Synthesis, Self-Assembly, and Drug-Loading Capacity of Well-Defined Cyclodextrin-Centered Drug-Conjugated Amphiphilic $A_{14}B_7$ Miktoarm Star Copolymers Based on Poly(ε-caprolactone) and Poly(ethylene glycol)

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Novel drug-conjugated amphiphilic $A_{14}B_7$ miktoarm star copolymers composed of 14 poly(ε-caprolactone) (PCL) arms and 7 poly(ethylene glycol) (PEG) arms with β-cyclodextrin (β-CD) as core moiety were synthesized by the combination of controlled ring-opening polymerization (CROP) and "click" chemistry. ^{1}H NMR, FT-IR, and SEC-MALLS analyses confirmed the well-defined $A_{14}B_7$ miktoarm star architecture. These amphiphilic miktoarm star copolymers could self-assemble into multimorphological aggregates in aqueous solution, which were characterized by dynamic light scattering (DLS) and transmission electron microscopy (TEM). Moreover, the drug-loading efficiency and drug-encapsulation efficiency of the drug-conjugated miktoarm star copolymers were higher than those of the corresponding non-drug-conjugated miktoarm star copolymers.

Introduction

Great interest has been evoked for the design of polymeric micelles self-assembled from amphiphilic copolymers as drug carriers due to their unique characteristics such as core−shell structure, mesoscopic size range, and prolonged blood circulation.[1−4] Naturally, biodegradable and biocompatible polymeric micelles are of special interest in the delivery system.[5] As a U.S. Food and Drug Administration (FDA) approved biomedical polymer, poly(ε-caprolactone) (PCL) is one of the most attractive and promising biodegradable and biocompatible aliphatic polyesters that can be used as a synthetic biomaterial or a controlled drug release matrix due to its good drug permeability, biocompatibility, and nontoxicity.[6] Poly(ethylene glycol) (PEG) is also a FDA approved hydrophilic and nonionic polymer that has been widely investigated as a biocompatible polymer in both academia and industry for chemical and biological applications.[7] Polymeric micelles containing PEG as the hydrophilic shell can prevent the adsorption of proteins and enzymes and thus increase their residence time in systemic circulation.[8,9]

Up to this date, although micelles self-assembled from PCL- and PEG-based copolymers have been extensively studied for biomedical applications, most of the work focused on utilizing linear block copolymers.[10−19] It has been proved that the architecture of amphiphilic copolymer may influence the morphology, stability, and dimensions of the micelles,[20−23] which are important parameters to determine the drug loading capacity, release behavior, and circulation in vivo.[24,25] Therefore, rational design and synthesis of PCL- and PEG-based copolymers with novel architecture may provide promising drug carrier candidates for clinical applications in delivery systems. Jérôme and co-workers reported the synthesis and micellization of comblike PCL- and PEG-based graft copolymers through the ring-opening copolymerization (ROP) of ε-CL and a novel ε-CL-terminated PEG macromonomer.[26,27] As the "click" reaction has appeared to be an efficient method for the preparation of polymers with complex structures,[28−34] Jérôme's group developed a facile strategy to synthesize PCL- and PEG-based graft copolymers via the combination of "click" reaction and ROP.[35−37] Recently, Yuan et al. synthesized a cylindrical brush copolymer with linear PCL-*b*-PEG as side chains and studied its thermal and crystallization behaviors.[38] As an extension of this work, Wang et al. investigated in detail the doxorubicin (DOX) loading capacity and release behavior of these cylindrical brush copolymer micelles and found that they were preferable potential drug carriers for efficient drug delivery compared with their linear PCL-*b*-PEG micelle analogues.[39] Quite interestingly, Dong et al. described the synthesis of novel linear-dendron-like PCL-*b*-PEG copolymers composed of linear PEG blocks and dendron-like PCL blocks.[40] These new types of copolymers provide an approach to fabricate worm-like DOX-loaded nanoparticles which showed a higher drug loading efficiency and a longer drug-release time than the linear counterparts.[41]

Star polymers consisting of several equal or unequal (miktoarm star) linear chains together at one central core have attracted considerable attention of polymer chemists because they are special types of branching polymers and always showing particular bulk and solution properties.[42,43] Moreover, several recent publications also demonstrated that star polymers have some advantages in gene and drug delivery compare to the linear polymers.[44−47] For example, Bae et al. investigated the formation of doxorubicin hydrochloride encapsulated polymersome from AB_2 miktoarm star copolymers [PEG-*b*-$(PLLA)_2$] and observed sustained in vitro release of the loaded drug.[48] Roovers et al. reported that micelles self-assembled from PCL- and PEG-based multiarm star block copolymers exhibited high drug loading capacity as well as facile release kinetics.[49,50] Therefore, it is expected that developing new types of star polymers with unique architectures may provide new insights for fabricating superior drug carriers for special delivery system.

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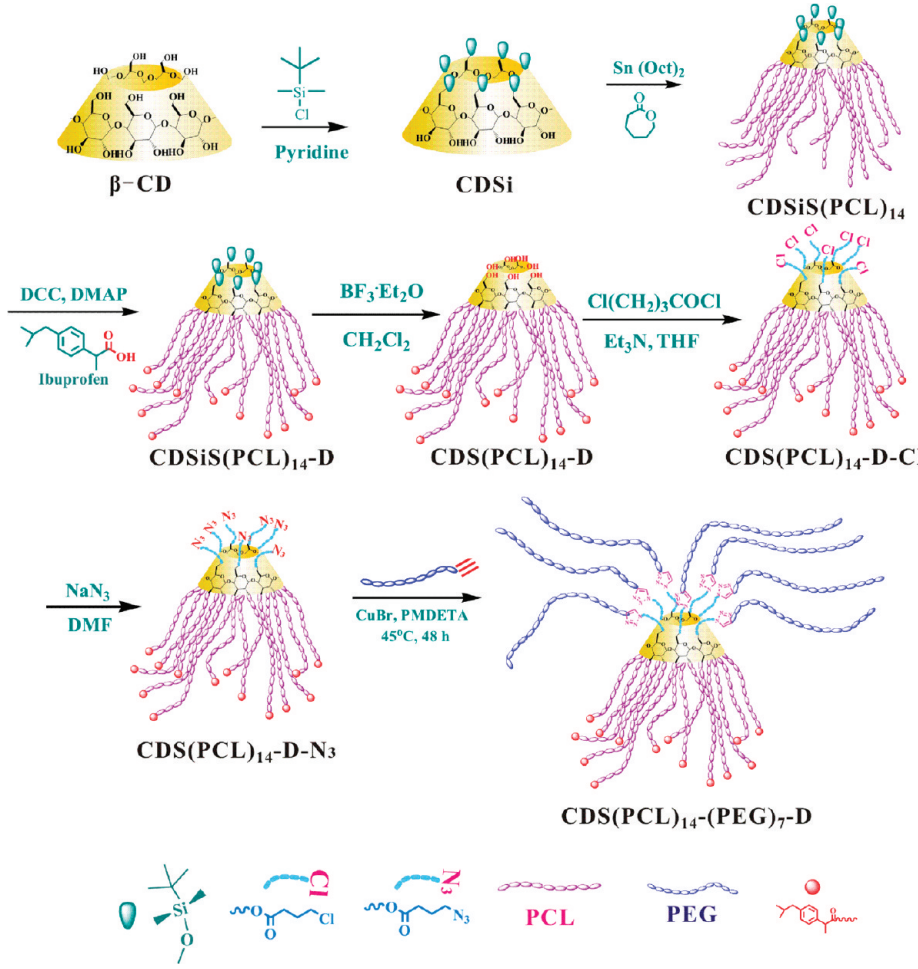
Scheme 1. Synthetic Route of Cyclodextrin-Centered Drug-Conjugated Amphiphilic A14B7 Miktoarm Star Copolymers via the Combination of Controlled Ring-Opening Polymerization (CROP) and "Click" Chemistry



Meanwhile, traditional polymeric micellar drug carrier system by simple encapsulating hydrophobic drugs to the hydrophobic core is hampered by either premature drug release before the micelle reaches the targets or insufficient intracellular delivery owing to the low drug loading capacity.[51] To overcome these shortcomings, conjugation of drugs to the polymer chains by covalent bonds have been developed in recent years.[52−60] Employing drug conjugated polymeric micelles as drug carriers not only increases the drug loading capacity but also enhances the controllability of the drug delivery system.

