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Hollow spheres with α-cyclodextrin nanotube assembled shells

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ABSTRACT

Monodisperse hollow spheres with radially oriented α-cyclodextrin nanotube assembled shells were synthesized using PEG-grafted silica as templates. (3-Aminopropyl)triethoxysilane-modified silica core was synthesized by the Stöber method and subsequently grafted with mPEG-succinimidyl carbonate through amide linkage. Maleic anhydride modified α-cyclodextrins were threaded onto the grafted-PEG chains, forming tubular polypseudorotaxanes. Adjacent polypseudorotaxanes were immobilized by crosslinking. After the extraction of the inner silica template by etching and the included PEG template by heating, hollow spheres of uniform size with α-CD nanotube assembled shells were prepared. The products were composed of intact and dispersed hollow spheres with diameter of about 50 nm, possessed uniform shell thickness of 12 nm as confirmed by transmission electron microscopy (TEM) measurement. α-CD nanotubes have a function of molecular recognization with PEG, which may endow the hollow nanospheres as promising target drug delivery vehicles by forming inclusion complexes with end-functionalized PEG.

1. Introduction

In recent years, hollow spheres have emerged as an intriguing nanostructure due to the properties of low density, high specific surface area and large cavity volume (Zou, Wu, & Shen, 2008). As nanocarriers, they have a wide range of applications in different fields, such as catalysis (Mihalcik & Lin, 2008; Zhao, Zhang, Li, Zhang, & Han, 2009), controlled drug delivery (Ruiz-Hernandez et al., 2007; Zhu et al., 2005), adsorption and separation (Wang, Wang, Wang, Cai, & Zhang, 2008; Zhu & Fujiwara, 2007). Up to now, their synthesis are often relied on templating approaches, including the hard (e.g. inorganic, metal, and polymer particles) and soft sacrificial templates (e.g. supramolecular assemblies of surfactant and polymer) (Mitchell et al., 2002; Qi, Li, & Ma, 2002; Sun et al., 2003; Yang, Wang, & Yang, 2008). Lately, hierarchical hollow spheres with the shell composed of many kinds of nanostructure including mesochannels or nanobubbles have been focused on because of the large spectrum of potential applications endowed by their special structural characteristics. Budded mesoporous silica hollow spheres were prepared in emulsions (Wang et al., 2006). Nanotube-based hierarchical copper silicate hollow spheres were synthesized using silica colloidal spheres as chemical templates (Wang et al., 2008). Hollow silica spheres with ordered and radially oriented amino-functionalized mesochannels were constructed using anionic surfactant as the templates (Wang et al., 2009). Furthermore, supramolecular nanocapsules were also synthesized by threading of multiple cyclodextrins over PEG-modified gold nanoparticles (Wu & Li, 2009). This kind of materials has combined some advantages of ordinary molecular sieves (e.g. MCM-41) and hollow spheres. Therefore, it would be of great significance to fabricate such combinatorial structure.

In this communication, using PEG-grafted silica as template, we prepared a novel hierarchical structure of hollow spheres with α-CD nanotube assembled shells. Supramolecular nanotubes that formed by self-assembly of α-cyclodextrins have a special function of molecular recognization with PEG (Ikeda, Okumura, Shimomura, Ito, & Hayakawa, 2000). Liner PEG formed inclusion complex with α-CD nanotubes at room temperature and dissociated from α-CD nanotubes with increasing the temperature, which may enable the nanospheres as promising target drug delivery vehicles by inclusion with end-functionalized PEG.

2. Experimental

2.1. Materials

α-Cyclodextrin (α-CD, 98%), 2,2,6,6-tetramethyl-1-piperidineoxyl (TEMPO), N-hydroxysuccinimide (NHS) and N,N-dicyclohexylcarbodiimide (DCC) were purchased from Sigma. Tetraethoxysilane (TEOS) and (3-aminopropyl)triethoxysilane (APS, 98%) were ordered from Alpha. Monomethoxyl poly (ethylene glycol) (CH_3O–PEG_{114}–OH) (M_n = 5000 and PDI = 1.05) and bis-(trimethoxysilylpropyl) amine (BTMOSPA, 90%) were purchased from Fluka. Maleic anhydride (MAH, 99.5%) was of analytic

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grade and recrystallized from chloroform before use. Ammonium hydroxide (28%), ethylene diamine (99%), and all other reagents were of analytic grade and used without further purification. Milli-Q water (18 MΩ) was used for the aqueous solutions.

