAL

Materials

SA (99%, Aladdin, Shanghai, China), MA (99%, Aladdin, Shanghai, China), DG (98%, Aladdin, Shanghai, China), dicyclohexylcarbodiimide (DCC; 99%, Aladdin, Shanghai, China), 4-dimethylaminopyridine (DMAP; 99%, Aladdin, Shanghai, China), mPEG [Sigma-Aldrich, Louis, Missouri, number-average molecular weight (M_n) = 1000], and other chemicals were used as received. The synthesis of $Dy(OTf)_3$[33] and mPEG-COOH[34] were reported in our previously work.

Synthesis of PDSOH

A typical procedure is described as follows: 1.35 g (0.01 mol) of MA, 10.7 g (0.09 mol) of SA, 17. 8 g (0.1 mol) of DG, and 0.716 g (1.0 mmol) of $Dy(OTf)_3$ were added to a 100-mL flask equipped with a mechanical stirrer. The mixture was stirred at 80°C under nitrogen gas flow and became homogeneous after it reacted for 1 h. Then, polycondensation started under a reduced pressure, which was gradually increased to 0.1 mmHg within 2 h and maintained for 6 h to complete the condensation. After the reaction, the crude product was dissolved in methylene chloride and passed through a neutral aluminum oxide column to remove the catalyst. After concentration, the copolymer was precipitated in cold ethyl ether, isolated by filtration, and dried *in vacuo* to a constant weight at room temperature (yield = 22.7 g or 87.5%)

Synthesis of PDS-*g*-PEG

The PDS-*g*-PEG graft copolymers were synthesized by the esterification of PDSOH and mPEG-COOH. Briefly, 2.6 g (1.0 mmol of hydroxyl) of PDSOH, 1.21 g (1.1 mmol) of mPEG-COOH (M_n = 1100), 0.23 g (1.1 mmol) of DCC, and 13.6 mg (0.11 mol) of DMAP were dissolved in 50 mL of anhydrous tetrahydrofuran (THF) and stirred for 72 h at room temperature under a nitrogen atmosphere. The reaction byproduct, dicyclohexylcarbodiurea, was removed by filtration. After most of the solvent was evaporated, the crude product was precipitated in cold diethyl ether (yield = 2.53 g or 93.1%).

Pure PDS-*g*-PEG was obtained by dialysis (with a dialysis membrane with a molecular weight cutoff of 14,000) and lyophilization. The abovementioned crude product (0.2 g) was first dissolved in 10 mL of THF, and then, distilled water (10 mL) was added dropwise to the solution with vigorous stirring. Then, the solution was stirred overnight and dialyzed against distilled water over 72 h to remove THF and excess unreacted mPEG-COOH. The final solid-state sample was recovered by lyophilization (yield = 0.162 g or 81%).

Preparation of the Micelles

The micelles were prepared by a dialysis technique. Briefly, 25 mg of purified graft copolymer was dissolved in 5 mL of THF, and then, 5 mL of distilled water was added dropwise to the solution under vigorous stirring. A light blue tint appeared, which indicated the formation of aggregates. The micelle solution was stirred overnight and dialyzed against distilled water over 24 h to remove THF. The final volume of the aqueous solution was adjusted to 25 mL with a concentration of 1.0 mg/mL.

Measurements

^{1}H-NMR spectra were recorded on a Bruker Avance DMX500 spectrometer (Billerica, Massachusetts) in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard.

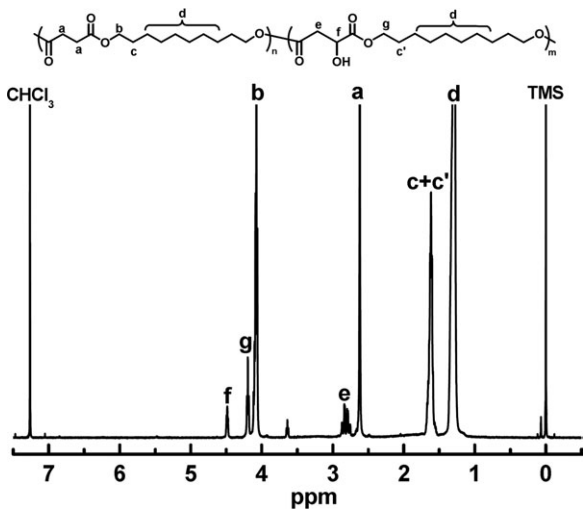

Figure 1. ^{1}H-NMR spectrum of PSDOH-10.