In this paper, using per-6-(*tert*-butyldimethylsilyl)-β-CD (CDSi) as a heteromultifunctional initiator, a facile strategy to prepare amphiphilic drug-conjugated $A_{14}B_7$ miktoarm star copolymer [CDS$(PCL)_{14}$-$(PEG)_7$-D] has been successfully developed via the combination of controlled ring-opening polymerization (CROP) and "click" reaction (Scheme 1). First, CDSi with 14 secondary hydroxyl groups were first synthesized for the CROP of ε-CL to generate 14-arm star PCL homopolymers [CDS$(PCL)_{14}$]. Second, model hydrophobic drug ibuprofen was incorporated onto the end of the PCL chains in the presence of DCC and DMAP at room temperature. Next, after desilylation of the *tert*-butyldimethylsilyl ether groups from the β-CD core, seven "clickable" azide groups were introduced by tandem treating with 4-chlorobutyryl chloride and NaN_3. Finally, alkyne-terminated poly(ethylene glycol) (A-PEG) was coupled with the 14-arm drug-conjugated azide-functionalized star PCL [CDS$(PCL)_{14}$-D-N_3] by "click" reaction to produce the target amphiphilic $A_{14}B_7$ miktoarm star copolymers [CDS$(PCL)_{14}$-$(PEG)_7$-D]. These new types of amphiphilic copolymers could self-assemble into multimorphological aggregates in aqueous solution which were composed of biocompatible PEG corona surrounding with both biodegradable cyclodextrin core and PCL arms. In addition, the hydrophobic drug ibuprofen-loaded nanoparticles fabricated from these drug-conjugated copolymers showed a higher drug loading efficiency than the non-drug-conjugated counterpart. Furthermore, covalently linked drug may prolong the drug release time, potentially making them promising carriers for the delivery of hydrophobic drugs.

Experimental Section

Materials. β-Cyclodextrin hydrate (β-CD) was dried over P_2O_5 at 80 °C under reduced pressure overnight before use. Pyridine, toluene, and triethylamine (TEA) were dried over CaH_2 and distilled just before use. ε-Caprolactone (99%; Acros) and 2-propyny-1-ol (99%; Aladdin, China) were distilled under reduced pressure prior to use. THF was distilled from the ketyl prepared from sodium and benzophenone. Methoxy poly(ethylene glycol)s (Fluka; M_n = 1.1 K, 2 K) denoted as mPEG25 and mPEG45 were dried by azeotropic distillation in the presence of dry toluene. *N*,*N*,*N*′,*N*″,*N*″-Pentamethyldiethylenetriamine (PMDETA; 99%; Aldrich), dicyclohexylcarbodiimide (DCC; 99%; Fluka), 4-dimethylaminopyridine (DMAP; 99%; Fluka), 4-chlorobutyryl chloride (98%; Acros), *tert*-butylchlorodimethylsilane (TBDMSCl; 98%; Acros), and ibuprofen (99%; Juhua Group Corporation, China) were used as received. Succinic anhydride (99%; Fluka) was crystallized from acetic anhydride. CuBr (99%; Acros) was purified by stirring overnight in acetic acid. After filtration, it was washed with ethanol

and then dried in vacuum. Boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$; 48% BF_3), stannous octoate [$Sn(Oct)_2$; 97%], and other reagents were purchased from Sinopharm Chemical Reagent Co., Ltd. (China), and used as received.

Synthesis of Cyclodextrin-Centered 14-Arm Star Poly(ε-caprolactone)s [CDSiS(PCL)$_{14}$] by Controlled Ring-Opening Polymerization (Scheme 1). CDSiS(PCL)$_{14}$ was synthesized by controlled ring-opening polymerization of ε-CL using per-6-(*tert*-butyldimethylsilyl)-β-CD (CDSi; see Supporting Information) as the multifunctional initiator in the presence of $Sn(Oct)_2$. A typical polymerization procedure was as follows: CDSi (0.773 g, 5.6 mmol of OH group) was dried at 70 °C under reduced pressure overnight and transferred into a flame-dried ampule. Then, ε-CL (3.88 g, 34 mmol) and a magnetic stirring bar were added to the ampule under an argon atmosphere. After CDSi was dissolved in ε-CL completely, the tube was then connected to a Schlenk-line, where an exhausting−refilling process was repeated three times. A total of 20 mg $Sn(Oct)_2$ in 1 mL of dry toluene was added to the mixture, and the exhausting−refilling process was carried out again to remove the toluene. The ampule was put into an oil bath at 125 °C for 24 h bulk polymerization. The crude polymer was dissolved in THF and poured into excess methanol to precipitate the product, which was dried in vacuum to constant weight. Yield: 4.58 g (98%).

Synthesis of Ibuprofen Conjugated Cyclodextrin-Centered 14-Arm Star Poly(ε-caprolactone)s [Scheme 1, CDSiS(PCL)$_{14}$-D]. The hydroxyl end groups of the CDSiS(PCL)$_{14}$ were blocked by ibuprofen. A typical procedure was as follows: CDSiS(PCL6)$_{14}$ (3.0 g, 3.53 mmol of OH group), ibuprofen (1.45 g, 7.06 mmol), DCC (3.20 g, 15.5 mmol), and DMAP (172 mg, 1.41 mmol) were dissolved in 80 mL of anhydrous THF, and the reaction was performed at room temperature for 48 h under an argon atmosphere. The byproduct dicyclohexylcarbodiurea was removed by filtration. After evaporating most of the solvent, the ibuprofen-terminated 14-arm star poly(ε-caprolactone) [CDSiS(PCL6)$_{14}$-D] was precipitated by the addition of cold diethyl ether, which was dried in vacuum to constant weight. Yield: 3.17 g (85% for polymer weight).

Desilylation of CDSiS(PCL)$_{14}$-D (Scheme 1). The primary hydroxyl groups on the cyclodextrin-core were recovered by desilylation of the *tert*-butyldimethylsilyl ether groups in the presence of $BF_3 \cdot Et_2O$. A typical procedure was as follows: $BF_3 \cdot Et_2O$ (0.5 mL, 2 mmol) in 10 mL of anhydrous CH_2Cl_2 was added dropwise to a solution of CDSiS(PCL6)$_{14}$-D (2.0 g, 0.95 mmol of *tert*-butyldimethylsilyl group) in 80 mL of anhydrous CH_2Cl_2 under stirring. The reaction mixture was stirred for 12 h under an argon atmosphere at room temperature and then washed successively with $NaHCO_3$ (100 mL, 1 M) and distilled water. 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 (denoted as CDS(PCL6)$_{14}$-D, Scheme 1) was dried in vacuum at room temperature for 24 h. Yield: 1.69 g (90% for polymer weight).

Synthesis of Chloride Functionalized Ibuprofen-Conjugated 14-Arm Star Poly(ε-caprolactone)s [Scheme 1, CDS(PCL)$_{14}$-D-Cl]. A typical procedure was as follows: CDS(PCL6)$_{14}$-D (1.4 g, 0.71 mmol of OH group) was dissolved in 40 mL anhydrous THF, followed by the introduction of triethylamine (TEA; 0.72 g, 7.1 mmol, 1.0 mL) via a syringe. 4-chlorobutyryl chloride (1.0 g, 7.1 mmol, 0.8 mL) in 5 mL of anhydrous THF was added dropwise to the vigorously stirred solution at 0 °C over 30 min. The reaction mixture was stirred at room temperature overnight. The precipitated byproduct was removed by filtration, and the solution was evaporated to dryness. The crude product was dissolved in 40 mL of methylene chloride, and then washed successively with 1 M $NaHCO_3$ aqueous solution and 40 mL of distilled water, and finally dried over anhydrous $MgSO_4$. The concentrated solution was poured into methanol to precipitate the product. The resulting white solid was dried in vacuum at room temperature for 24 h. Yield: 1.13 g (75% for polymer weight).

Synthesis of Azide Functionalized Ibuprofen-Conjugated 14-Arm Star Poly(ε-caprolactone)s [Scheme 1, CDS(PCL)$_{14}$-D-N$_3$]. A typical procedure was as follows: CDS(PCL6)$_{14}$-D-Cl (1.0 g, 0.47 mmol of Cl group) was dissolved in DMF (50 mL) and sodium azide (306 mg, 4.7 mmol) was added. The reaction mixture was stirred for 48 h at 30 °C, then filtered and evaporated to remove DMF. Methylene chloride (40 mL) was added, and the mixture was washed three times with distilled water. The organic layer was dried with anhydrous $MgSO_4$, and the solvent was evaporated to obtain a white solid, which was dried in vacuum to constant weight. Yield: 0.95 g (95% for polymer weight).