2.2. Characterization

^{1}H NMR, ^{13}C NMR and two-dimensional nuclear overhauser effect (2D NOE) spectra were recorded on a Varian UNITY-plus 400 spectrometer at room temperature. Transmission electron microscopy (TEM) measurement was conducted using a Philips T20ST electron microscopy at an acceleration voltage of 200 kV. Field emission scanning electron microscope (FESEM) was performed on a JEOLJSM-6700F field emission scanning electron microscope. Fourier transform-infrared (FTIR) spectroscopy of the samples was conducted at room temperature with a KBr pellet on a VECTOR-22 (Bruker) spectrometer ranging from 400 to 4000 cm^{-1}.

2.3. Preparation of modified α-cyclodextrin (MAH-α-CD)

MAH-α-CD was synthesized according to the literature method (Liu & Fan, 2002). Typically, α-CD (1.46 g, 1.5 mmol) and maleic anhydride (1.47 g, 15 mmol) were dissolved in dry DMF (9 mL) and then stirred for 10 h at 80 °C. The reaction mixture was then cooled to room temperature and poured into an excess of chloroform. The resulting precipitates were filtered, washed by acetone for three times, and dried in vacuum at 80 °C for 3 days with a yield of 73%.

2.4. Synthesis of mPEG-succinimidyl carbonate (SCM-PEG)

Carboxymethylated polyethylene glycol (CM-PEG) (5 kDa) was previously prepared quantitatively by the oxidation of corresponding mPEG with TEMPO as catalysis, hypochlorite as regenerating oxidant and water as solvent. Then CM-PEG was activated to SCM-PEG according to the reported method (Yin, Kang, & Bae, 2009). CM-PEG (5 g, 1 mmol) was dissolved in 30 mL of dried methylene chloride. To this solution was added N-hydroxysuccinimide (138 mg, 1.2 mmol) and stirred in the ice-water bath for 1 h. N, N-dicyclohexylcarbodiimide (216 mg, 1.05 mmol) was subsequently added to this solution. The reaction mixture was allowed to stand overnight at room temperature. The dicyclohexyl urea was removed by filtration and the succinimidyl ester of CM-PEG (SCM-PEG) was precipitated with cold ether and purified by recrystallization from isopropyl alcohol and dried in vacuum with a yield of 96%. The ^{1}H NMR spectrum of the SCM-PEG is as follows: δ 3.38 (3H, PEG CH_3O–CH_2–CH_2–O–); 3.69 (multi H, PEG backbone –OCH_2CH_2–); 2.71 (4H, –CO–CH_2–CH_2–CO– of NHS); 4.15 (2H, PEG–O–CH_2COO–NHS).

