Carbohydrate Polymers 92 (2013) 1566–1572

Contents lists available at SciVerse ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Studies on the orthogonal assembly of β-cyclodextrin-poly (ε-caprolactone) and ferrocene-poly (ethylene oxide)

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ARTICLE INFO

Article history:
Received 25 July 2012
Received in revised form 26 October 2012
Accepted 1 November 2012
Available online 10 November 2012

Keywords:
Biodegradable
Micelle
Supramolecular copolymers
Self-assembly
β-Cyclodextrin

ABSTRACT

A biodegradable multi-arm polymer β-cyclodextrin-poly (ε-caprolactone) (CD-PCL) with a "jellyfish-like" structure was obtained, in which flexible and hydrophobic PCL arms were selectively grafted to the wide side of the hydrophilic torus-shaped β-CD. The amphiphilic "jellyfish-like" polymer with a hollow cavity and hydrophobic tails could orthogonally self-assemble into a new amphiphilic supramolecular copolymer CD-PCL/FcPEG with poly (ethylene oxide) end-decorated by ferrocene (FcPEG) in aqueous solution based on terminal hydrophobic interactions. The chemical structures of CD-PCL and CD-PCL/FcPEG were characterized by IR, NMR and UV and their self-assembled structures in water were investigated by transmission electron microscopy (TEM) and dynamic light scattering (DLS). CD-PCL alone self-assembled into nano vesicles in water, while CD-PCL/FcPEG into nanospheres. The supramolecular nanospheres were further investigated by cyclic voltammogram. The results indicated that the ferrocenyl groups which were embedded into the hydrophobic core of the supramolecular nanospheres could not transmit electrons or carry out electrochemical oxidation and reduction reaction.

1. Introduction

Amphiphilic copolymers, especially those with biodegradability and biocompatibility, are widely explored for their ability to self-assemble into nano micellar aggregates with various morphologies as well as their applications in the fields of biotechnology and pharmaceutics (Discher & Eisenberg, 2002; Endres, Beck-Broichsitter, & Samsonova, 2011; Hickey, Haynes, Kikkawa, & Park, 2011; Jain & Bates, 2003; Lee, Zeng, & Dunne, 2005; Liu, Pang, & Huang, 2011; Neiser et al., 2004; Song et al., 2010). The molecular composition and the molecular topological architectures of copolymers are both very important factors in determining the self-assembled morphology. For example, various self-assembled morphologies can be obtained through variation of the block lengths ratio of block copolymers (Terreau, Bartels, & Eisenberg, 2004; Terreau, Luo, & Eisenberg, 2003; Zhang & Eisenberg, 1996). At the same time, not only linear block copolymers but also branched copolymers can self-organize into micelles in selective solvent (Cheng et al., 2010; Liu, Tian, & Hu, 2004; Tan, Hussain, Liu, He, & Davis, 2010; Štepánek et al., 2010; Hu et al., 2002; Xia et al., 2008).

Over the past few years, biodegradable and biocompatible saccharide-based branched amphiphiles have attracted much attention for their applications as biomaterials (Gou et al., 2010aGou, Zhu, & Shen, 2010; Gou et al., 2010bGou, Zhu, Xu, & Shen, 2010; Nouvelet al., 2004; Ouchi, Kontani, & Ohya, 2003; Pang, Zhao, Akinc, Kim, & Lin, 2011; Qiu, Wang, Shen, & Jiang, 2011; Wang, Dong, & Tan, 2003; Wang, Li, & Guo, 2005). β-CD is a kind of cyclic oligosaccharide with seven D-glucose units linked by α-1,4-glucose bonds. This oligosaccharide looks like a truncated cone in which the 7 primary hydroxyl groups are directed to the narrow side of the torus and the 14 secondary hydroxyl groups are to the wide side of the torus. β-CD is not only a suitable backbone for designing functional branched copolymers but also a suitable hydrophilic component with inclusive ability to generate amphiphiles. However reports on β-CD-based copolymers mostly focused on multi-arm star copolymers, in which β-CD with multi-OH groups was only used as a core moiety. The hydrophilicity of its outer surface and the inclusive ability of its hydrophobic cavity were not utilized (Gou, Zhu, & Shen, 2010; Gou, Zhu, Xu, & Shen, 2010; Pang et al., 2011). Kawabata et al. first reported the synthesis and self-assembly of amphiphilic cyclodextrins in 1986 (Kawabata et al., 1986). The hydrophobicity of the primary face of β-CD increased with alkylsulfinyl groups of various lengths. Monolayer formed at the air–water interface with the hydrophilic secondary-OH face oriented towards water and inclusion of cholesterol by the layers was studied. Since then, amphiphilic CDs have been designed to form different supramolecular assemblies (Fernando, Fernández, Pennies, Gil, & De Rossi, 2008; Lemos-Senna, Wouessidjewe, Duchêne, & Lesieur, 1998; Kuo, Tung, & Chang, 2009; Mazzaglia et al., 2009; Nolan, Darcy, & Ravoo, 2003; Wang et al., 2011).