Synthesis of Ibuprofen-Conjugated $A_{14}B_7$ Miktoarm Star Copolymer [CDS(PCL)$_{14}$-(PEG)$_7$-D] by "Click" Reaction. Ibuprofen-conjugated $A_{14}B_7$ miktoarm star copolymer [CDS(PCL)$_{14}$-(PEG)$_7$-D] was synthesized by "click" reaction between azide functionalized ibuprofen-conjugated 14-arm star poly(ε-caprolactone)s [CDS(PCL)$_{14}$-D-N$_3$] and alkyne-terminated PEG (A-PEG; see Supporting Information). A typical example is given below. CDS(PCL6)$_{14}$-D-N$_3$ (400 mg, 0.19 mmol of azide group) and A-PEG25 (250 mg, 0.21 mmol of alkyne group) were dissolved in argon-purged DMF (15 mL) in a flame-dried ampule. CuBr (30 mg, 0.21 mmol) and PMDETA (36 mg, 0.21 mmol) were added in order, and the reaction mixture was degassed by three freeze−pump−thaw cycles, left in argon, and stirred at 45 °C for 48 h. The solution was passed through an alumina column to remove the copper salt. The polymer was recovered by precipitation into cold diethyl ether and dried in vacuum. Yield: 540 mg (83% for polymer weight).

Pure CDS(PCL)$_{14}$-(PEG)$_7$-D was obtained by dialysis (dialysis membrane, MWCO 14000) and lyophilization. Typically, a 540 mg mixture of CDS(PCL6)$_{14}$-(PEG25)$_7$-D and linear A-PEG25 was first dissolved in 20 mL of THF, and then the distilled water (ca. 10 mL) was added dropwise to the solution with vigorous stirring. Then the solution was stirred overnight and dialyzed against distilled water over 7 days at room temperature to remove THF and the excess unreacted A-PEG. The final solid-state sample was recovered by lyophilization. Yield: 440 mg (81.9% for polymer weight).

Non-ibuprofen-conjugated $A_{14}B_7$ miktoarm star copolymers [CDS(PCL)$_{14}$-(PEG)$_7$] were synthesized using the similar methods (see Supporting Information).

Micelles/Aggregates Formation. Typically, CDS(PCL)$_{14}$-(PEG)$_7$-D or CDS(PCL)$_{14}$-(PEG)$_7$ (25 mg) was dissolved in 5 mL of THF, and then distilled water (ca. 5 mL) was added dropwise to the solution with vigorous stirring. The micelle solution was stirred overnight and dialyzed against distilled water over 48 h to remove THF. The final concentration of the micelle solution was adjusted to 1.0×10^3 mg/L.

Preparation of Drug-Loaded Micelles/Aggregates of CDS(PCL)$_{14}$-(PEG)$_7$-D and CDS(PCL)$_{14}$-(PEG)$_7$ Miktoarm Star Copolymers. CDS(PCL)$_{14}$-(PEG)$_7$-D or CDS(PCL)$_{14}$-(PEG)$_7$ (50 mg) and the calculated amount of ibuprofen were dissolved in 10 mL of THF, and then distilled water (ca. 5 mL) was added dropwise to the solution under vigorous stirring to induce the hydrophobic ibuprofen incorporated into the micellar core. The micelle solution was stirred overnight and dialyzed against distilled water over 48 h to remove THF. The unloaded ibuprofen precipitate was filtered through 0.45 μm filter, and the solid-state drug-loaded miktoarm star copolymers were recovered by lyophilization. The drug-loading capacity of the samples was investigated by ^{1}H NMR spectra. The loading capacity and the encapsulation efficiency were calculated using eqs 1 and 2, respectively.

$$\text{loading capacity}(\%) = (W_{DM} - W_{DC})/W_P \quad (1)$$

$$\text{encapsulation efficiency}(\%) = (W_{DM} - W_{DC})/W_{Dt} \quad (2)$$

where W_{DM} is the weight of ibuprofen measured by ^{1}H NMR spectra, W_{DC} is the weight of conjugated ibuprofen [for CDS(PCL)$_{14}$-(PEG)$_7$, $W_{DC} = 0$], W_p is the weight of the star copolymer, and W_{Dt} is the total weight of ibuprofen used in drug-loading experiment.

Characterization. *Proton Nuclear Magnetic Resonance Spectroscopy (^1H NMR).* ^1H NMR spectra were recorded on a Bruker Avance DMX500 spectrometer in $CDCl_3$ with tetramethylsilane as internal standard.

ESI-Positive Mass Spectrometry (MS). ESI-MS was performed using Bruker Esquire 3000 plus spectrometer with an ESI interface.

Size Exclusion Chromatography (SEC). The molecular weight and molecular weight distribution were determined by size-exclusion chromatography/multiangle laser light scattering (SEC-MALLS). The SEC system consisted of a Waters degasser, a Waters 1515 Isocratic HPLC pump, a Wyatt Optilab DSP interferometric refractometer, a Wyatt DAWN DSP multiangle laser light scattering detector, and columns: Styragel, HT 3, HT 4. Tetrahydrofuran (THF) was used as the mobile phase at a flow rate of 0.8 mL·min^{-1} at 30 °C. Polystyrenes with the M_w ranging from 580 to 600000 were used as calibration standards. The refractive-index increment (dn/dc) was determined with a Wyatt Optilab DSP differential refractometer at 690 nm.

Dynamic Light Scattering (DLS). The hydrodynamic diameter and size distribution of micelles were determined by dynamic light scattering (DLS) at 90° angle to the incident beam and at 25 °C on a Brookhaven 90 Plus particle size analyzer. All micellar solutions had a final polymer concentration of 300 mg/L and were filtered through a 0.45 μm filter.

Transmission Electron Microscopy (TEM). TEM images were obtained using JEM-1230 operating at an acceleration voltage of 60 kV. A drop of 300 mg/L micellar solution was placed onto the surface of Formvar-carbon film-coated copper grids. Excess solution was quickly wicked away with a filter paper. All grids were finally negatively stained by 2 wt % phosphotungstic acid.

Fluorescence Spectroscopy. The critical micelle concentration (CMC) was determined by fluorescence measurement using pyrene as a fluorescent probe. Fluorescence excitation spectra were recorded on Hitachi F-4500 fluorescence spectrometer at 390 nm emission wavelength and 2.5 nm slit width. The pyrene concentration in the solution was chosen to be 6.0×10^{-7} M.

Results and Discussion

Synthesis of Cyclodextrin-Centered 14-Arm Star Poly(ε-caprolactone)s [CDSiS(PCL)$_{14}$] by Controlled Ring-Opening Polymerization. In our previous work, we described the synthesis of well-defined seven-arm star poly(ε-caprolactone)s initiated from the seven primary hydroxyl groups of β-CD with stannous octoate as catalyst.[61] Very recently, we found that the 14 secondary hydroxyl groups of β-CD were also suitable as the initiating sites for the controlled ring-opening polymerization (CROP) of ε-CL. Thereby, in this paper, per-6-(*tert*-butyldimethylsilyl)-β-CD (CDSi) with 14 s hydroxyl groups was designed as the multifunctional initiator to generate 14-arm star poly(ε-caprolactone)s [CDSiS(PCL)$_{14}$], as shown in Scheme 1. *tert*-Butyldimethylsilyl ether groups as hydroxyl protecting groups not only increased the solubility of β-CD in ε-CL, which permits the simultaneous initiating of all the 14 secondary hydroxyl groups for the CROP of ε-CL, but also provided a convenient platform to design $A_{14}B_7$ miktoarm star copolymers in the following steps. The chemical structure of CDSi was fully characterized by ^1H NMR and MS (see Supporting Information), which demonstrate that it has designed chemical structure and can be used as initiator for the following polymerization. Then, using CDSi as a multifunctional initiator, CDSiS(PCL)$_{14}$ were synthesized by the controlled ring-opening bulk polymerization of ε-CL in the presence of $Sn(Oct)_2$ at 125 °C. Two different monomer/initiator ratios were utilized to achieve CDSiS(PCL)$_{14}$ with different polymerization degrees.