2.5. Synthesis of PEG-grafted silica nanoparticles (SiO_2–PEG)

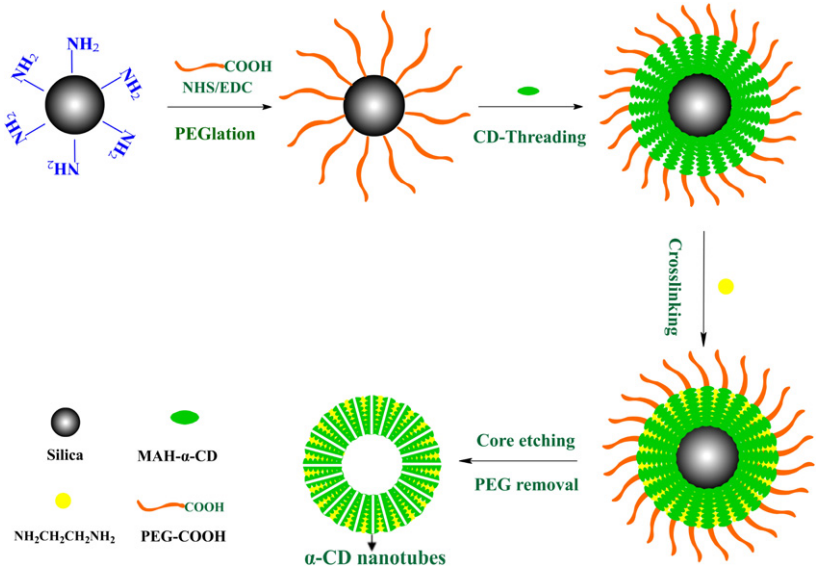
APS was used to prepare silica particles pre-coated with primary amine groups (SiO_2–NH_2 nanoparticle) according to a modified Stöber method (Park, Kim, Kim, & Kim, 2009). Then SCM-PEG with a molecular weight of 5×10^3 g/mol was grafted onto the SiO_2–NH_2 particles via ultrasonication. In a typical experiment, 10 mg SCM-PEG was added into 1 mL of the pure pre-coated SiO_2–NH_2 dispersion ultrasonically. Then the reaction was allowed to continue for 3 h. The resulting particles were separated from excessive SCM-PEG by three cycles of centrifugation and redispersion in methanol (with 0.1 mM $NaHCO_3$).

2.6. Preparation of hollow spheres with α-CD nanotube assembled shell

A homogeneous dispersion of SiO_2–PEG particles (0.1 mg/mL) was prepared and subsequently a solution of MAH-α-CD (4 mg/mL) was added dropwise under vigorous stirring. Then the mixed solutions were immersed into an ultrasonic bath for 10 min, followed by keeping at room temperature for 12 h under gentle stirring. Then, ethylene amine was added to crosslink adjacent polypseudorotaxanes. Purified nanoparticles with a silica core and a cross-linked polypseudorotaxane shell were prepared by three cycles of centrifugation and redispersion in neutral water. The inner silica templates were etched by wt. 10% hydrofluoric acid (HF). Finally, hollow spheres with α-CD nanotube assembled shell were successfully obtained by extraction of included PEG via dialysis against neutral water at 50 °C for a week.

3. Results and discussion

The use of silica as sacrificial template is an effective method to construct hollow spherical nanoparticles (Lou, Archer, & Yang, 2008). Linear polymer chains are always employed to prepare CD-



Scheme 1. Synthesis of hollow spheres with α-CD nanotube assembled shells.

based nanotubes (Harada, Takashima, & Yamaguchi, 2009). Herein, PEG-grafted silica (SiO_2–PEG) was adopted as template to fabricate hollow spheres with α-CD nanotube assembled shells. The whole project was carried out through four steps (Scheme 1): (1) PEGlation: N-succinimidyl esters of monomethoxy poly(ethylene glycol) carboxylic acids (SCM-PEG) were grafted onto APS-modified silica nanoparticles through amide bond formation; (2) α-CD threading: α-CDs modified by maleic anhydride (MAH-α-CD) were threaded onto grafted PEG chains, resulting in tubular polypseudorotaxanes; (3) crosslinking: adjacent polypseudorotaxanes were fixed by crosslinking with ethylene amine; (4) template removing: the inner silica templates were etched by HF and the included PEG in α-CD nanotubes were eliminated by heating.

Monodisperse APS-modified silica microspheres (SiO_2–NH_2) were prepared from the hydrolysis of siloxane TEOS via a sol–gel process with the successive coating of APS to incorporate reactive amino groups on the surface. SCM-PEG terminated with reactive N-succinimidyl ester groups was obtained by activating the carboxylic acid groups of as-synthesized carboxymethylated polyethylene glycol with N-hydroxysuccinimide (NHS) and N, N-dicyclohexylcarbodiimide (DCC). N-succinimidyl group with high activity can react quickly with primary amine group. Therefore, SCM-PEG, which possess N-succinimidyl group could be efficiently grafted onto the silica surface through the reaction between the N-succinimidyl group of SCM-PEG and the primary amine group of the silica. The resulting PEG-grafted silica nanoparticles (SiO_2–PEG) are uniform spherical shapes wrapped with a layer of collapsed polymer chains observed from the TEM image in Fig. 1(B). Meanwhile, compared with the bare SiO_2–NH_2 nanoparticles, the SiO_2–PEG nanoparticles also display bigger average diameter because of the PEGlyation.