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http://dx.doi.org/10.1016/j.carbpol.2012.11.001

In general, the polymerizing processes of conventional amphiphilic copolymers based on covalent interaction are very complicated. On the contrary, amphiphilic supramolecular copolymers based on non-covalent interactions such as hydrogen bonding interactions (Binder, Kunz, Kluger, Hayn, & Saf, 2004; Jang, Kramer, & Hawker, 2011; Moughton & O'Reilly, 2010; Ostas et al., 2011), metal-ligand interactions (Fustin, Guillet, Schubert, & Gohy, 2007; Leggio et al., 2007; Meier, Lohmeijer, & Schubert, 2003), and host–guest recognition (Giacomelli, Riegel, Petzhold, Da Silveira, & Stepánek, 2009; Tancini et al., 2010; Yan et al., 2010; Zhang & Ma, 2009), attract wide attention due to easy operation and hierarchical self-assembly of these novel types of copolymers possessing unique characteristics. Ferrocene is of particular research interest in designing supramolecular assemblies due to its unique sandwich structure, hydrophobic character and redox property (Li et al., 2010; Saji, Hoshino, & Aoyagui, 1985). It is reported that ferrocene or its derivative can form a stable inclusion complex with β-CD (Harada, 2001). Recently, Yan et al. (2010) constructed a supramolecular block copolymer β-cyclodextrin-polystyrene/ferrocene-poly (ethylene glycol) (β-CD-PS/FcPEG) in aqueous solution based on terminal host–guest interaction of β-cyclodextrin and ferrocene and obtained voltage-responsive reversible vesicles. However, the application as drug-loaded nanocapsules of the above voltage-responsive supramolecular vesicles is restricted because of the non biodegradablility of PS block. β-CD-based amphiphiles consisting of completely biodegradable components are especially attractive due to their promising applications as biomaterials.

In this paper, a kind of biodegradable "jellyfish-like" polymer CD-PCL with a hollow cavity and hydrophobic tails was designed, in which the hydrophobicity of the secondary face of β-cyclodextrin increased with the introduction of flexible poly(ε-caprolactone) arms. The amphiphile can self-assemble into vesicular micelles in aqueous solution. The polymer CD-PCL can also orthogonally self-assemble into a new amphiphilic supramolecular copolymer CD-PCL/FcPEG with FcPEG based on terminal hydrophobic interaction and the resultant amphiphile forms spherical micelles in aqueous solution. The biodegradable CD-PCL and related self-assembled micelles should be useful as functional biomaterials for many applications such as drug delivery.

2. Experimental

2.1. Materials

β-Cyclodextrin (Beijing Solarbio Science & Technology Co., Ltd., PR China) was recrystallized twice from water and dried at 60 °C under vacuum 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 inert atmosphere. Methoxy poly (ethylene glycol) (Aldrich, 99%, PEG, M_n = 2000 g/mol) was dried by azeotropic distillation in the presence of toluene. P-Xylene and DMSO were dried by refluxing over CaH_2 and Na/benzophenone complex was distilled just before use. Stannous octoate ($Sn(Oct)_2$) (Alfa Aesar), Boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$, 48%BF_3), 1,1,1,3,3,3-hexamethyldisilazane (HMDS), dicyclohexylcarbodiimide (DCC, Alfa Aesar, 99%, USA). 4-Dimethylaminopyridine (DMAP, Alfa Aesar, 98%, USA) and ferrocenecarboxylic acid (FcA, Acros Organics, 99%, USA), were utilized as received. All solvents were used as received.

3.1. Synthesis of CD-PCL polymer

The biodegradable "jellyfish-like" polymer CD-PCL was synthesized through a three-step method, as described in our recent publication (Jiang, Guo, Wang, & Wang, 2012).Yield: 98%.

IR (KBr, powder, cm^{-1}): 3440(O—H), 2950(C—H), 2866(C—H), 1730(C=O), 1180–1000 (pyranose). ^1H NMR (600MHz, $CDCl_3$, δ, ppm): 4.1(2H, —CH_2—O—C(O)—), 3.0–4.9(H-1, -2, -3, -4, -5, and -6 of pyranose), 2.3(2H, —O—C(O)—CH_2—), 1.6(4H, —O—C(O)—C—CH_2—, —CH_2—C—O—C(O)—), 1.3(2H, —C(O)—C—C—CH_2—C—C—O—).

3.2. Synthesis of FcPEG polymer

FcPEG was synthesized through a typical esterification between methoxy poly (ethylene glycol) and ferrocenecarboxylic acid according to the procedure described (Yan et al., 2010). Yield: 83%. The degree of the end-functionalization reached 99%, as determined by ^1H NMR and IR.

FT-IR (KBr, powder, cm^{-1}): 2886(C—H), 1736(C=O), 1620(C=C in ferrocene), 1157(C—O). ^1H NMR (600 MHz, $CDCl_3$, δ, ppm): 4.8(2H, =CHC(COOH)CH=), 4.4(2H, —CH=CH—), 4.2(5H, another cyclopentyl), 3.7(178H, —OCH_2CH_2O—), 3.4(3H, terminal CH_3O—).