Figure 1 exhibits a representative ^1H NMR spectrum of CDSiS(PCL)$_{14}$ [CDSiS(PCL18)$_{14}$]. It clearly shows that besides the major proton signals of PCL chains (H^{c-f}), there are

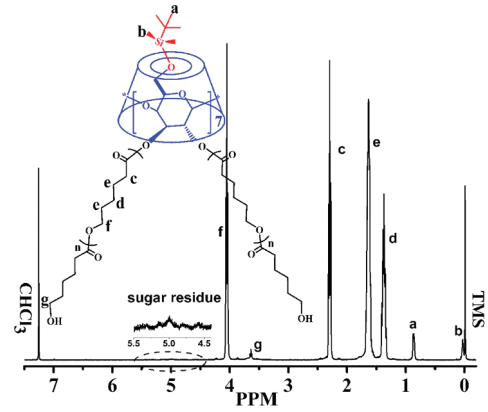


Figure 1. ^1H NMR spectrum (500 MHz) of CDSiS(PCL18)$_{14}$ in $CDCl_3$.

additional signals of the per-6-(*tert*-butyldimethylsilyl)-β-CD core moiety, that is, signals corresponding to methyl protons (H^b) and *tert*-butyl protons (H^a) of the *tert*-butyldimethylsilyl ether groups. The triplet at 3.65 ppm (H^g) is assigned to the PCL methylene protons conjoint with the hydroxyl end groups. Notably, the ratio of peak areas of H^a and H^g (I^a/I^g) is 2.15, which is close to the theoretical value (2.25). This result clearly demonstrates the 14-arm star structure of the samples prepared. The number average molecular weight of the CDSiS(PCL)$_{14}$ ($M_{n,NMR}$) can be calculated by the integral of signals at 4.05 ppm (H^f) of the PCL repeat units and that of signals at 0.89 ppm (H^a) of the *tert*-butyldimethylsilyl ether groups, which are close to the values calculated by observed conversion and [CL]$_0$/[CDSi] ($M_{n,Cal}$; see Table 1). All these observations confirm that CDSiS(PCL)$_{14}$ with designed chemical structure and molecular weight has been successfully synthesized.

SEC traces (Figure 2) of the resulting 14-arm star PCL [CDSiS(PCL)$_{14}$] homopolymers reveal unimodal elution peaks with reasonably narrow polydispersity (<1.20), although slight tailing was detected in the low-molecular-weight region, which was attributed to unavoidable chain transfer side reactions during the polymerization. Furthermore, the actual molecular weights of the CDSiS(PCL)$_{14}$ homopolymers ($M_{n,MALLS}$) measured by connecting a multiangle laser light scattering detector to the SEC have confirmed the values obtained from ^1H NMR spectroscopy ($M_{n,NMR}$; Table 1). These results demonstrate that CDSiS(PCL)$_{14}$ with well-defined architectures have been successfully prepared and their molecular weights can be controlled by adjusting the molar ratio of the monomer to the initiator. It should be pointed out that only CDSiS(PCL)$_{14}$ homopolymers with relatively low molecular weight have been prepared in this paper. This is due to the fact that the tailing in the low-molecular-weight region increased with the increasing of molecular weigh (data not shown), leading to ill-defined structures. On the other hand, it is difficult to functionalize the β-CD core moiety of the CDSiS(PCL)$_{14}$ homopolymers with high molecular weight in the following steps.

Synthesis of Ibuprofen Conjugated Cyclodextrin-Centered 14-Arm Star Poly(ε-caprolactone)s [CDSiS(PCL)$_{14}$-D]. The reactive hydroxyl groups at the end of the PCL arms provide opportunities for covalent attachment of functional groups or biological molecules (such as biotin, folic acid, and drug).[62] Ibuprofen is a nonsteroidal anti-inflammatory drug that is commonly used for the relief of symptoms of arthritis and fever. In this present work, as a model drug, ibuprofen was conjugated to the hydroxyl end groups of the 14-arm star poly(ε-caprolactone)s [CDSiS(PCL)$_{14}$] in the presence of DCC and DMAP at

Table 1. Characterization of Cyclodextrin-Centered 14-Arm Star PCL Homopolymers

sample[a]	$[CL]_0/[CDSi]$ (molar ratio)	conv[b] (%)	d*n*/d*c* (mL/g)	$M_{n,Cal}$[c] (g·mol^{-1})	$M_{n,NMR}$[d] (g·mol^{-1})	$M_{n,SEC}$[e] (g·mol^{-1})	$M_{n,MALLS}$[f] (g·mol^{-1})	PDI[e]
$CDSiS(PCL6)_{14}$	85	98.2	0.065	11400	11900	14000	11200	1.19
$CDSiS(PCL18)_{14}$	255	97.8	0.061	30400	30700	36300	29200	1.11

[a] Polymerization conditions: bulk, 125 °C, 24 h; 6 and 18 represent the polymerization degree (DP) of each PCL arm determined by ^{1}H NMR; 14 represents the number of arms of the star PCL. [b] Conversion was calculated on the basis of gravimetric method. [c] Calculated from the equation: $M_{n,Cal} = ([CL]_0/[CDSi]) \times 114 \times$ conversion (%) + M_{CDSi}. [d] This calculation is based on the integral of the CL units as compared to that of the *tert*-butyl protons of the CD-core in ^{1}H NMR spectra: $M_{n,NMR} = ((I_f)/(2)) \times ((9 \times 7)/(I_a)) \times 114 + M_{CDSi}$ (see Figure 1). [e] Determined by SEC analysis with polystyrene standards. [f] Measured by connecting a multiangle laser light scattering detector to the SEC ($M_{n,MALLS} = M_{w,MALLS}$/PDI).

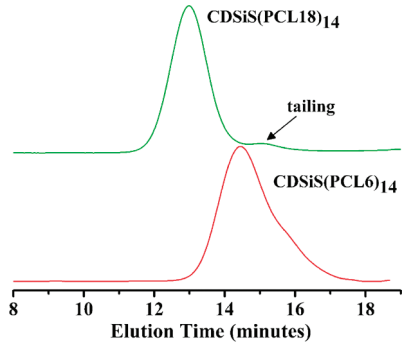


Figure 2. SEC traces of the cyclodextrin-centered 14-arm star PCL homopolymers.

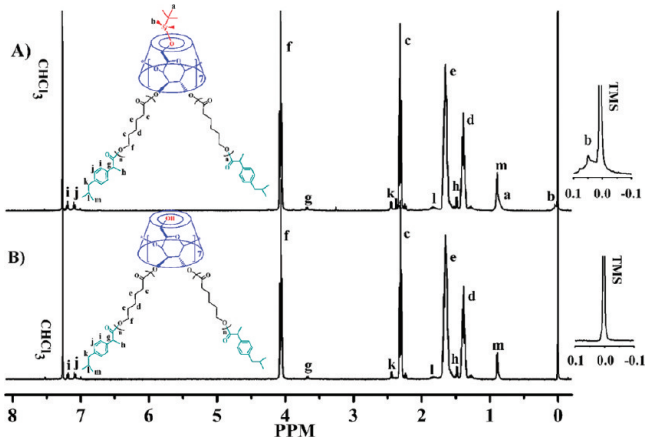


Figure 3. ^{1}H NMR spectra (500 MHz) of $CDSiS(PCL18)_{14}$-D (A) and $CDS(PCL18)_{14}$-D (B) in $CDCl_3$.

room temperature. Other hydrophobic drugs with carboxyl group (such as ketoprofen, naproxen, and indomethacin) could also be conjugated using the similar method. From the ^{1}H NMR spectrum shown in Figure 3A, resonance of the phenyl protons at 7.09 ppm (H^i) and 7.20 ppm (H^i) indicate that ibuprofen has been linked to the end of the PCL arms. Furthermore, the integral of H^{i+j} is in well agreement with the theoretical value, suggesting the successful and efficient synthesis of ibuprofen-conjugated 14-arm star poly(ε-caprolactone)s [$CDSiS(PCL)_{14}$-D].

