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Self-assembled nano-wire of an amphiphilic biodegradable oligosaccharide-based graft copolymer in water

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ABSTRACT

A kind of amphiphilic biodegradable oligosaccharide-based graft copolymer was prepared and characterized by IR, H NMR and GPC, in which each hydrophobic poly(ε-caprolactone) (PCL, average length $\overline{DP} \approx 6$) was controlled grafted onto the 3-position hydroxyl group of the short and water soluble maltoheptaose (MH, DP = 7) backbone. The self-assembled structures in water of the amphiphilic MH-g-PCL_6 copolymer with a short main chain and controlled branched structure were investigated by transmission electron microscopy (TEM) and dynamic light scattering (DLC). The graft copolymer with a unique asymmetric structure self-assembled into wire-like micelles with average diameters of 76 nm. And the length of the nano-wire increased with increased initial copolymer concentration in dimethylformamide. Thus, a new route to form self-assembled nano-wires with different lengths and interesting biodegradable properties was developed using amphiphilic oligosaccharide-based graft copolymer in water. The possible formation mechanism of nano-wire micelles was also discussed.

1. Introduction

Copolymers are of considerable interest for the preparation of well-defined self-assembled structures in selected solvents (He et al., 2009; Hickey, Haynes, Kikkawa, & Park, 2011; Jain & Bates, 2003; Neiser et al., 2004) and for their applications in biotechnology and pharmaceutics (Discher & Eisenberg, 2002; Ren, Feng, Zhang, Li, & Li, 2011; Rösler, Vandermeulen, & Klok, 2001; Song et al., 2010). In general, linear block copolymers and graft copolymers both are important building blocks forming self-assembled aggregates. And compared with linear block copolymers, their branched counterpart may provide considerable functionalities onto the polymer backbone that can be chemically addressed after a self-assembly process (Breitenkamp & Emrick, 2003; Sato et al., 2005). However, in most cases, graft copolymers tend to form compound spherical micelles (Akiyoshi, Deguchi, Tajima, Nishikawa, & Sunamoto, 1997; Jeong, Kang, Yang, & Kim, 2003; Philippova et al., 2001), whereas linear block copolymers can organize into different morphologies such as sphere, wire and vesicle (Cheng, Huang, Tang, Chen, & Xi, 2005; Jenekhe & Chen, 1998; Zhang & Eisenberg, 1996). It seems difficult for graft copolymers to organize into non-spherical micelles in water.

Actually, earlier studies on the synthesis and the self-assembly of graft copolymers mostly focused on traditional graft copolymers with long main chains ($M_n \approx$ several tens of thousands) as well as random branch lengths and densities (Akiyoshi et al., 1997; Jeong et al., 2003; Philippova et al., 2001). It is possible for the branched structures to easily undergo intermolecular entanglement, and thereby they tend to form complex spherical micelles. This problem must be addressed to enable the formation of a graft copolymer into non-traditional morphologies in water if the branched structure of a graft copolymer could be properly manipulated or its main chain length could be shortened to decrease the above mentioned influence. However, studies on non-spherical self-assembled structures of graft copolymers with short main chains and controlled branched architectures are limited (Borisov & Zhulina, 2005; Cai, Lin, Chen, & Tian, 2009; Kim, Huh, & Jo, 2003; Wang, Li, & Guo, 2005).

Saccharide-based graft copolymers have recently attracted much attention because of their potential in controlled drug release and their possible alternatives to existing non-biodegradable formulated systems (Hua et al., 2002; Liu, Tian, & Hu, 2004). In particular, the protection and deprotection of partial hydroxyl groups via trimethylsilyl (TMS) groups have been successfully used in the preparation of polysaccharide-based graft copolymers with controlled branched structures in a homogeneous system (Nouvel, Dubois, Dellacherie, & Six, 2004; Nouvel, Frochot, Sadtler, Dubois, & Dellacherie, 2004; Ohya, Maruhashi, & Ouchi, 1998; Ouchi, Kontani, & Ohya, 2003; Wang, Dong, & Tan, 2003; Wang et al., 2005; Ydens et al., 2000).

In our previous work, we (Qiu, Wang, Shen, & Jiang, 2011) have reported a new kind of biodegradable oligosaccharide-based graft copolymer with a controlled branched structure, in

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which hydrophobic poly(ε-caprolactone) (PCL) chains with different length was controlled grafted onto the 3-position hydroxyl groups of a water soluble maltoheptaose (MH, degree of polymerization = 7) backbone. PCLs are frequently employed as implantable carriers for drug delivery systems and as surgical repair materials because of their excellent mechanical strength, biodegradable properties, biocompatibility, and permeability to drugs (Kumari, Yadav, & Yadav, 2010; Woodruff & Hutmacher, 2010). Therefore hybrid copolymers containing MH and PCL may be used as novel biomaterials.