3.3. Preparation of CD-PCL polymer micelles

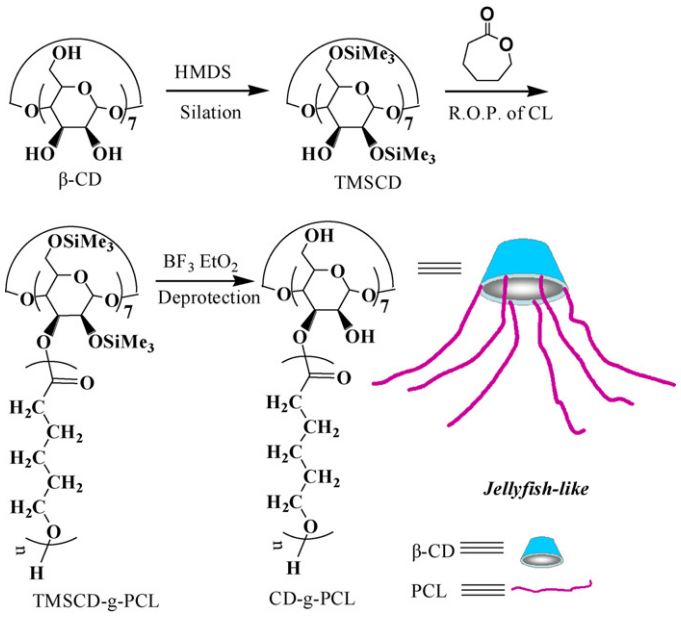
CD-PCL (10 mg) was initially dissolved in a common solvent DMF (10 mL) and dropped into deionized water (30 mL) under vigorous stirring. The solution was stirred for another 2 h and then dialyzed against water to remove the remaining DMF solvent. After 72 h, the volume of the solution was increased to 50 mL with the addition of deionized water to obtain an aggregated solution with a concentration of 0.2 mg/mL for further experiments.

3.4. Preparation of supramolecular copolymer CD-PCL/FcPEG and micelles

CD-PCL (10 mg) was initially dissolved in DMF (10 mL) and dropped into 30 mL FcPEG aqueous solution (1 mg/mL) under vigorous stirring. The solution was stirred for another 2 h and then dialyzed (cut-off molecular weight of dialysis bag is 3500) against water to remove excessive FcPEG and remaining DMF solvent. After 72 h, the volume of the solution was increased to 50 mL with the addition of deionized water to obtain an aggregated solution with a concentration of 0.2 mg/mL for further experiments. A 5 mL CD-PCL/FcPEG supramolecular micellar solution was used to perform cyclic voltammetry studies. For IR and ^1H NMR characterization, the solid specimens of CD-PCL/FcPEG supramolecular copolymer were obtained by freeze drying under vacuum.

3.5. Measurements

^1H NMR analysis was carried out on a JOEL JNM-ECA600 spectrometer in $CDCl_3$, in DMSO-d_6, or in D_2O at room temperature (solvents without TMS). FT-IR measurements were carried out on an AVATAR 360 FT-IR spectrometer (Thermo Nicolet). The samples for FT-IR measurement were prepared by dispersing the powder in KBr and compressing the mixtures to form disks. Molecular weight (M_n) and molecular weight distribution (M_w/M_n) were measured by a Viscotek TDA GPC instrument equipped with tetrahydrofuran (THF) as mobile phase and polystyrene as calibration standard. Fluorescence was measured with a Fluorolog-3, HORIBA Jobin Yvon spectrofluorometer. The critical micelle concentration (CMC) of polymer in water was measured by fluorescent probe method. 5 μL of 6×10^{-3} mg/mL pyrene solution in acetone was added to polymer aqueous solutions with different concentrations respectively and the solutions were sonicated for 10 min before fluorescence emission measurement. The UV–vis spectra and kinetics were recorded on a UV-2550 spectrophotometer (Shimadzu, Japan), using 1 cm path length quartz cuvetts for measurement. Transmission electron microscopy (TEM) was performed on a TECNAI T20 electron microscope. Samples for TEM measurement were



Scheme 1. Synthetic route of biodegradable β-cyclodextrin-poly(ε-caprolactone) polymer.

prepared by ultrasonic dispersion of the micelle solution onto 200-mesh gilder copper TEM grids and air-dried at room temperature. The sample for CD-PCL micelles was stained by 0.2% phosphotungstic acid hydrate before observation. 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°. The electrochemical experiments were performed on a CHI 660A electrochemical work station (Shanghai CH Instruments Co., China) with a conventional three-electrode system consisted of a modified glass carbon electrode as working electrode, a platinum wire as auxiliary electrode, and a saturated calomel electrode (SCE) as reference electrode.

4. Results and discussion

4.1. Synthesis and self-assembly of amphiphilic CD-PCL polymer

β-CD, containing 21 hydroxyl groups on the narrow and wide side of the torus-shaped backbone, has hydrophilic outer surface and hydrophobic cavity. So it is a suitable hydrophilic component with inclusive ability for generating amphiphilic multi-arm polymer. In this work, we synthesized a kind of amphiphilic biodegradable polymer CD-PCL through protection/deprotection technique of β-CD *via* trimethylsilyl groups and ring-opening polymerization (ROP) of CL monomer. Thus flexible and hydrophobic PCL arms were selectively connected to the wide side of hydrophilic β-CD as shown in Scheme 1.