Desilylation of $CDSiS(PCL)_{14}$-D. In order to recover the seven primary hydroxyl groups on β-CD core moiety for further modification and avoid any damage to PCL arms or conjugated ibuprofen moieties, the *tert*-butyldimethylsilyl ether groups had to be removed under mild conditions. Herein, boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$) was employed to desilylate the *tert*-butyldimethylsilyl ether groups at room temperature. The ^{1}H NMR spectrum of a representative desilylated $CDSiS(PCL18)_{14}$-D [denoted as $CDS(PCL18)_{14}$-D] is shown in Figure 3B. Compared with the ^{1}H NMR spectrum of $CDSiS(PCL18)_{14}$-D in Figure 3A, after desilylation, there is obvious decrease of the signals at 0.89 ppm, and signals at 0.04 ppm

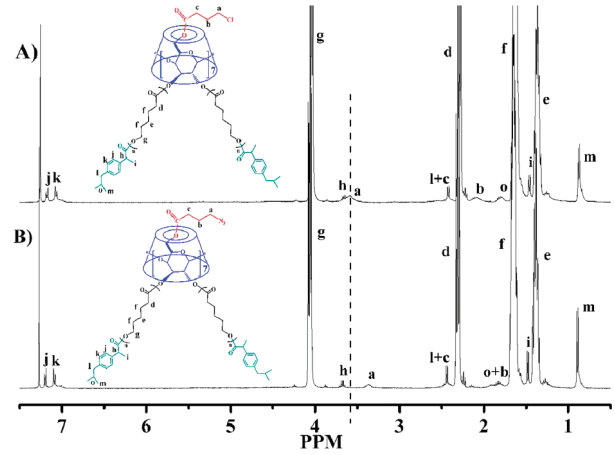


Figure 4. ^{1}H NMR spectra (500 MHz) of $CDS(PCL18)_{14}$-D-Cl (A) and $CDS(PCL18)_{14}$-D-N_3 (B) in $CDCl_3$.

(H^b) assigned to the methyl protons of the *tert*-butyldimethylsilyl ether groups have totally disappeared, indicating that the seven *tert*-butyldimethylsilyl ether groups on the β-CD core moiety have been completely removed. In addition, the major proton signals of PCL chains (H^{c-f}) and conjugated ibuprofen (H^{h-j}) remain essentially intact, which suggests there was no degradation of the PCL arms occurred.

Synthesis of Chloride Functionalized Ibuprofen-Conjugated 14-Arm Star Poly(ε-caprolactone)s [$CDS(PCL)_{14}$-D-Cl]. Considering the steric hindrance of the seven primary hydroxyl groups on the β-CD core moiety of $CDS(PCL)_{14}$-D, highly efficient "click" reaction between an azide and an alkyne should be the best way to introduce the seven hydrophilic PEG arms onto the presynthesized ibuprofen-conjugated 14-arm star poly(ε-caprolactone) [$CDS(PCL)_{14}$-D]. There are roughly two strategies to convert hydroxyl group into azide group: one can resort to blocking the hydroxyl group with tosyl chloride and followed by nucleophilic substitution reaction with NaN_3; the alternative way is to construct halogenated ester group by capping the hydroxyl group with acyl halide and subsequently treated with NaN_3. In this work, the latter approach was employed and 4-chlorobutyryl chloride was used to introduce a four atom spacer group between the bulky β-CD core and the chlorine atom, which could minimize the steric hindrance in the following "click" reaction step. A large excess of 4-chlorobutyryl chloride was used to ensure all the hydroxyl groups could be capped. The ^{1}H NMR spectrum of a representative chloride functionalized ibuprofen-conjugated 14-arm star poly(ε-caprolactone) [$CDS(PCL18)_{14}$-D-Cl] was shown in Figure 4A. After esterification, new signals corresponding to chloromethylene protons (H^a) of the 4-chlorobutyl ester group appeared at 3.60 ppm, which is partially overlapped with that of the methine proton of ibuprofen moiety. By comparing the integral of the methylene protons of PCL chain at 4.05 ppm (H^g) to that of the methylene protons of 4-chlorobutyl ester group at 2.10 ppm (H^b), the esterification efficiency was

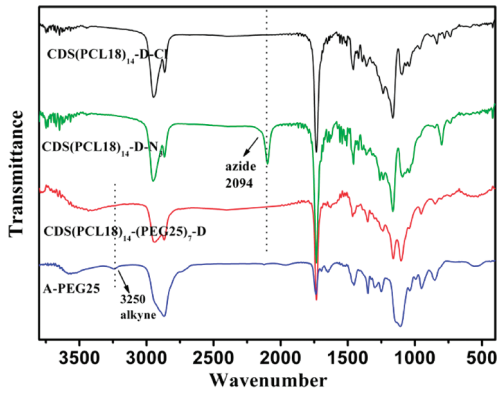


Figure 5. FT-IR spectra of $CDS(PCL18)_{14}$-D-Cl, $CDS(PCL18)_{14}$-D-N_3, $CDS(PCL18)_{14}$-$(PEG25)_7$-D, and A-PEG25.

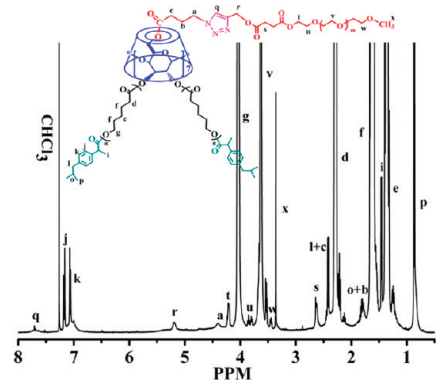


Figure 6. ^{1}H NMR spectrum (500 MHz) of $CDS(PCL18)_{14}$-$(PEG25)_7$-D in $CDCl_3$.

calculated to be about 91.5%. It is therefore demonstrated that nearly all the primary hydroxyl groups on the β-CD core moiety of $CDS(PCL18)_{14}$-D have been acylated. In addition, the integral of the PCL arms has not been changed, suggesting that no hydrolysis of the PCL arms occurred.

Synthesis of Azide Functionalized Ibuprofen-Conjugated 14-Arm Star Poly(ε-caprolactone)s [$CDS(PCL)_{14}$-D-N_3]. The chloride groups of the $CDS(PCL)_{14}$-D-Cl were converted to the azide form in the presence of excess NaN_3 in DMF at 30 °C. The ^{1}H NMR spectrum of $CDS(PCL18)_{14}$-D-N_3 is shown in Figure 4B. It is noteworthy that the signal of the chloromethylene protons [Figure 4A (H^a)] has entirely disappeared, whereas the new signal corresponding to methylene protons connected with azide groups [Figure 4B (H^a)] appears at 3.36 ppm, which indicates that the chloride groups have been converted into azide groups entirely. SEC analysis proved that the molecular weight and polydispersity (M_w/M_n) of the samples were not obviously decreased after substitution, which suggests that no degradation of the PCL arms occurred during the substitution process.

FT-IR measurements were performed to further confirm the azide functionalized ibuprofen-conjugated 14-arm star poly(ε-caprolactone) [$CDS(PCL)_{14}$-D-N_3]. As shown in Figure 5, compared with the IR spectrum of $CDS(PCL18)_{14}$-D-Cl, a new absorption peak related to azide group at 2097 cm^{-1} has appeared, which convincingly verifies the successful synthesis of $CDS(PCL)_{14}$-D-N_3.

Synthesis of Ibuprofen-Conjugated $A_{14}B_7$ Miktoarm Star Copolymers [$CDS(PCL)_{14}$-$(PEG)_7$-D] by "Click" Reaction. "Click" chemistry strategy was employed to prepare ibuprofen-conjugated $A_{14}B_7$ miktoarm star copolymers [$CDS(PCL)_{14}$-$(PEG)_7$-D] between $CDS(PCL)_{14}$-D-N_3 and alkyne-terminated PEG (A-PEG, characterization results see Supporting Information) using CuBr/PMDETA as catalyst in DMF solution, and the detailed results for miktoarm star copolymers preparation are summarized in Table 2. Although a four atom spacer between the bulky β-CD core moiety and the azide group was introduced to decrease the steric hindrance in the "click" coupling process, 10% excess A-PEG precursor and a slightly high reaction temperature (45 °C) were both adopted to prepare well-defined $CDS(PCL)_{14}$-$(PEG)_7$-D. After the "click" reaction, linear unreacted A-PEG was removed by dialysis. From the ^{1}H NMR spectrum of $CDS(PCL18)_{14}$-$(PEG25)_7$-D (Figure 6), the signal at 7.72 ppm (H^q) due to the proton of the triazole ring and signal at 5.20 ppm (H^r) due to the methylene protons of A-PEG conjoint to the triazole ring indicate the formation of $A_{14}B_7$ miktoarm star architecture. Notably, compared with the IR spectra of $CDS(PCL18)_{14}$-D-N_3 and A-PEG25 (Figure 5), the characteristic absorption peak related alkyne group at 3295 cm^{-1} and azide group at 2094 cm^{-1} completely disappear from the IR spectrum of $CDS(PCL18)_{14}$-$(PEG25)_7$-D, which also confirms the successful synthesis of well-defined $A_{14}B_7$ miktoarm star copolymers by "click" reaction.