Table I. Polycondensation of SA, MA, and Decamethyl Glycol Catalyzed by $Dy(OTf)_3$[a]

Sample	SA/MA (molar ratio)[c]	M_n (kg/mol)[d]	MWD[d]	SWCA (°)	T_m (°C)[f]	T_c (°C)[f]
PDS	100/0	20.3	2.13	103.0	71.8	48.1
PDSOH-10[b]	90.3/9.7	19.0	2.40	90.5	68.4	42.4
PDSOH-20	79.4/20.6	19.9	1.68	84.0	65.1	36.8
PDSOH-50	50.2/49.8	19.2	2.29	73.5	43.1	9.5

[a]Polycondensation conditions: 80°C and 9 h. The molar ratio of $Dy(OTf)_3$ to monomer (MA + SA) was 1/100, [b]The numbers 10, 20, and 50 refer to the molar fraction of MA in the feed, [c]Molar ration of MA to SA units in the copolymer, as determined by ^{1}H-NMR, [d]Determined by GPC–MALLS, [f]Determined by DSC.

The molecular weight and molecular weight distribution were determined by gel permeation chromatography (GPC) which consisted of a Waters degasser, a Waters 1525 HPLC pump, a Waters 2414 refractive-index (RI) detector and a Wyatt DAWN DSP multiangle light scattering photometer with THF as the mobile phase at a flow rate of 1.0 mL/min at 40°C. Linear polystyrene standards were used for calibration.

Differential scanning calorimetry (DSC) measurements were performed on a TA Q100 apparatus (TA Instruments, New Castle, Delaware). The samples were heated from 0 to 100°C, held for 2 min to erase the thermal history, then cooled to 0°C at a rate of 20°C/min, and finally heated to 100°C at a rate of 10°C/min.

The static water contact angle (SWCA) was determined by the sessile drop method with a CTS-200 contact angle system (Mighty Technology Pvt Ltd,. Shanghai, China) at room temperature. The copolymer films were prepared by the coating of a methylene chloride solution of the copolymers (50 mg/mL) onto glass slides. The films were dried *in vacuo* at room temperature overnight. A water drop (2 μL) was laid onto the copolymer film with a microsyringe, and then, the SWCA was recorded after 5 s. Each reported SWCA was an average of at least five different measurements.

The hydrodynamic diameter and size distribution of the micelles were determined by dynamic light scattering (DLS) at an angle 90° to the incident beam and at 25°C on a Brookhaven 90 Plus particle size analyzer (Brookhaven Instruments, Holtsville, New York). All micelle solutions measured by DLS had a concentration of 0.3 mg/mL.

The critical micelle concentration (cmc) was determined by a fluorescence technique with pyrene as a fluorescent probe. Fluorescence excitation spectra were recorded on a Hitachi F-4500 fluorescence spectrometer (Hitachi, Ltd., Tokyo, Japan) at a 390-nm emission wavelength and a 2.5-nm slit width. The concentration of the sample solutions ranged from 1.0×10^{-6} to 0.1 mg/mL. The pyrene concentration in the solution was 6.0×10^{-7} *M*.

Transmission electron microscopy (TEM) images were obtained with a JEM-1230 (JEOL Ltd., Tokyo, Japan) operating at an acceleration voltage of 60 kV. A drop of a 0.3 mg/mL micelle solution was placed onto the surface of Formvar carbon-film-coated copper grids. Excess solution was quickly wicked away with a filter paper. All of the grids were finally negatively stained by a 2 wt % phosphotungstic acid aqueous solution.