Fig. 1A exhibits a representative ^{1}H NMR spectrum of CD-PCL$_{18}$ that 18 means the average polymerization degree of a single PCL arm attached to the glucose unit of CD. It clearly shows that besides the methlene proton signals of PCL chains (Hc-f, 3.9 ppm, 2.5 ppm, 1.5 ppm, 1.2 ppm), there are additional proton signals of β-CD moiety (H of pyranose, 3.0–5.0 ppm). Fig. 2A exhibits a representative CD-PCL$_{18}$IR spectrum. The signal at 1000–1100 cm^{-1} is attributed to the C—O—C bond of CD ring and the peak at around 3430 cm^{-1} is attributed to the stretching vibration of the –OH groups of CD regenerated after the deprotection of TMS groups. A peak at 1730 cm^{-1} assigned to the C=O stretching of the PCL segment is also observed besides the major peaks of CD moiety. The resulting

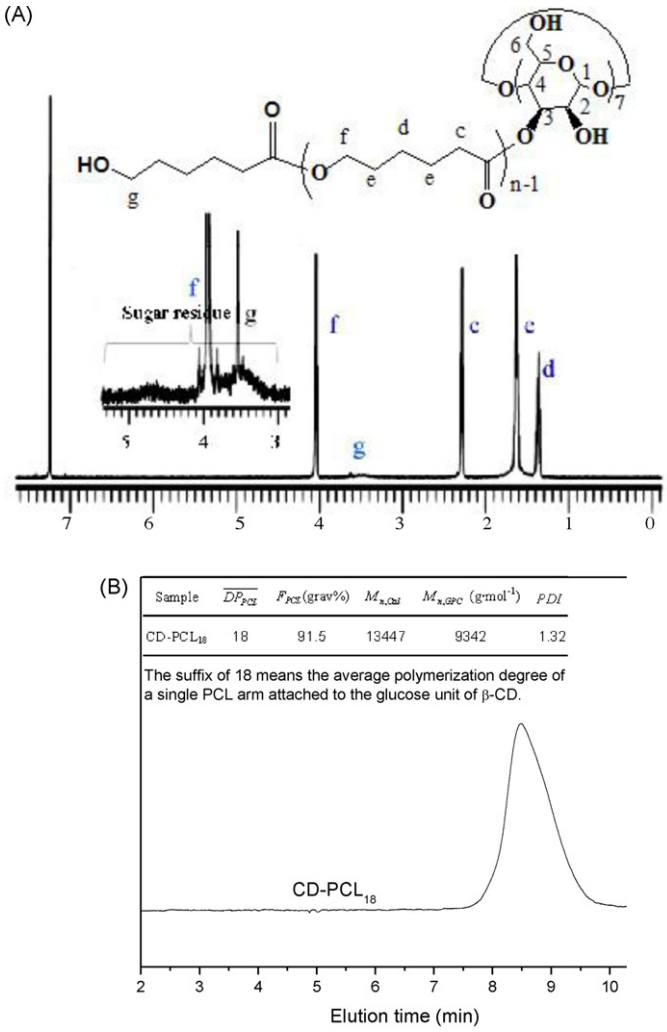


Fig. 1. (A) ^{1}H NMR spectrum of CD-PCL$_{18}$ (in CDCl$_3$ without TMS); (B) GPC trace of CD-PCL$_{18}$.

CD-PCL$_{18}$ was also characterized by GPC. In Fig. 1B, the GPC curve of CD-PCL$_{18}$ polymer reveals unimodal elution peak, which suggest that CD-PCL$_{18}$ was not contaminated by linear PCL. Due to the protection/deprotection of TMS groups to the hydroxyl groups of the β-CD, the outer surface of β-CD remains hydrophilic and the

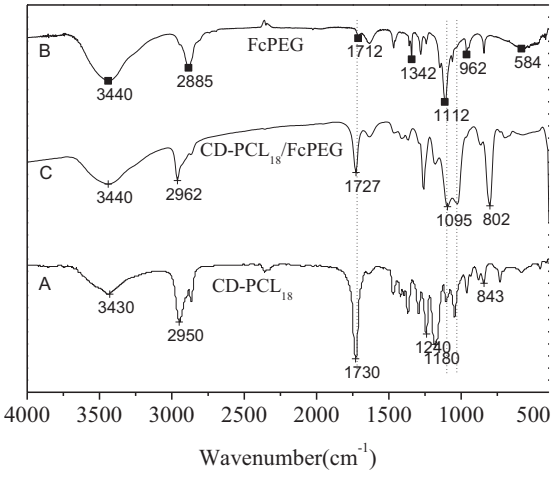


Fig. 2. IR spectrum. (A) CD-PCL$_{18}$ (B) FcPEG (C) CD-PCL$_{18}$/FcPEG.