Figure 7 shows the representative SEC traces of the miktoarm star coplymers [$CDS(PCL6)_{14}$-$(PEG25)_7$-D and $CDS(PCL6)_{14}$-$(PEG45)_7$-D] in comparison with those of the corresponding $CDS(PCL6)_{14}$-D-N_3 homopolymer and A-PEG precursors. After "click" reaction, the unimodal and symmetrical traces (PDI < 1.20) shifted to higher molecular mass region, indicating the incorporation of PEG macromolecules. Meanwhile, not any trace of A-PEG precursors were found, which demonstrates that the excess A-PEG had been completely removed by simple dialysis. As for $CDS(PCL18)_{14}$-$(PEG25)_7$-D and $CDS(PCL18)_{14}$-$(PEG45)_7$-D, similar results were observed as listed in Table 2. From the detailed information of the miktoarm star copolymers summarized in Table 2, the actual molecular weights obtained by ^{1}H NMR spectra ($M_{n,NMR}$) and SEC-MALLS ($M_{n,MALLS} = M_{w,MALLS}/PDI$) are in agreement with the calculated values

Table 2. Characterization of $CDS(PCL)_{14}$-$(PEG)_7$-D and $CDS(PCL)_{14}$-$(PEG)_7$ Miktoarm Star Copolymers via "Click" Reaction[a]

sample[b]	$M_{n,Cal}$ (g·mol^{-1})[c]	$M_{n,NMR}$ (g·mol^{-1})[d]	$M_{n,SEC}$ (g·mol^{-1})[e]	$M_{n,MALLS}$ (g·mol^{-1})[f]	PDI[e]	yield (%)[g]
$CDS(PCL6)_{14}$-$(PEG25)_7$-D	23200	21400	19200	23500	1.10	81.9
$CDS(PCL6)_{14}$-$(PEG45)_7$-D	29500	31600	22100	30300	1.07	78.2
$CDS(PCL18)_{14}$-$(PEG25)_7$-D	42000	40300	37700	39700	1.11	72.1
$CDS(PCL18)_{14}$-$(PEG45)_7$-D	48300	46100	40500	48000	1.15	66.3
$CDS(PCL6)_{14}$-$(PEG25)_7$	20300	19300	18100		1.12	83.8
$CDS(PCL6)_{14}$-$(PEG45)_7$	26600	27500	22600		1.14	80.2

[a] "Click" reaction condition: [CuBr]/[PMDETA]/[azide]/[alkyne] = 1:1:1:1.1, DMF, 45 °C, 48 h. The synthetic process of $CDS(PCL)_{14}$-$(PEG)_7$ was described in Supporting Information. [b] $CDS(PCL6)_{14}$-$(PEG25)_7$-D, 6 and 25 represent the polymerization degree of PCL and PEG, respectively; 14 and 7 represent the number of arms of the PCL and PEG, respectively; D represents the drug-conjugated sample. [c] Calculated from the equation: $M_{n,Cal} = M_{CDS(PCL)_{14}\text{-}D\text{-}N_3}$ or $M_{CDS(PCL)_{14}\text{-}N_3} + M_{A\text{-}PEG} \times 7$. [d] This calculation is based on the integration of the CL units as compared to that of the methyl protons of A-PEG: $M_{n,NMR} = M_{CDS(PCL)_{14}\text{-}D\text{-}N_3}$ or $M_{CDS(PCL)_{14}\text{-}N_3} + DP_{CDSiS(PCL)_{14}} \times (I_x)/(I_g) \times (28)/(3) \times M_{A\text{-}PEG}$. [e] Determined by SEC analysis with polystyrene standards. [f] Measured by connecting a multiangle laser light scattering detector to the SEC ($M_{n,MALLS} = M_{w,MALLS}/PDI$). [g] The yield of these purified copolymers were determined gravimetrically after dialysis.

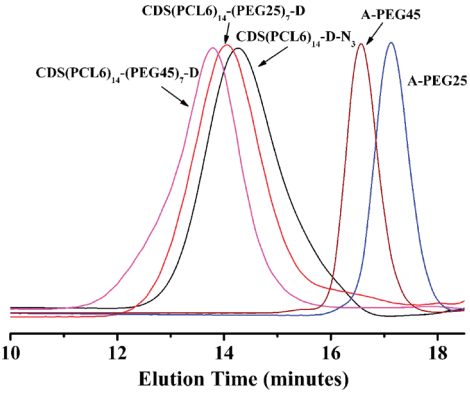


Figure 7. SEC traces of A-PEG25, A-PEG45, $CDS(PCL6)_{14}$-D-N_3, $CDS(PCL6)_{14}$-$(PEG25)_7$-D, and $CDS(PCL6)_{14}$-$(PEG45)_7$-D.

($M_{n,Cal}$) within the error of measurements, which convincingly confirmed the well-defined structure of these miktoarm star copolymers.

Self-Assembly Behaviors of Amphiphilic Ibuprofen-Conjugated $A_{14}B_7$ Miktoarm Star Copolymers [$CDS(PCL)_{14}$-$(PEG)_7$-D]. These synthesized drug-conjugated amphiphilic $A_{14}B_7$ miktoarm star copolymers provide an opportunity to form aggregates in water. The hydrophilic PEG arms serve as the shell stabilizing the nanoparticles, and the hydrophobic PCL arms and drug moieties constitute the core domain. The critical micelle concentration (CMC) of amphiphilic copolymer was usually measured by fluorescence technique using pyrene as a probe.[63] Pyrene will preferentially incorporate into hydrophobic microdomains showing strong fluorescence intensity while weak fluorescence intensity and a shift of excitation peak in a polar environment (aqueous solution). In addition, the sharp rise in intensity ratio of peaks at 338 and 333 nm of pyrene in the excitation spectra indicates the on-set of micellization (CMC) for amphiphilic copolymer. Figure 8 shows the relationship of the intensity ratios (I_{338}/I_{333}) as a function of copolymer concentration at room temperature. It can obviously be observed that the CMC values of these amphiphilic miktoarm star copolymers were relatively low (ranging from 1.35 to 6.46 mg/L), increasing as the weight fraction of PEG increased (Table 3), which was probably due to the highly branched architecture. These results indicate that the aggregates in the aqueous solution are stable and the conjugated hydrophobic drug moieties could be fully protected by the PEG shell.

The morphologies of the self-assembled aggregates from these amphiphilic $A_{14}B_7$ miktoarm star copolymers were investigated by DLS and TEM as shown in Figure 9 and Table 3. Generally speaking, with the decreasing of the weight fraction of the PEG segment, $CDS(PCL)_{14}$-$(PEG)_7$-D prefers to form large aggregates because the short hydrophilic PEG segment could not evade the hydrophobic interaction and van der Waals interaction between exposed hydrophobic domains of the aggregates.[64] Nearly spherical micelles with number average mean diameters ranging from 10−20 nm were observed when the weight fraction of the PEG segment is 46.2% for $CDS(PCL6)_{14}$-$(PEG45)_7$-D (Figure 9B) and 32.8% for $CDS(PCL6)_{14}$-$(PEG25)_7$-D (Figure

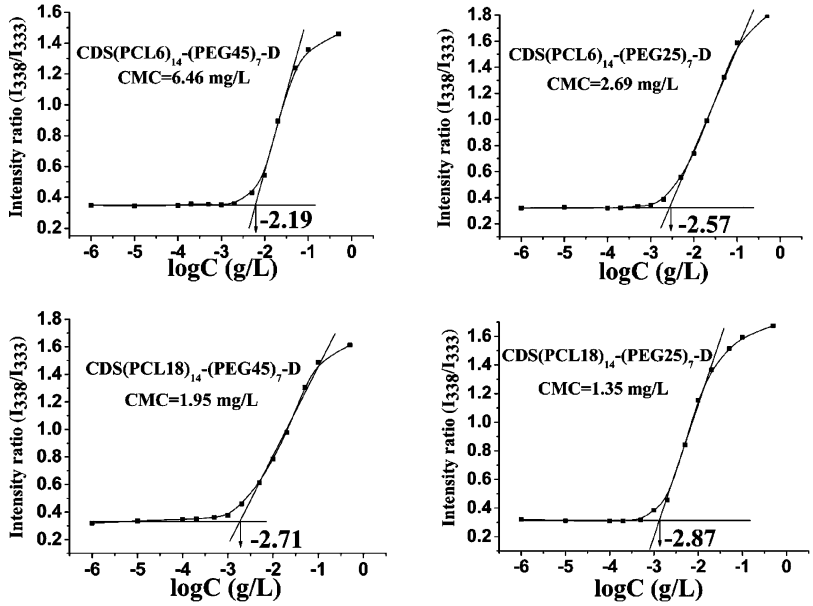


Figure 8. Plots of fluorescence intensity ratio I_{338}/I_{333} from pyrene excitation spectra vs log C for $CDS(PCL6)_{14}$-$(PEG45)_7$-D, $CDS(PCL6)_{14}$-$(PEG25)_7$-D, $CDS(PCL18)_{14}$-$(PEG45)_7$-D, and $CDS(PCL18)_{14}$-$(PEG25)_7$-D.