In this paper, we prepared the oligosaccharide-based graft copolymer MH-g-PCL_6 that the average polymerization degree of every PCL graft chain is 6 and investigated the self-assembled structures of MH-g-PCL_6 in water. Our aim is to develop a new route to form non-spherical self-assembled structures using amphiphilic MH-g-PCL_6 copolymer with a short main chain and controlled branched structure as building block.

2. Experimental

2.1. Materials

β-Cyclodextrin (β-CD, Beijing Solarbio Science & Technology Co., Ltd., PR China) was recrystallized twice from water and vacuum dried at 60 °C before use. ε-Caprolactone (CL, Acros Organics, 99%) was dried over CaH_2 for 48 h, distilled under reduced pressure with the fraction collected at 96–98 °C (5 mmHg), and stored under an inert atmosphere. Stannous octoate ($Sn(Oct)_2$) (Alfa-Aesar) was used without further purification. p-Xylene and dimethylsulfoxide (DMSO) were dried by refluxing over CaH_2 as well as Na/benzophenone complex, and distilled just before use. Boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$, 48% BF_3), 1,1,1,3,3,3-hexamethyldisilazane (HMDS), and other reagents were purchased from commercial sources and used as received.

MH was prepared by the cleavage of the α-1,4 glucose bond, and the ring-opening of β-CD in an appropriate acidic solution (Braunmiihl, Jonas, & Stadler, 1995). Trimethylsilylated maltoheptaose (TMSMH) was synthesized and characterized from MH and HMDS, as described in our recent publication (Qiu, Wang, Shen, & Jiang, 2011). The TMS substitution degree (DS_{TMS}) of TMSMH in the current study was 68.24%.

2.2. Preparation of MH-g-PCL_6 copolymer

2.2.1. Synthesis of TMSMH-g-PCL_6 by ring-opening polymerization (ROP)

TMSMH-g-PCL_6 was synthesized by the ROP of ε-CL in the presence of $Sn(Oct)_2$, where TMSMH was used as the multifunctional initiator as described in our recent publication (Qiu et al., 2011). Briefly, $TMSMH_{DS=68.24\%}$ (1.0 g, 3.2 mmol OH group) was dried overnight at 70 °C under reduced pressure and transferred into a dried two-necked round-bottom flask equipped with a stopcock and a rubber septum, purged with nitrogen. ε-CL (2.19 g, 19.2 mmol), dry p-xylene and a magnetic stirring bar were added to the flask under an N_2 atmosphere. After $TMSMH_{DS=68.24\%}$ was completely dissolved, the flask was then connected to a Schlenk-line, where an exhausting-refilling process was repeated three times. Subsequently, 10 mg of $Sn(Oct)_2$ in 1 mL of dry p-xylene was added to the mixture, and the exhausting-refilling process was repeated. The flask was placed in an oil bath at 120 °C for 24 h of solution polymerization. The crude polymer was dissolved in $CHCl_3$, and poured into excess methanol to precipitate the product. The product was then dried in a vacuum to constant weight. The yield was 3.13 g (99%).

^{1}H NMR (600 MHz, $CDCl_3$, δ, ppm): 4.2–4.9 (H-1 of pyranose), 3.0–4.0 (H-2, -3, -4, -5, and -6 of pyranose), 3.9 (–CH_2–O–C(O)–), 2.5 (–O–C(O)–CH_2–), 1.5 (–O–C(O)–C–CH_2– and –CH_2–C–O–C(O)–), 1.2 (–C(O)–C–C–CH_2–C–C–O–), 0.1 (–O–Si$(CH_3)_3$).

2.2.2. Deprotection of TMSMH-g-PCL_6

The protected hydroxyl groups on the MH main chain backbone were recovered by desilylation of the TMS ether groups in the presence of $BF_3{\cdot}Et_2O$. Typically, $BF_3{\cdot}Et_2O$ (0.5 mL, 2 mmol) in 10 mL of anhydrous CH_2Cl_2 was added dropwise to a solution of TMSCD-g-PCL (1.0 g, 0.95 mmol TMS group) in 80 mL of anhydrous CH_2Cl_2 under stirring. The reaction mixture was stirred at room temperature for 12 h under a nitrogen atmosphere. Washing with $NaHCO_3$ (100 mL, 1 M) and distilled water followed. The organic phase was dried over anhydrous $MgSO_4$. The concentrated solution was poured into cold methanol to precipitate the product. The resulting white solid was dried in a vacuum at room temperature for 24 h. The yield was 0.8 g (80%).