RESULTS AND DISCUSSION

Synthesis and Characterization of PDSOH

PDSOHs with various functionalities were synthesized by the direct random polycondensation of SA, MA, and DG in the presence of $Dy(OTf)_3$. Figure 1 shows a typical ^{1}H-NMR spectrum of PDSOH-10. The triplet at 4.2 ppm (H^g) was the resonance of the end methylene of decamethyl glycol esterified by the malic carboxyl close to the secondary hydroxyl group of the malic unit. Another characteristic triplet at 4.5 ppm (H^f) was assigned to the proton of the methylidyne conjoined with the secondary hydroxyl group. If this secondary hydroxyl group were esterified, the signal of the methylidyne would have shifted to about 5.5 ppm theoretically. However, no significant signal at about 5.5 ppm was detected; this indicated that the secondary hydroxyl group stayed stable during the polycondensation process, and a linear PDSOH with multiple pendant hydroxyl groups was prepared facilely and precisely. The molar fraction of malicate in the copolymer could be calculated by the integral intensity ratio of H^e to H^a, which was very close to the feeding fraction (Table I). The molecular weights of the copolymers were not significantly influenced by the ratio of dicarboxylic acids. All of these facts indicated that SA

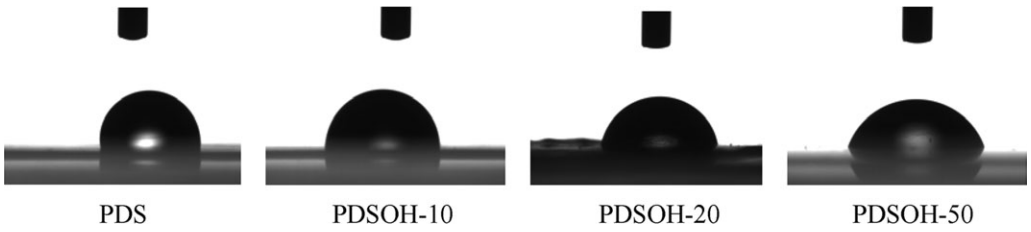

Figure 2. Water contact angle images of PDS, PDSOH-10, PDSOH-20, and PDSOH-50 over glass slides.

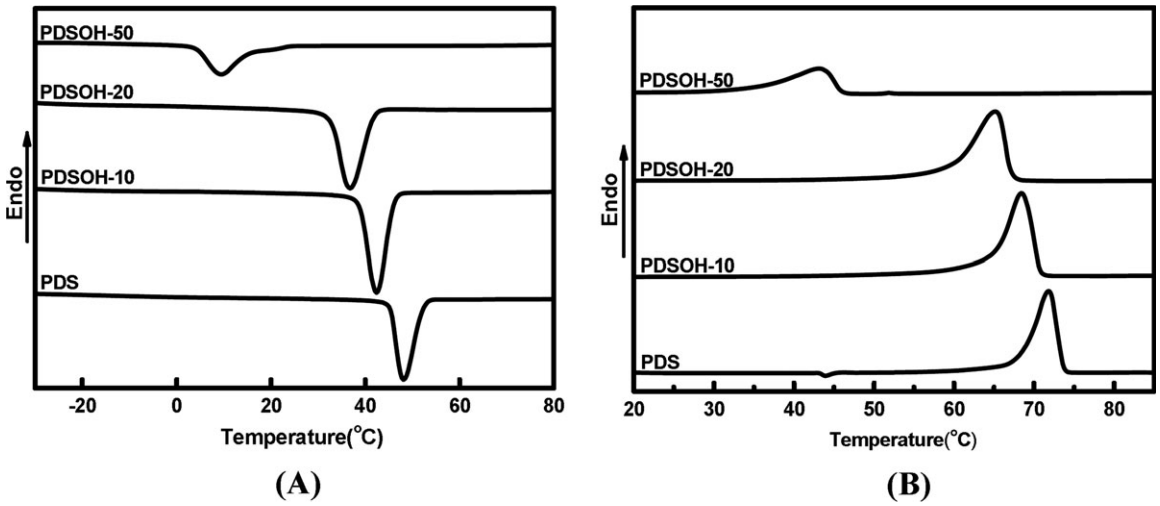

Figure 3. DSC curves of PDS, PDSOH-10, PDSOH-20, and PDSOH-50 in the (A) cooling run and (B) second heating run.

and MA showed similar polymerization activities under the set polycondensation conditions.