Table 3. Characterization of Amphiphilic $CDS(PCL)_{14}$-$(PEG)_7$-D and $CDS(PCL)_{14}$-$(PEG)_7$ Miktoarm Star Copolymer Aggregates

sample[a]	weight fraction of PEG (%)	particle size[b] (nm)	PDI[c]	CMC ($mg \cdot L^{-1}$)
$CDS(PCL6)_{14}$-$(PEG25)_7$-D	32.8	17.3	0.301	2.69
$CDS(PCL6)_{14}$-$(PEG45)_7$-D	46.2	11.8	0.270	6.46
$CDS(PCL18)_{14}$-$(PEG25)_7$-D	19.4	61.3	0.232	1.35
$CDS(PCL18)_{14}$-$(PEG45)_7$-D	29.2	59.4	0.312	2.24
$CDS(PCL6)_{14}$-$(PEG25)_7$	33.6	16.5	0.275	2.95
$CDS(PCL6)_{14}$-$(PEG45)_7$	47.3	10.5	0.215	6.53

[a] $CDS(PCL6)_{14}$-$(PEG25)_7$-D, 6 and 25 represent the polymerization degree of PCL and PEG arms, respectively; 14 and 7 represent the number of arms of the PCL and PEG, respectively; D represents the drug-conjugated sample. [b] Number-average mean diameters measured by dynamic light scattering (DLS). [c] PDI denotes the polydispersities of aggregates in aqueous solution.

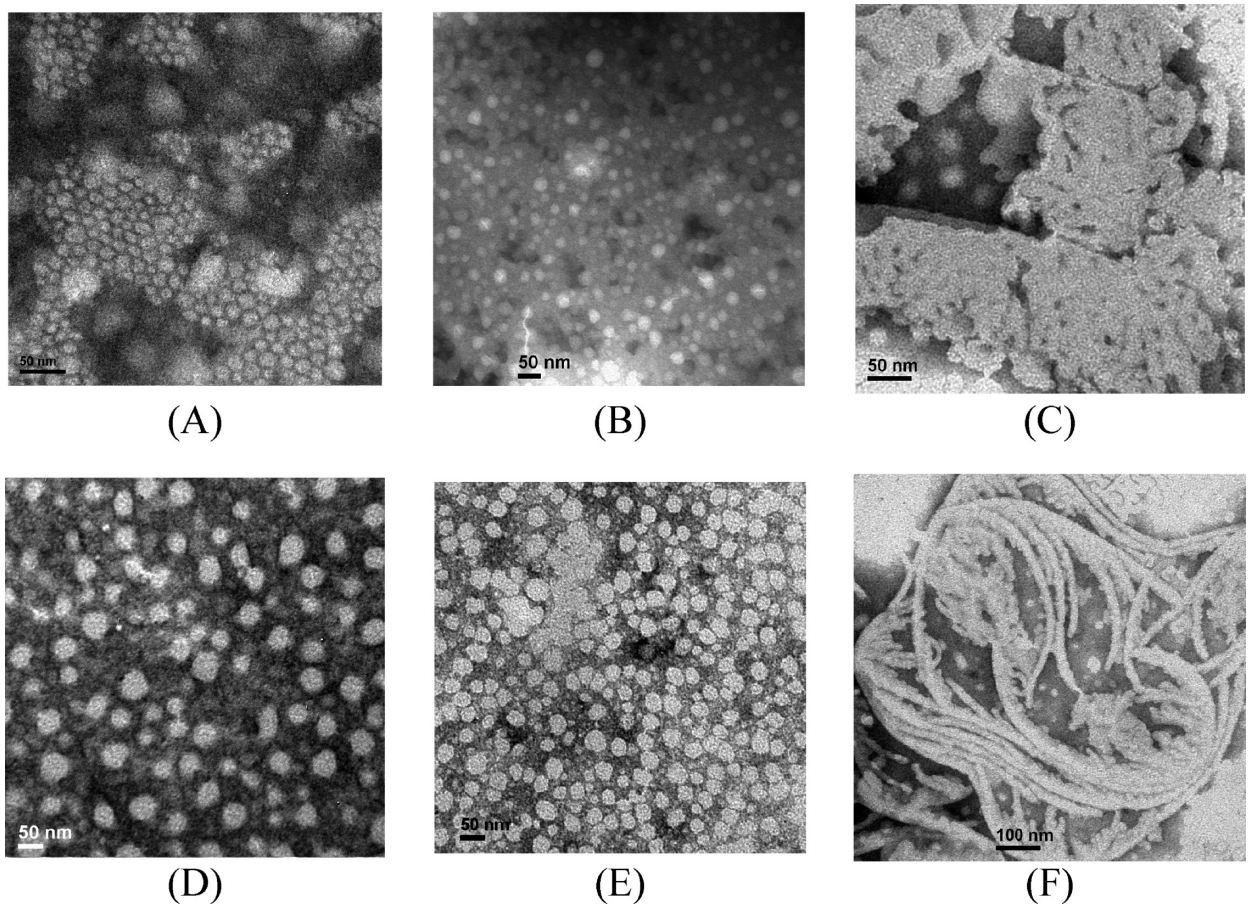


Figure 9. TEM micrography of micelles/aggregates from (A) CDS(PCL6)$_{14}$-(PEG45)$_7$, (B) CDS(PCL6)$_{14}$-(PEG45)$_7$-D, (C) CDS(PCL18)$_{14}$-(PEG45)$_7$-D, (D) CDS(PCL6)$_{14}$-(PEG25)$_7$, (E) CDS(PCL6)$_{14}$-(PEG25)$_7$-D, and (F) CDS(PCL18)$_{14}$-(PEG25)$_7$-D.

9E). Nevertheless, in the case of CDS(PCL18)$_{14}$-(PEG45)$_7$-D having a similar PEG weight fraction (29.2%) compared with CDS(PCL6)$_{14}$-(PEG25)$_7$-D, wormlike aggregates were observed (Figure 9C). With further decreasing of the weight fraction of the PEG segment, band-like aggregates appeared from CDS(PCL18)$_{14}$-(PEG25)$_7$-D (PEG weight fraction 19.4%, Figure 9F). It should be pointed out that the sizes of these wormlike and band-like aggregates measured by DLS are not in accordance with the TEM results (Table 3), which is attributed to the fact that the basic equations to calculate the hydrodynamic diameter in DLS measurement are originated from the correlation function cumulant analysis based on the assumption that the particles are noninteracting spheres and not anisotropic objects.[65] As a comparison, the morphologies self-assembled from non-drug-conjugated samples CDS(PCL6)$_{14}$-(PEG25)$_7$ and CDS(PCL6)$_{14}$-(PEG45)$_7$ were also investigated, but similar results were observed compared with the drug-conjugated samples (Figure 9D,A). Therefore, from these results we could conclude that both the architecture of the copolymers and the PEG composition affect the morphology and dimension of the self-assembled aggregates, and the conjugated drug moieties have no apparent effect on the morphology of the aggregates in aqueous solution. However, the influence of the $A_{14}B_7$ miktoarm star architecture on the morphology of aggregates is still unclear, which deserves to be further investigated in the near future.