^{1}H NMR (600 MHz, $CDCl_3$, δ, ppm): 4.2–4.9 (H-1 of pyranose) 3.9 (–CH_2–O–C(O)–), 3.2–3.9 (H-2, -3, -4, -5, and -6 of pyranose), 2.5 (–O–C(O)–CH_2–), 1.5 (–O–C(O)–C–CH_2– and –CH_2–C–O–C(O)–), 1.2 (–C(O)–C–C–CH_2–C–C–O–). Gel permeation chromatography (GPC): M_n = 12,814, molecular weight distribution (M_w/M_n) = 1.98.

2.3. Preparation of MH-g-PCL_6 micelles

The obtained MH-g-PCL_6 copolymer was initially dissolved in the common solvent DMF to form a series of copolymer solutions with different initial concentrations (0.01–5.0 mg/mL). Deionized water was added dropwise to the MH-g-PCL_6 solutions at a rate of 0.2%/min under vigorous stirring until a predetermined water contents were reached. The solutions were further stirred for 2 h and they were dialyzed against water to remove the remaining DMF solvent. The final concentration of the obtained aggregates solution is about in the range of 0.001–0.5 mg/mL.

The critical aggregate concentration (CAC) of MH-g-PCL_6 in water was measured by the fluorescent probe method. 5 μL of 5×10^{-3} mg/mL pyrene solution in acetone was added to MH-g-PCL_6 aqueous solutions with different concentrations and the solutions were sonicated for 10 min before fluorescence emission measurements.

2.4. Measurements

^{1}H NMR analyses were carried out using a JOEL JNM-ECA600 spectrometer in $CDCl_3$, DMSO-d_6, or D_2O at room temperature (solvents without TMS). Fourier transform infrared (FT-IR) measurements were carried out on an AVATAR 360 FT-IR spectrometer (Thermo Nicolet). The samples for FT-IR measurements were prepared by dispersing the powdered KBr and compressing the mixtures to form disks. The M_n and M_w/M_n were measured using a Viscotek triple detector array GPC instrument equipped with tetrahydrofuran (THF) as the mobile phase. Polystyrene was used as the calibration standard. Transmission electron microscopy (TEM) was performed on a TECNAI T20 electron microscope. A drop of micellar solution was placed onto the surface of Formvar carbon film-coated copper grids. The excess solution was quickly removed with a filter paper. All grids were negatively stained by 2 wt% phosphotungstic acid. The size distribution of the aggregates was analyzed by a Malvern 3000HS Zetasizer using a monochromatic coherent He–Ne laser (633 nm) as the light source and a detector that detected the scattered light at an angle of 90°. Fluorescence was measured with a Fluorolog-3, Horiba Jobin Yvon spectrofluorometer.

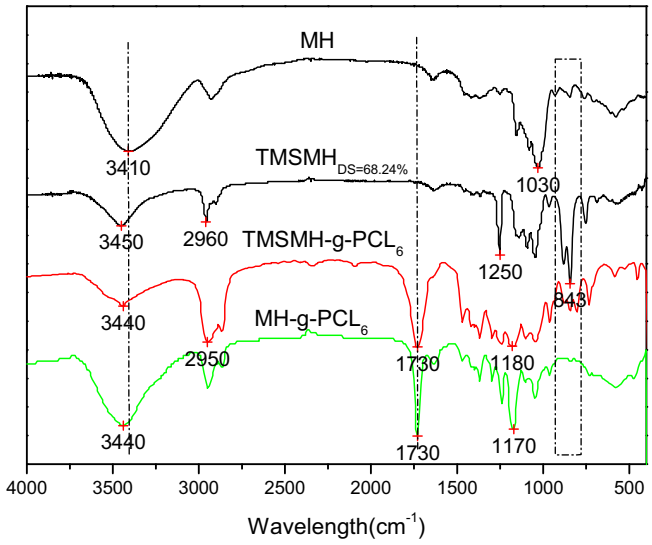


Fig. 1. IR spectra of (A) MH, (B) TMSMH$_{DS=68.24\%}$, (C) TMSMH-g-PCL$_6$ and (D) MH-g-PCL$_6$.