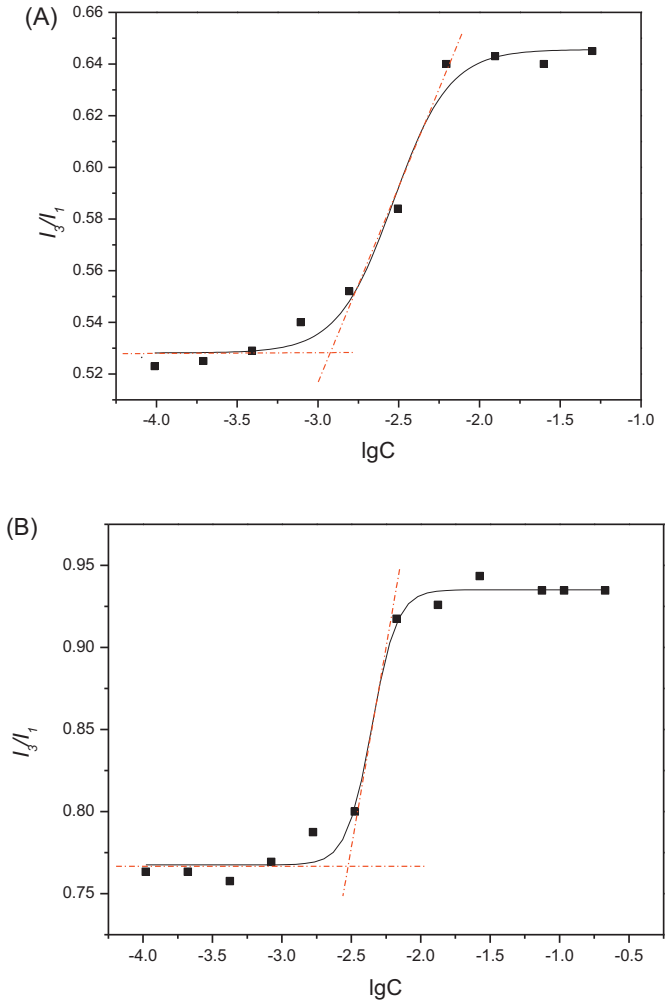
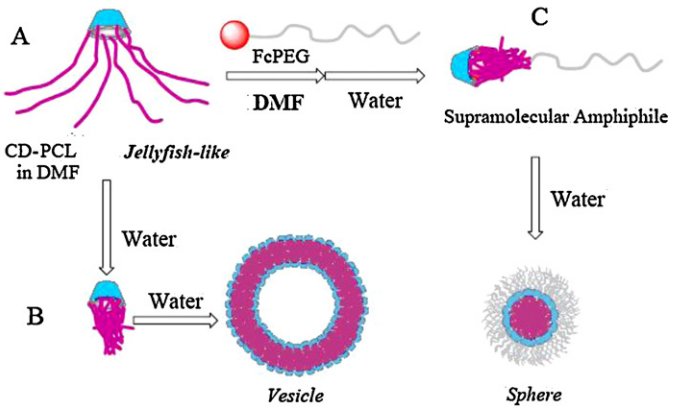


Fig. 3. Determination of CMC using the fluorescent method with pyrene as a probe. (A) CD-PCL_{18} (B) CD-PCL_{18}/FcPEG.



Scheme 2. A proposed mechanism leading to the self-assembled micelles in water of polymer CD-PCL_{18} and supramolecular copolymer CD-PCL_{18}/FcPEG.

obtained CD-PCL polymer is amphiphilic, forming a "jellyfish-like" topological structure as shown in Scheme 1.

The self-assembled aggregation in water of the amphiphilic CD-PCL polymer with jellyfish-like topological architecture was firstly studied by an indirect method described as follows, where CD-PCL_{18} with long PCL arms and highly hydrophobic PCL segments (the gravity percent of PCL branches is 91.5%) was taken into consideration. CD-PCL_{18} polymer was first dissolved in a common solvent DMF and dropped into deionized water under vigorous stirring. The solution was then dialyzed against water to remove the organic solvent. The CMC of CD-PCL_{18} in water was measured by fluorescent probe method (Fig. 3A). The CMC was chosen as the concentration when pyrene exhibited an apparent increase in the I_3/I_1 ratio with an increasing concentration of the polymer, indicating that aggregation of the polymer occurred. The results show that the CMC of CD-PCL_{18} in water was about 1.2×10^{-3} mg/mL. The morphology of CD-PCL_{18} aggregates was observed by TEM. When the initial concentration in DMF was 1.0 mg/mL, vesicular micelles were observed as shown in Fig. 4A. The size of CD-PCL_{18} aggregates was further determined by DLS measurements, which showed an average diameter of about 369 nm (Fig. 4C).

Scheme 2 exhibits a possible mechanism leading to the self-assembled vesicles of amphiphilic polymer CD-PCL_{18} in water. Before the addition of water, CD-PCL_{18} is unwound unimolecules in DMF and its molecular morphology is like a jellyfish (Scheme 2A). Upon the addition of poor solvent water to the DMF solution of the polymer, the solvent progressively becomes incompatible with PCL branches. It is easy to understand that the PCL branches tied to a β-CD ring firstly tend to aggregate together to form an intermediate state B in dilute solution. At this time, the amphiphile behaves like a highly asymmetric diblock copolymer as shown in Scheme 2B, in which PCL arms tied to a β-CD ring as a whole are treated as hydrophobic block and rigid β-CD as hydrophilic block. Apparently, the formation of intermediate state B drives the microphase separation of β-CD and PCL chains, leading to the formation of self-assembled "crew-cut" micelles characterized by long PCL branches as hydrophobic core and short β-CD as hydrophilic shell. And CD-PCL_{18} copolymer can form vesicle nanostructures at higher initial concentration in DMF. The result is similar to those of diblocks containing longer unsoluble blocks and shorter soluble blocks (Giacomelli et al., 2009; Terreau et al., 2004; Terreau et al., 2003; Zhang & Eisenberg, 1996).