Drug-Loading Capacity of Ibuprofen-Conjugated $A_{14}B_7$ Miktoarm Star Copolymer [CDS(PCL)$_{14}$-(PEG)$_7$-D] Aggregates. Ibuprofen was employed as a model drug to evaluate the drug-loading capacity of CDS(PCL)$_{14}$-(PEG)$_7$-D aggregates. In the meantime, the corresponding non-ibuprofen-conjugated samples [CDS(PCL6)$_{14}$-(PEG25)$_7$ and CDS(PCL6)$_{14}$-(PEG45)$_7$] were also included as comparisons. The initial weight ratio of ibuprofen to copolymer was kept equal to 3:10, and the results were summarized in Table 4. Briefly, with the decreasing of the weight fraction of the hydrophilic PEG segment, both the drug-loading efficiency and the drug-encapsulation efficiency increase. Moreover, it is worth noting that the drug-loading efficiency and drug-encapsulation efficiency of the ibuprofen-conjugated miktoarm copolymers are significantly higher than those of the corresponding non-ibuprofen-conjugated counterparts. These results could be attributed to the following factors: first, the conjugated ibuprofen may enhance the hydrophobicity of the miktoarm star copolymers, leading to an increase of drug loading amount; on the other hand, the presence of covalently bonded ibuprofen may have interactions (such as $\pi-\pi$ aromatic stacking force) with the free ibuprofen, which force the free ibuprofen to incorporate into the micellar core. Typical TEM images of the ibuprofen-loaded micelles were shown in Figure 10. It can be clearly observed that the loaded hydrophobic drug influenced the final morphology and dimension of the self-assembled aggregates. In the case of CDS(PCL6)$_{14}$-(PEG45)$_7$-D, the number average mean diameters of the spherical micelles slightly increased after the drug-loading process (Figure 10A,B). As for CDS(PCL6)$_{14}$-(PEG25)$_7$-D, spherical micelles have transformed into wormlike aggregates after the drug-loading process (Figure 10C,D). These results indicate that the loaded ibuprofen increases the hydrophobic property of the micellar core, leading to the formation of larger aggregates with more stable morphologies.

Table 4. Preparation and Properties of Ibuprofen-Loaded Aggregates from $CDS(PCL)_{14}$-$(PEG)_7$-D and $CDS(PCL)_{14}$-$(PEG)_7$ Miktoarm Star Copolymers

sample[a]	weight fraction of PEG (%)	load efficiency[b] (%)	encapsulation efficiency[b] (%)	weight fraction of conjugated drug[b] (%)
$CDS(PCL6)_{14}$-$(PEG25)_7$-D	32.8	8.2	27.3	12.3
$CDS(PCL6)_{14}$-$(PEG45)_7$-D	46.2	6.1	20.3	9.5
$CDS(PCL6)_{14}$-$(PEG25)_7$	33.6	3.5	11.7	N/A
$CDS(PCL6)_{14}$-$(PEG45)_7$	47.3	2.3	7.7	N/A
$CDS(PCL18)_{14}$-$(PEG25)_7$-D	19.4	13.8	46.0	6.7
$CDS(PCL18)_{14}$-$(PEG45)_7$-D	29.2	10.2	34.0	6.0

[a] The initial weight ratio of ibuprofen to copolymer ($drug_{wt}$/$polymer_{wt}$) was kept equal to 3:10. $CDS(PCL6)_{14}$-$(PEG25)_7$-D, 6 and 25 represent the polymerization degree of PCL and PEG arms, respectively. D represents the drug-conjugated sample. [b] Determined by ^1H NMR. For the ibuprofen-conjugated sample, the weight of conjugated ibuprofen has been deducted from the ^1H NMR results.

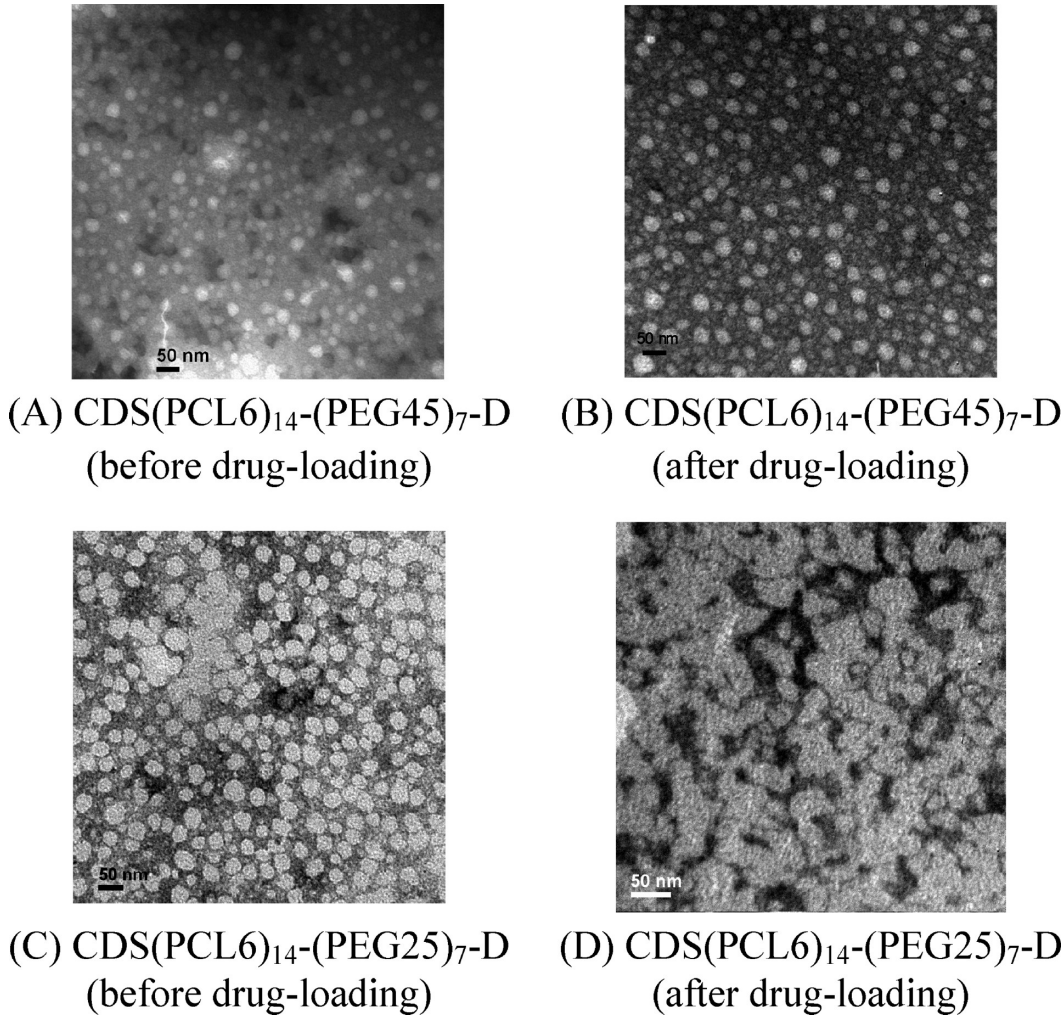


Figure 10. TEM micrography of aggregates before and after the drug-loading process.

Conclusions

Well-defined cyclodextrin-centered drug-conjugated amphiphilic $A_{14}B_7$ miktoarm star copolymers [$CDS(PCL)_{14}$-$(PEG)_7$-D] have been successfully synthesized via the combination of CROP and "click" chemistry. ^1H NMR, SEC-MALLS, and FT-IR analyses confirmed the designed structures. These copolymers could self-assemble into various morphologies in aqueous solution, which can be controlled by both the macromolecular architecture and the composition of the copolymer. Therefore, a promising strategy to synthesize novel highly branched biocompatible and biodegradable copolymers as potential multifunctional nanodrug carriers in delivery system has been developed. The drug-loading efficiency and drug-encapsulation efficiency of the drug-conjugated miktoarm star copolymers were higher than those of the corresponding nondrug-conjugated miktoarm star copolymers. Moreover, the drug release behavior could be controlled not only by the loaded free drug molecules, but also by the hydrolysis of conjugated drug moieties from PCL arms within long periods of time. Further investigations on release behaviors of these copolymers are ongoing in our laboratory.

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Supporting Information Available. The syntheses and characterizations of per-6-(*tert*-butyldimethylsilyl)-β-CD, alkyne-terminated PEG and non-ibuprofen-conjugated $A_{14}B_7$ miktoarm star copolymers. This material is available free of charge via the Internet at http://pubs.acs.org.

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