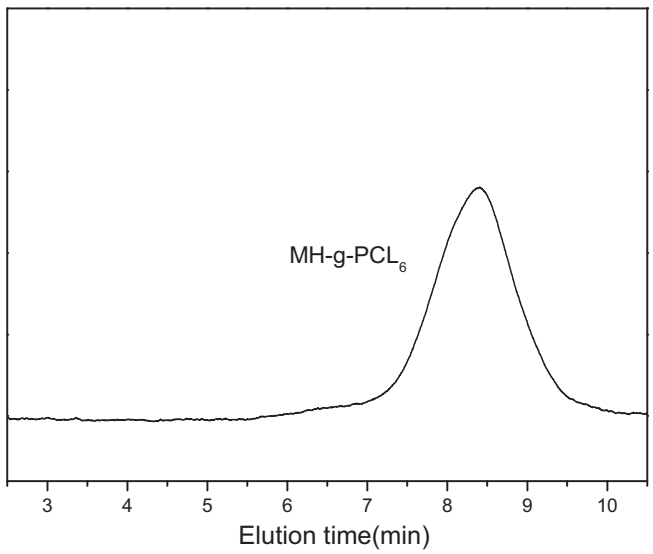


Fig. 3. GPC traces of MH-g-PCL$_6$.

3. Results and discussion

3.1. Preparation and characterizations of MH-g-PCL$_6$ copolymer

As shown in Scheme 1, the synthesis of the biodegradable MH-g-PCL copolymer with a controlled branched structure was carried out via a three-step method. In one of our previous works, the synthesis of TMSMH from MH and HMDS has been described. The trimethylsilyl substitution (D_{TMS}) of TMSMH reached 68.24% when the ratio of HMDS to MH was 1.5. The chemical structure of TMSMH$_{DS=68.24\%}$ was characterized by FT-IR and ^{1}H NMR (Figs. 1B and 2A). For the highly trimethylsilylated MH, the glucose units were nearly ditrimethylsilylated. The majority of the remaining free hydroxyl groups was in the third position (3-OH) due to the relatively weak reactivity of the 3-OH group in each glucose unit toward silylation (Nouvel, Dubois, et al., 2004). About 7 3-OH groups on the MH backbone remained, and served as multi-initiating points for the subsequent ROP of ε-CL. At the same time, TMSMH$_{DS=68.24\%}$ achieved solubility in a variety of organic solvents. Consequently, the ring-opening grafting copolymerization of ε-CL onto TMSMH$_{DS=68.24\%}$ was successfully carried out in a homogeneous xylene solution. The 7 remaining free 3-OH served as multi-initiating points, and Sn(Oct)$_2$ served as a catalyst. The reaction temperature was set to 120 °C to reduce transesterification. Nearly all CLs were ring-opening polymerized (yields = 99%) when the reaction time was 24 h. The incorporation of the TMS groups ensured the proper control of the PCL graft number and position on the MH backbone. Assuming that all the remaining free hydroxyl groups of TMSMH$_{DS=68.24\%}$ can effectively initiate the ROP of CL, the average length of every PCL branch ($\overline{DP_{PCL}}$) can be calculated as 6 when the feed molar ratio of CL and TMSMH glucose units is 6. The obtained TMSMH-g-PCL$_6$ was characterized by IR and ^{1}H NMR. As shown in the IR spectrum of TMSMH-g-PCL$_6$ (Fig. 1C), a new peak at 1730 cm^{-1} assigned to the C=O stretching of the PCL segment was observed, besides the major peaks of the TMSMH moiety. Fig. 2B exhibits a representative TMSMH-g-PCL$_6$. It clearly shows that apart from the methylene proton signals of the PCL chains (Ha-e, 3.9, 2.5, 1.5, and 1.2 ppm), there were additional signals from TMSMH moieties (–H of pyranose and –O–Si(CH$_3$)$_3$, 3.0–5.0 and 0.1 ppm, respectively).