4.2. Construction and self-assembly of amphiphilic supramolecular copolymer CD-PCL/FcPEG

β-CD is known to have the ability to form inclusion complexes with low-molecular-weight compounds. In our work, flexible and hydrophobic PCL arms were selectively connected onto the wide side of hydrophilic torus-shaped β-CD forming a jellyfish-like topological structure. Since PCL chains may exhibit unfolding formations in hydrophobic solutions and contracted conformations in hydrophilic solutions. It is worth investigating whether PCL arms can act as the switch to the hollow cavity of β-CD and the "jellyfish-like" polymer with a hollow cavity and hydrophobic tails can encapsulate guest molecules in water like jellyfish. Ferrocene or its derivative is known to can form a stable inclusion complex with β-CD and the variation of its microenvironment can be analyzed by UV and cyclic voltammogram. So in our work, poly (ethylene oxide) end-decorated by ferrocene (FcPEG) was used to investigate the inclusive ability of CD-PCL to ferrocene group and the possibility of constructing a new amphiphilic supramolecular copolymer CD-PCL/FcPEG.

UV measurements of FcPEG, CD-PCL_{18} and CD-PCL_{18}/FcPEG in water provide direct evidence of the inclusive interaction. After electrons-rich ferrocene guest was enclosed into the hydrophobic cavity, the high electron density of hydrophobic cavity may induce the movement of electrons of ferrocene groups, resulting in the change of the intensity and location of peaks of ferrocene groups. Fig. 5A shows the variation of the UV spectrum of FcPEG polymer before and after being mixed with CD-PCL_{18} polymer. The ultraviolet absorption peaks at 263 nm and 315 nm are attributed to the ferrocene group of FcPEG. However, the peak at 263 nm shifts to