The incorporation of pendant hydroxyl groups into the PDS chain increased the hydrophilicity of the copolymers; this was evaluated by SWCA measurements. Figure 2 shows the SWCA images measured on glass slides coated with copolymers with different compositions. As summarized in Table I, pure PDS showed an SWCA of 103°, which was a typical value of a hydrophobic polyester. The SWCAs decreased to 90.5, 80.4, and 73.5° when the malicate contents were increased to 9.7, 20.6, and 49.8%.

The crystallization and melting behaviors of the PDSOHs and the nonfunctionalized PDS were investigated by DSC. To eliminate the heat history, the samples were heated quickly from room temperature to 100°C, then cooled to −50°C, and heated to 100°C again. The cooling run and second heating run were recorded, as shown in Figure 3 and summarized in Table I. The melting temperature (T_m) and the crystallization temperature (T_c) of the polymers were influenced by their compositions. Both the T_m and T_c values of the PDSOHs were obviously lower than that of PDS and decreased with increasing malicate fraction (Table I); this indicated that the crystallinities of the copolymers were greatly reduced by the random structure.

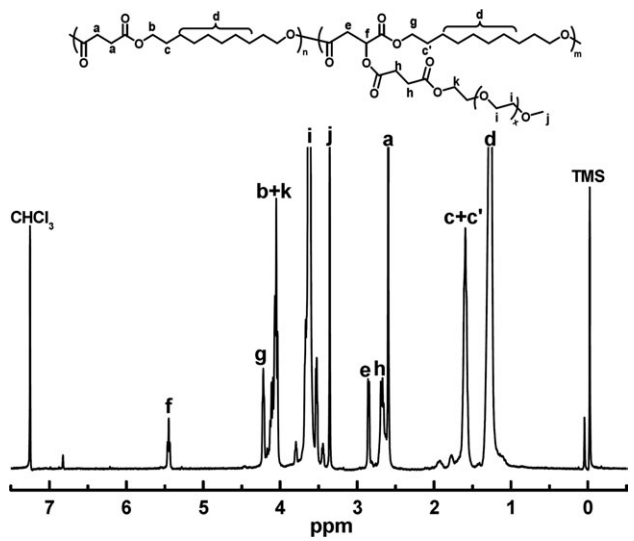

Figure 4. ^{1}H-NMR spectrum of PDS-*g*-PEG-10.

Synthesis and Characterization of PDS-*g*-PEG

PDS-*g*-PEG graft copolymers with various grafting densities were prepared by the simple esterification of PDSOH and mPEG-COOH and purified by dialysis. The ^{1}H-NMR spectrum of PDS-*g*-PEG-10 is shown in Figure 4. Compared with that of the PDSOH-10 precursor (Figure 1), the signal of the methylidyne proton shifted from 4.5 to 5.4 ppm (H^f); this demonstrated that the pendant hydroxyl groups were entirely esterified by the end carboxyl group of the PEG. Other signals attributed to the PEG side chains could be also detected very clearly (H^h, H^i, and H^j), and their integral intensity fit the theoretic value quite well. Figure 5 shows the GPC trace (detected by RI) of PDS-*g*-PEG-10 in comparison with the corresponding PDSOH-10 precursor. After the grafting of the PEG side chains, the GPC trace of PDS-*g*-PEG-10 remained unimodal and symmetrical. However, compared with the PDSOH-10 precursor, the GPC trace of PDS-*g*-PEG-10 only shifted slightly to a high-molecular-mass region; this was attributed to the fact that the brush copolymer owned a more compact conformation than a linear