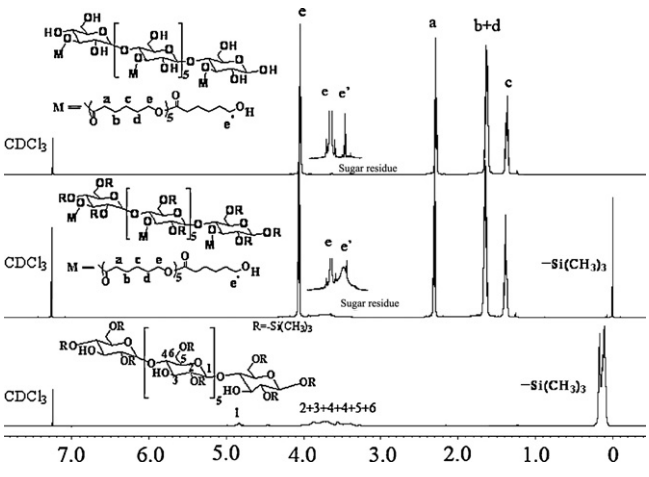
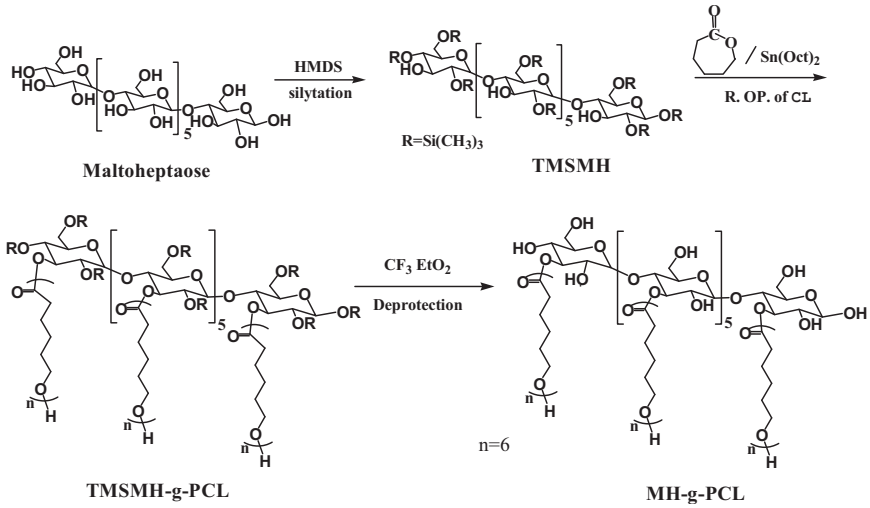


Fig. 2. ^{1}H NMR spectrum of (A) TMSMH$_{DS=68.24\%}$, (B) TMSMH-g-PCL$_6$ and (C) MH-g-PCL$_6$.

In order to recover the protected hydroxyl groups on the MH backbone and avoid any damage to PCL moieties, the trimethylsilyl (TMS) ether groups had to be removed under mild conditions such as in the presence of fluoride ion or aqueous acid. The TMS ether groups were easily and fully removed in the presence of fluoride ion. So $BF_3{\cdot}Et_2O$ was used to desilylate the TMS groups of the TMSMH-g-PCL copolymers at room temperature in the present work. Consequently, MH-g-PCL$_6$ was prepared and characterized by IR, ^{1}H NMR, and GPC. As shown in the FT-IR spectrum of MH-g-PCL$_6$ (Fig. 1D), the disappearance of the peak of the Si–Me group at 1250, 881, and 843 cm^{-1} indicated the successful cleavage of the TMS groups to the benefit of a large absorption at 3440 cm^{-1} typical of hydroxyl groups. Fig. 2C exhibits a representative MH-g-PCL$_6$ ^{1}H NMR spectrum. It clearly shows that the proton signal of the –O–Si(CH$_3$)$_3$ groups at 0.1 ppm was not detected. However, the major proton signals of the PCL chains and MH glucose residue remained essentially intact. These findings suggested that there was no degradation of the MH backbone and PCL branch. As shown in Fig. 3 and Table 1, the resulting MH-g-PCL$_6$ was characterized by GPC. THF was the mobile phase, and linear polystyrene was the calibration standard. The GPC curves of the resulting MH-g-PCL$_6$ copolymers revealed unimodal elution peaks, which suggested that no linear PCL was formed.

Thus, MH-g-PCL$_6$ copolymer with a short main chain and controlled branched structure was prepared, in which each



Scheme 1. Synthetic route of biodegradable maltoheptaose-g-poly(ε-caprolactone) copolymer with controlled branched structure.

Table 1
Characterization of $TMSMH_{DS=68.24\%}$ and MH-g-PCL_6 copolymer.

Sample	$[CL]_0/[OH]$[a] (molar ratio)	F_{PCL}[b] (grav%)	$M_{n,Cal}$[b]	$M_{n,GPC}$[c]	PDI[c]
$TMSMH_{DS=68.24\%}$	–	–	2282	2249	1.03
MH-g-PCL_6	6	78.3	6674	12814	1.98

The suffix 6 of MH-g-PCL_6 means the average polymerization degree of a single PCL branch attached to glucose unit and determined by the initial feed molar ratio of CL and every hydroxyl group of TMSMH. *DS* of the TMSMH employed was 68.24%.

[a] Calculated from the equation: $[OH] = 23 \times (1 - DS) \times [TMSMH]$.

[b] Calculated from the feeding molar ration of $[CL]_0/[OH]$.