The FTIR analytical results in Fig. 2 give additional supports to the successful grafting of PEG onto the silica surface. The appearance of a broad absorption band at 3700 cm^{-1} and two strong absorption bands at 1642 and 1525 cm^{-1} are characteristic absorption of amide bond that formed by N-succinimidyl ester groups of PEG and amino groups of APS-modified silica (Marla, Matthew, Yang, & Russell, 2010). The peak at 2933 cm^{-1} is assigned to the stretching vibration of CH_2CH_2 group in the grafted PEG chains (Shi, Matsusaki, & Akashi, 2009).

In order to crosslink adjacent α-CD nanotubes, hydroxyl groups of α-CDs were modified into vinyl carboxylic acid groups by maleic anhydride (MAH). ^1H NMR and ^{13}C NMR spectra of MAH-α-CDs are shown in Fig. 3. ^1H NMR (D_2O)/ppm (Fig. 3(A-b)): Multiple resonances appear at 3.32–3.79 ppm are chemical shifts of H_2–H_6 protons of α-CDs, and 4.83 ppm is ascribed to the H_1 proton. Compared with ^1H NMR spectrum of pure α-CD in Fig. 3(A-a), new peaks at 6.10, 6.40 ppm appear, which are attributed to the protons of maleic anhydride, corresponding to b,and d, respectively. ^{13}C NMR (D_2O)/ppm (Fig. 3(B)): aside from related characteristic carbon absorption of α-CDs ranging from 60 to 101 ppm, absorption peaks at 170, 133, 166, 170 ppm are belonging to the number 7–10 carbons of MAH, respectively. Both the ^1H NMR and the ^{13}C NMR spectra of MAH-α-CD reveal that α-CDs had been successfully modified by MAH. According to the ^1H NMR integral areas, H_1 of α-CD and b of MAH in Fig. 3(A-b), the calculated MAH-modification efficiency is 45%, which is high enough to ensure the following substantial crosslinking of adjacent α-CD nanotubes.

CDs are one of the most prominent host compounds in supramolecular chemistry. Their torus-shaped geometry with a cavity can include guest molecules ranging from small organic/inorganic compounds to polymers (Wenz, Han, & Müller, 2006). When linear PEG is mixed ultrasonically with α-CDs, inclusion complexes (ICs) with tubular structure are formed because of the hydrophobic and van der Waals interactions, usually named polyrotaxanes/polypseudorotaxanes (Li, Ni, Zhou, & Leong, 2003).