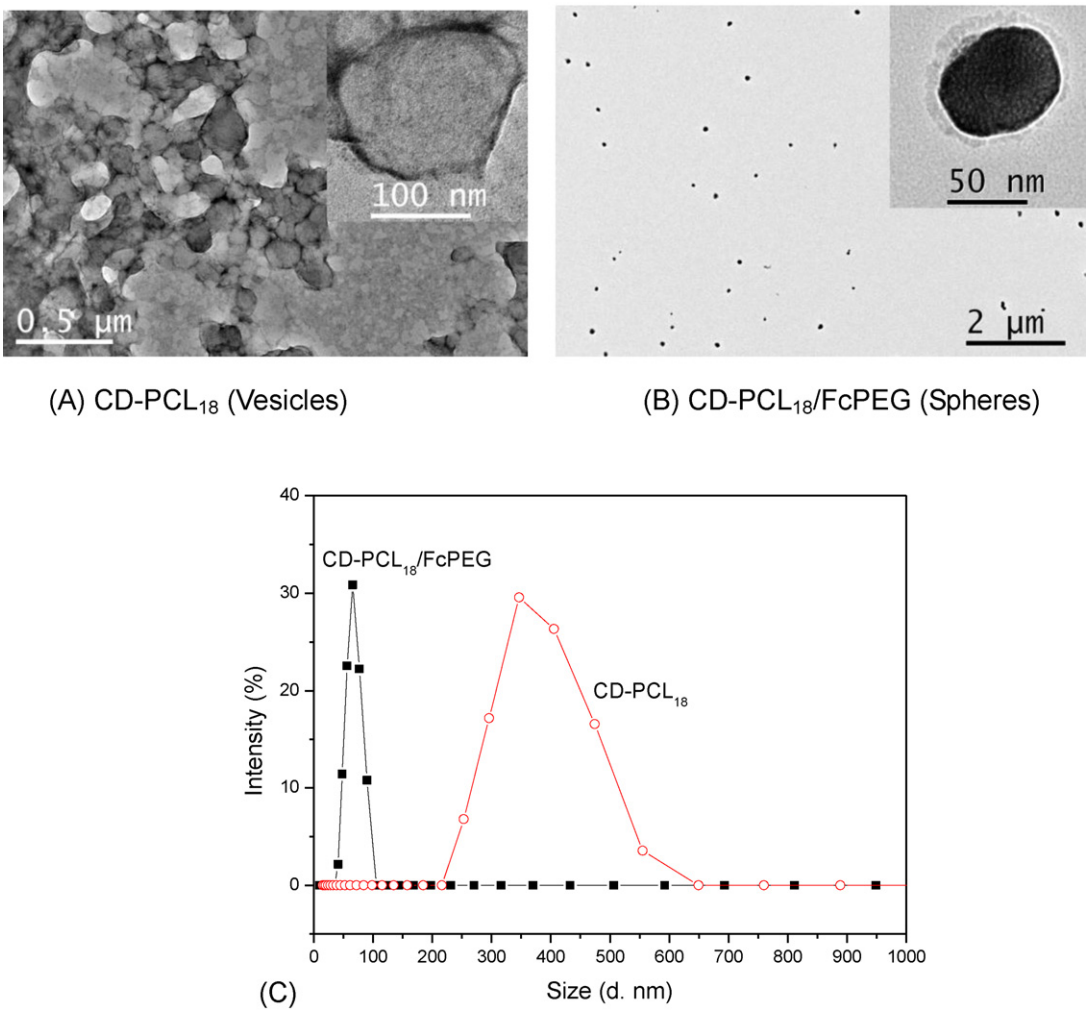


Fig. 4. Characterization of CD-PCL_{18} and CD-PCL_{18}/FcPEG self-assembled micelles in water with 1.0 mg/mL initial concentrations in DMF. (A and B) TEM images of CD-PCL_{18} and CD-PCL_{18}/FcPEG micelles (C) the DLS size distribution of CD-PCL_{18} and CD-PCL_{18}/FcPEG micelles in water.

278 nm and the peak at 315 nm disappear after being mixed with CD-PCL_{18} polymer. The results indicate that the ferrocene groups have been encapsulated into the hydrophobic cavities. The solid specimens of CD-PCL_{18}/FcPEG supramolecular copolymer were obtained by freeze drying under vacuum after the dialysis of CD-g-PCL/FcPEG solution to remove excessive FcPEG and remaining DMF solvent. The structure of the supramolecular block copolymer was characterized by IR spectroscopy (Fig. 2). The strong peak at 1100 cm^{-1} assigned to the C—O—C stretching of PEG chains is observed in the spectrum of FcPEG (Fig. 2B). Fig. 2C exhibits the spectrum of the above solid specimens of CD-PCL_{18}/FcPEG. The peak intensity at 1100 cm^{-1} assigned to the C—O—C stretching increased obviously and that at around 1730 cm^{-1} attributed to the C=O stretching of the PCL segment decreases obviously compared to those of CD-PCL_{18} polymer, which proves that FcPEG chains have been introduced. The structure of CD-PCL_{18}/FcPEG was also confirmed by ^{1}H NMR. Fig. 5B exhibits a representative ^{1}H NMR spectrum of CD-PCL_{18}/FcPEG in $CDCl_3$. It clearly shows that besides the methlene proton signals of PCL chains (Hc-f, 3.9 ppm, 2.5 ppm, 1.5 ppm, 1.2 ppm), there are additional methlene proton signals attributed to the PEG moiety at 3.65 ppm. The proton signals of CD and ferrocene are not observed due to small quantity in the inclusive complex.

The above results show that CD-PCL_{18} can orthogonally self-assemble into a supramolecular copolymer CD-PCL_{18}/FcPEG with FcPEG in aqueous solutions based on terminal hydrophobic interactions as shown in Scheme 2C. The new supramolecular copolymer CD-PCL_{18}/FcPEG is also amphiphilic and may further form self-assembled micelles in water. The CMC of CD-PCL_{18}/FcPEG in water was also measured by fluorescent probe method (Fig. 3B). The results show that it is about 3.0×10^{-3} mg/mL and higher than that of CD-PCL_{18}. The self-assembled aggregation of the amphiphilic supramolecular copolymer in water was studied under the same condition as that of CD-PCL_{18} by TEM and DLS (Fig. 4B and C). Interestingly, CD-PCL_{18}/FcPEG form spherical micelles with an average diameter of 65 nm, which is smaller than vesicular micelles (369 nm) of CD-PCL_{18} under the same condition (initial concentration in DMF being 1.0 mg/mL).

Scheme 2 exhibits a possible mechanism leading to the transformation from large vesicles to small spheres. The gravity percent of hydrophobic PCL branches in the CD-PCL_{18} is 91.5% and that of hydrophilic CD backbone is 8.5%. The CD-PCL_{18} with highly hydrophobic PCL segments and the jellyfish-like structure alone easily form vesicles based on the above analysis. However, the orthogonal self-assembly of including FcPEG to CD-PCL_{18} results in the decrease of the gravity percent of hydrophobic PCL segments (79.7%) and the increase of hydrophilic segments consisting of CD and PEG (20.3%). The supramolecular block copolymers easily form spherical micelles. The result is similar to those of diblock copolymers containing long hydrophilic segments (Terreau et al.,