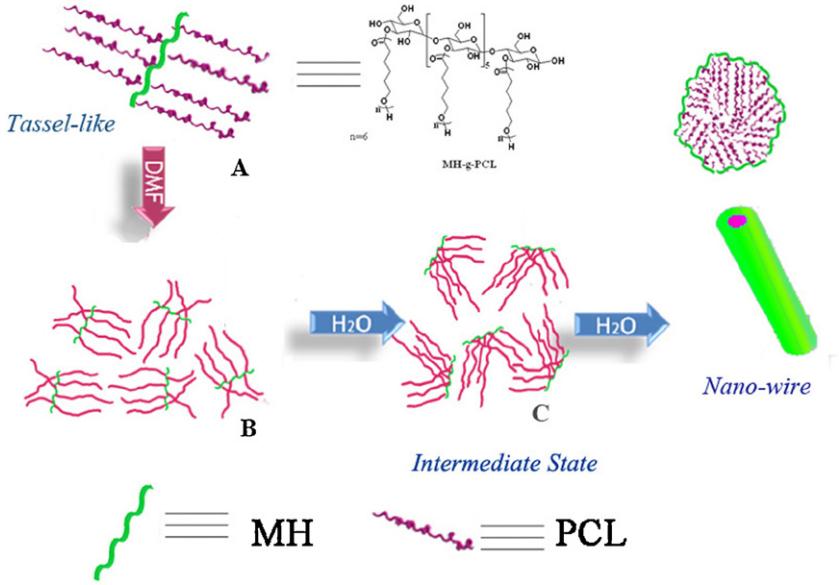
[c] Estimated by GPC in THF.

hydrophobic PCL branch ($\overline{DP_{PCL}} = 6$) was controlled grafted onto the 3-OH groups of the short water-soluble MH backbone ($M_n = 1153$, number of glucose units = 7). As shown in Scheme 2, the topological architecture of MH-g-PCL_6 resembled a tassel. Due to the protection/deprotection of the TMS groups to the hydroxyl groups of the MH, MH remained hydrophilic in character. Hence, the MH-g-PCL_6 copolymers were amphiphilic.

3.2. Self-assembled nanostructures of MH-g-PCL_6 copolymer

The self-assembled aggregation in water of the amphiphilic MH-g-PCL copolymer with a unique tassel-shaped branched architecture was studied by an indirect method where MH-g-PCL_6 was considered. The critical aggregate concentration (CAC) of MH-g-PCL_6 in water was measured by the fluorescent probe method. The CAC was chosen as the concentration when pyrene exhibited an apparent decrease in the I_1/I_3 ratio with an increasing concentration of the graft copolymer, indicating that the aggregation of the copolymer occurred. The results show that the CAC was about 8.9×10^{-4} mg/mL (Fig. 4A).

The morphology of the MH-g-PCL_6 aggregates was observed by TEM. When the initial concentrations of MH-g-PCL_6 in DMF varied from 0.01 to 5.0 mg/mL (the final concentration of the



Scheme 2. A proposed mechanism leading to the self-assembled nano-wire of amphiphilic copolymer MH-g-PCL_6 in water.

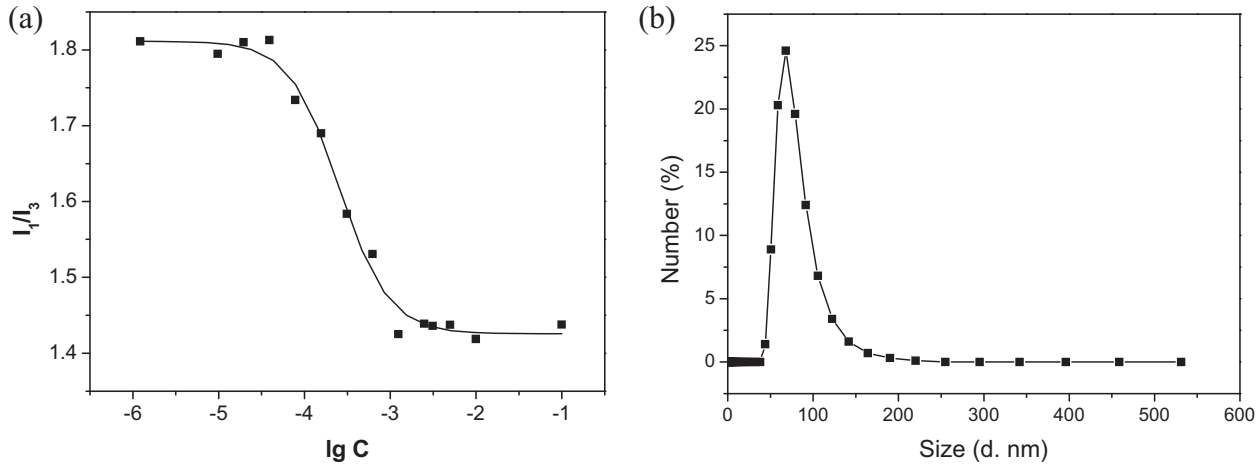


Fig. 4. (A) Determination of CAC for the graft copolymer using the fluorescent method with pyrene as a probe and (B) the DLS size distribution of the MH-g-PCL_6 micelles in water with 0.1 mg/mL initial concentrations in DMF.