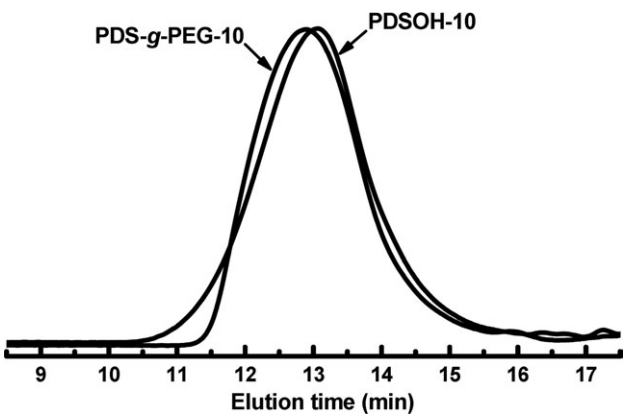

Figure 5. GPC traces of PSDOH-10 and PDS-*g*-PEG-10 (detected by GPC–RI).

Table II. Properties of the Amphiphilic PDS-*g*-PEG Copolymers

Sample	M_n (kg/mol)[a]	MWD	D_h (nm)[b]	PDI[b]	cmc (mg/L)
PDS-*g*-PEG-10	28.0	1.81	77.2	0.261	1.36
PDS-*g*-PEG-20	33.5	1.49	47.3	0.302	1.61
PDS-*g*-PEG-50	43.3	1.36	19.1	0.217	3.51

MWD, molecular weight distribution.
[a]Determined by GPC–MALLS, [b]Hydrodynamic diameter determined by DLS.

polymer. A similar phenomenon was observed and was discussed in our previous report concerning PEG-grafted copolymers.[15,19] The absolute molecular weights and molecular weight distributions of the PDS-*g*-PEG graft copolymers measured by GPC–multi-angle laser-light scattering (MALLS) are summarized in Table II; these imply that the molecular weight did increase after the grafting of the PEG chains onto the PDS backbone. The ^{1}H-NMR and GPC results provide strong evidence that PDS-*g*-PEG copolymers with well-defined comblike architectures were obtained.

Micellization of the PDS-*g*-PEG Copolymers

PEGylated amphiphilic polyesters can undergo self-assembly into nanosized micelles in aqueous solution with decreased adsorption of proteins, long circulating time in the blood, and reduced liver uptake; this makes them competent vectors for drug delivery. The cmc of an amphiphilic copolymer is a very important parameter in the determination of whether the polymer forms aggregates or exists as a unimer. Drug-loaded polymeric micelles would be largely diluted by the blood after intravenous injection. Therefore, micelles with low cmc values may achieve little drug leakage from the micelle core during their circulation time *in vivo*. Here, the cmc values of the amphiphilic PDS-*g*-PEG graft copolymers were measured by a fluorescence technique with pyrene as a probe. Figure 6 shows the fluorescence spectra of PDS-*g*-PEG-10 containing the pyrene probe at various concentrations. The ratio of the intensities (I_{338}/I_{333}) versus the logarithmic concentration (log *C*) from the excitation spectra is also represented. The cmc value was taken as the intersection of the tangent to the curve at the inflection with the horizontal tangent through the points at a low polymer concentration. As summarized in Table II, all of these amphiphilic graft copolymers possessed very low cmc values, in the range 1–4 mg/L, and decreased with increasing PEG grafting density.

The micellar size and distribution were then measured by DLS in aqueous solution with a fixed concentration of 0.3 mg/mL; this was well above the cmc. Table II also shows the DLS data of all of the polymeric micelles prepared by the PDS-*g*-PEGs, from which we concluded that the mean diameters of the grafted copolymers were all about dozens of nanometers and