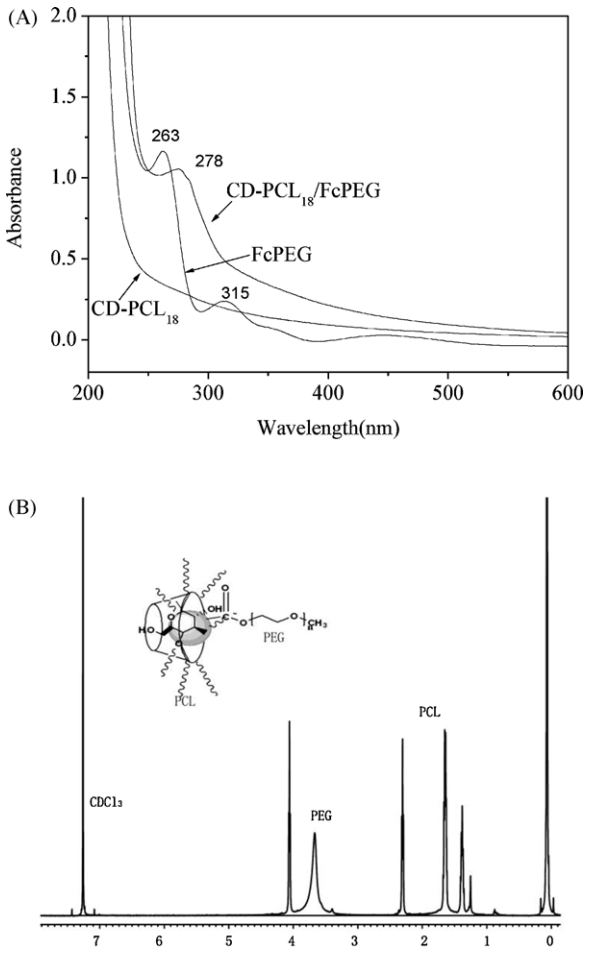


Fig. 5. (A) UV–vis spectra of FcPEG, CD-PCL_{18} and CD-PCL_{18}/FcPEG (B) ^1H NMR spectrum of CD-PCL_{18}/FcPEG (in $CDCl_3$).

2004; Terreau et al., 2003; Zhang & Eisenberg, 1996). Thus micellar morphology transformed through the orthogonal assembly of β-cyclodextrin-poly(ε-caprolactone) polymer and ferrocene-poly(ethylene oxide) polymer.

In order to find out whether ferrocene undergoes reversible one-electron redox or not, the state of enclosed ferrocene groups in the supramolecular micelles was analyzed by cyclic voltammogram. Fig. 6 shows the CV curves of the FcPEG and CD-PCL_{18}/FcPEG in

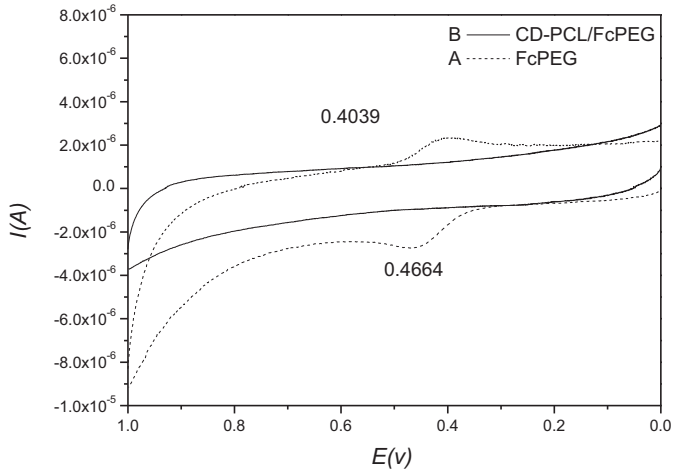


Fig. 6. CV curves. (A) FcPEG (B) CD-PCL_{18}/FcPEG.

NaCl solution. In a free state, the voltammetric wave of ferrocene in FcPEG is 0.466/0.404 V. However, the oxidation and reduction peak potentials were not detected in the supramolecular micelles solution. The reason is suggested as follows. The ferrocene groups enclosed into the hydrophobic cavity are further embedded into the micellar core consisting of PCL segments. It is difficult for the electrolyte to reach ferrocene groups so that the transfer of electrons is inhibited. The results further verify the terminal hydrophobic interactions between CD-PCL_{18} and FcPEG.

The stability of inclusive complex based on β-CD and different kinds of hydrophobic guest molecules depends on the size match between β-CD cavity and the guest molecule. If the size of the guest molecule is larger or smaller than that of the β-CD cavity, stable inclusive complexes cannot be obtained so that their applications to drug delivery are limited. In our work, the synthesized amphiphilic CD-PCL polymer has a unique "jellyfish-like" structure consisting of a hollow cavity and hydrophobic tails. It is possible for the amphiphile to form stable inclusive complexes with hydrophobic drugs with various sizes. So the biodegradable CD-PCL and related self-assembled micelles should be useful as functional biomaterials for many applications such as drug delivery.

5. Conclusions

In summary, a kind of biodegradable multi-arm polymer β-cyclodextrin-poly(ε-caprolactone) (CD-PCL) with a "jellyfish-like" structure was obtained, in which flexible and hydrophobic PCL arms were selectively connected to the wide side of the hydrophilic torus-shaped β-CD. The "jellyfish-like" polymer with a hollow cavity and hydrophobic tails can orthogonally self-assemble into a supramolecular diblock copolymer CD-PCL/FcPEG with FcPEG in aqueous solutions based on terminal hydrophobic interactions. CD-PCL could self-assemble into vesicles, however the supramolecular amphiphile self-assembled into spheres in water. Thus transformation of micellar morphology was realized through the orthogonal assembly by the inclusion of FcPEG to CD-PCL.

Acknowledgments

This research was financially supported by the Natural Science Foundation of China (Grant No. 20604033) and the Foundation of Graduate University of Chinese Academy of Sciences.

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