obtained aggregates solution in water is about in the range of 0.001–0.5 mg/mL), self-assembled nanowires with different lengths were obtained for the different initial concentrations of graft copolymers (Figs. 5 and 6).

At 0.01 mg/mL initial concentration, mixed micelles were observed. There were spherical micelles with average diameters of 100 nm, and short wire-like micelles with average diameters of 50 nm (Fig. 5A and B). The micelles comprised a shell made of the hydrophilic MH, and a dense core made of the hydrophobic PCL grafts. Interestingly, tadpole-shaped micelles were also observed (Fig. 5A–C). The head diameters were equal to that of the sphere, and the tail diameter equaled that of the short wire. Therefore, the tadpole-shaped micelle may be the transitional state. This observation showed that the graft copolymer tended to transform into wire-like micelles from spherical micelles, even at a low initial concentration. With increased initial concentration to 0.1 mg/m:, nearly all MH-g-PCL_6 copolymers aggregated into worm-like short wires with average diameters of 50 nm and average length of 1 μm (Fig. 6A). The size of the MH-g-PCL aggregates was further determined by DLS measurements, which gave a result of about 76 nm in average diameter (Fig. 4B).

With continued increase to 1.0 mg/mL, the micelles transformed into worm-like long wires with diameters of 50–100 nm and average length of 4 μm (Fig. 6B). With continued increase to 5.0 mg/mL, there was no vesicle, only long worm-like wires concomitant with a few unbent lines and spheres (Fig. 6C and D).

Scheme 2 displays the possible self-assembly mechanism of the graft copolymer in aqueous solution. The synthesized amphiphilic MH-g-PCL_6 had a short main chain and controlled branched structure. The hydrophobic PCL branches were control tied onto the

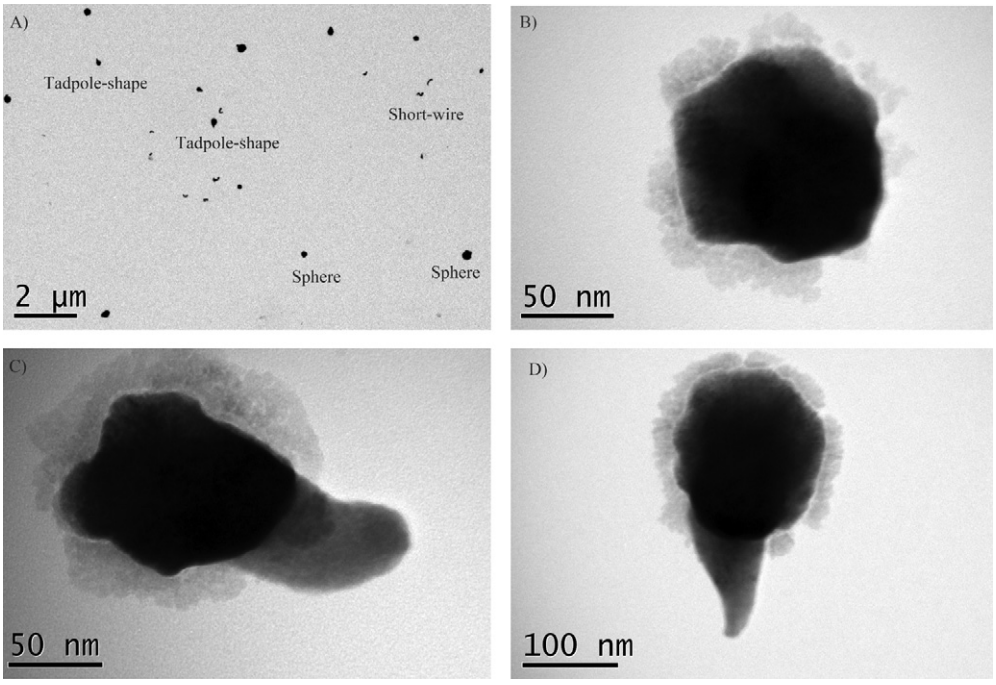


Fig. 5. TEM images of MH-g-PCL_6 self-assembled micelles in water with 0.01 mg/mL initial concentrations in DMF. (A) Sphere, tadpole and short-wire; (B) sphere; (C) and (D) tadpole.