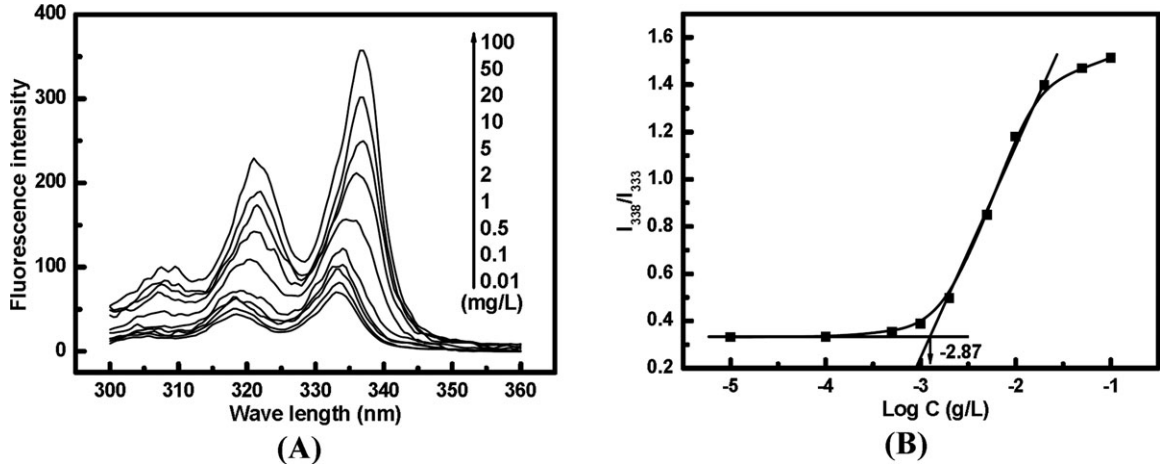

Figure 6. (A) Fluorescence excitation spectra and (B) plots of fluorescence I_{338}/I_{333} versus log *C* of PDS-*g*-PEG-10 micelle with pyrene probe.

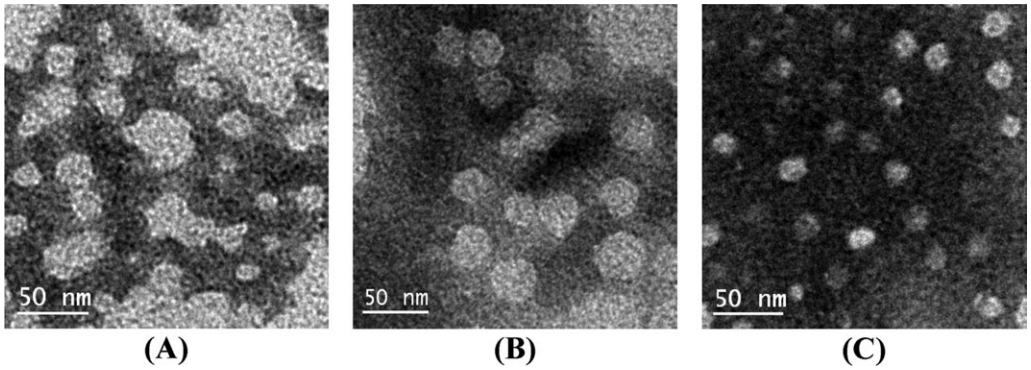

Figure 7. TEM images of (A) PDS-*g*-PEG-10, (B) PDS-*g*-PEG-20, and (C) PDS-*g*-PEG-50.

decreased with increasing PEG quantities. Furthermore, the morphologies of these micelles were observed by TEM after a 0.3 mg/mL aqueous solution was transferred to the carbon-coated copper grids. It can be seen from Figure 7 that the diameters of the polymeric micelles were consistent with the results of DLS. The graft copolymer with fewer PEG side chains [PDS-*g*-PEG-10, Figure 7(A)] preferred to form large particles with an irregular morphology; this may have been caused by the instability of the aggregation with a high hydrophobic proportion. However, increasing the PEG quantity led to a small diameter and regular spherelike aggregates [PDS-*g*-PEG-20, Figure 7(B), and PDS-*g*-PEG-50, Figure 7(C)]. As both the PDS and PEG segments were noncytotoxic and biocompatible, we assumed that these biodegradable amphiphilic graft copolymers were suitable carriers for drug delivery.

CONCLUSIONS

PDSOH was synthesized by direct polycondensation with MA as a functional monomer and $Dy(OTf)_3$ as a chemoselective catalyst under ambient conditions. PDS-*g*-poly(ethylene glycol)s (PDS-*g*-PEG) were prepared by means of the esterification reaction of PDSOH and mPEG-COOH. These well-defined amphiphilic graft copolymers could undergo self-assembly to form nanosized micelles in aqueous solution with diverse diameters and morphologies, that have potential applications in drug delivery.

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