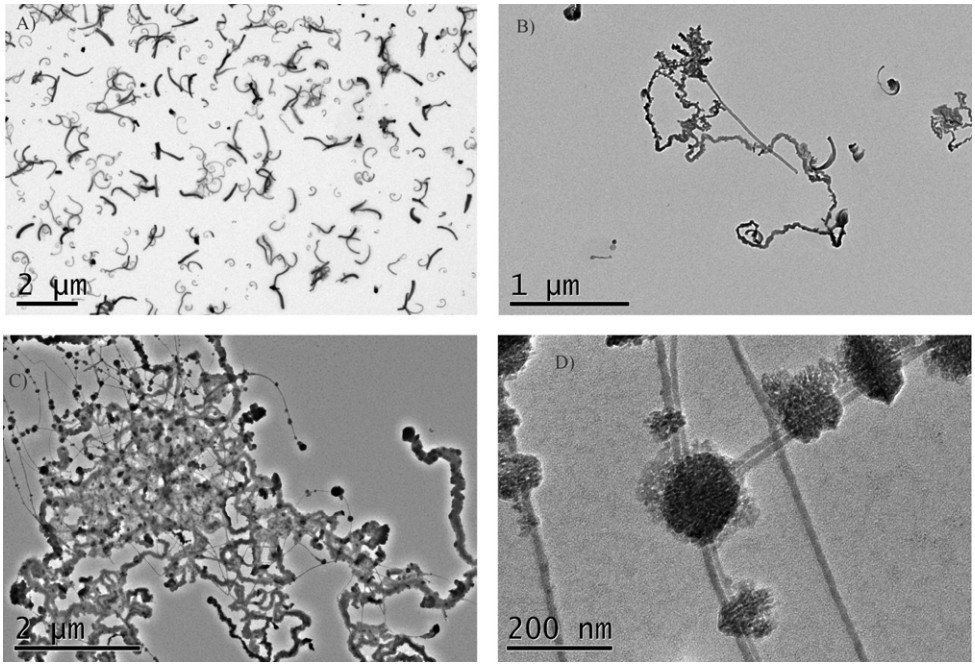


Fig. 6. TEM images of MH-g-PCL_6 self-assembled micelles in water with 0.1 mg/mL, 1.0 mg/mL and 5.0 mg/mL initial concentrations in DMF. (A) Short-wire (0.1 mg/mL); (B) worm-like long-rod (1.0 mg/mL); (C) worm-like and unbent long-wire (5.0 mg/mL) and (D) unbent long-wire and complex sphere (5.0 mg/mL).

3-OH groups in the hydrophilic MH. Before the addition of water, the MH-g-PCL_6 copolymers were unwound unimolecules in the common solvent DMF, and their molecular morphology was tassel-like (Scheme 2A and B). Upon the addition of the poor solvent water to the DMF solution of the copolymers, the solvent became progressively incompatible with the PCL branches. Intermolecular entanglement among the short MH main chains understandably decreased compared with that in traditional graft copolymers with long hydrophilic main chains. The PCL branches tied on a short chain of the MH first aggregated to form an intermediate state C in water. Under this condition, the amphiphile behaved like a highly asymmetric copolymer, as shown in Scheme 2C. The PCL branches tied on a short chain of the MH were entirely treated as hydrophobic segments, and the MH, as hydrophilic segments. Consequently, the microphase separation of the MH and PCL chains was further driven. The intermediate state C probably self-assembled into wire-like micelles with increased initial copolymer concentration.

4. Conclusions

In the present paper, a kind of biodegradable oligosaccharide-based graft copolymer with controlled branched structure was prepared in which every hydrophobic PCL with an average length $\overline{DP} \approx 6$ was control grafted onto the 3-OH groups of the short and water-soluble MH (DP = 7) backbone. The topological structure of the resulting MH-g-PCL_6 copolymer resembled a tassel. The amphiphilic graft copolymer with a unique short main chain and controlled branched structure self-assembled into wire-like micelles. Interestingly, the length of the nanowire increased with increased initial copolymer concentration in DMF. Therefore, a new route for synthesizing self-assembled nanowires with interesting biodegradable properties was developed using an amphiphilic oligosaccharide-based graft copolymer in water. The biodegradable graft copolymer bearing reactive hydroxyls and the formed supramolecular nanowires may serve as functional biomaterials with many potential applications.

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