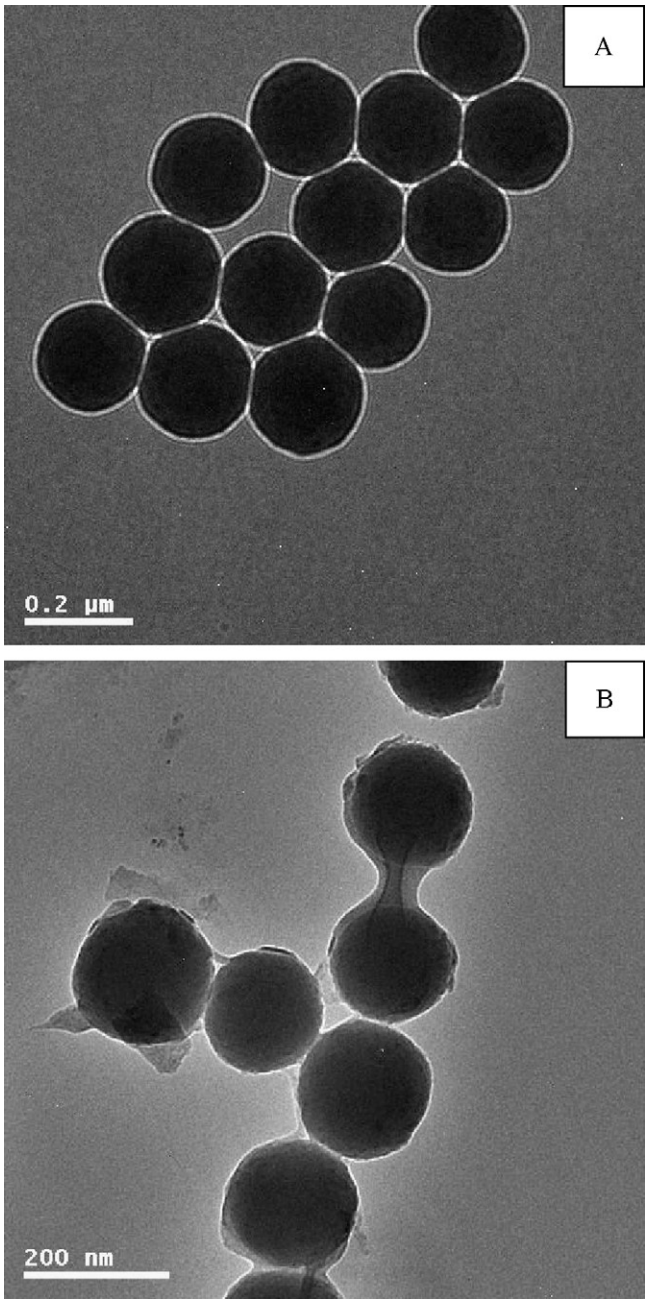


Fig. 1. TEM images of SiO_2–NH_2 (A) and SiO_2–PEG nanoparticles (B).

By mixing two solutions of MAH-α-CDs and SiO_2–PEG nanoparticles ultrasonically, modified α-CDs were threaded onto the grafted PEG chains, forming polypseudorotaxanes. Light shell with thickness of 15 nm which is ascribed to the polypseudorotaxanes that formed between MAH-α-CDs and the grafted PEG can be clearly seen around the dark silica core from the TEM image in Fig. 4(A). Furthermore, the FESEM results in Fig. 4(B) demonstrate that the as-prepared products are uniform spheres but of rough surface all over the whole spheres because of the rigid feature of the polypseudorotaxanes (Sabadini, Cosgrove, & Taweepreda, 2003).

The tubular structure of polypseudorotaxanes was verified by the 2D NOE spectrum in D_2O (Fig. 5). Correlation peaks between the protons H_3 and H_5 of inner annular α-CD and the ethylene protons (CH_2) of PEG chains indicate that inclusion complexes of polypseudorotaxanes are formed between MAH-α-CDs and PEG (Liu et al., 2009).

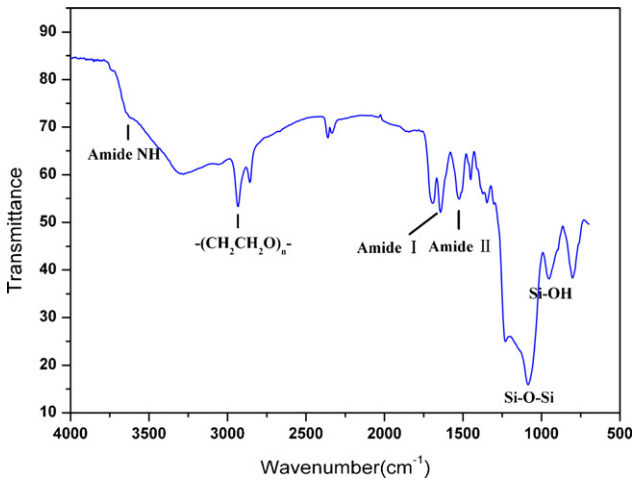


Fig. 2. FTIR spectrum of SiO_2–PEG nanoparticles.

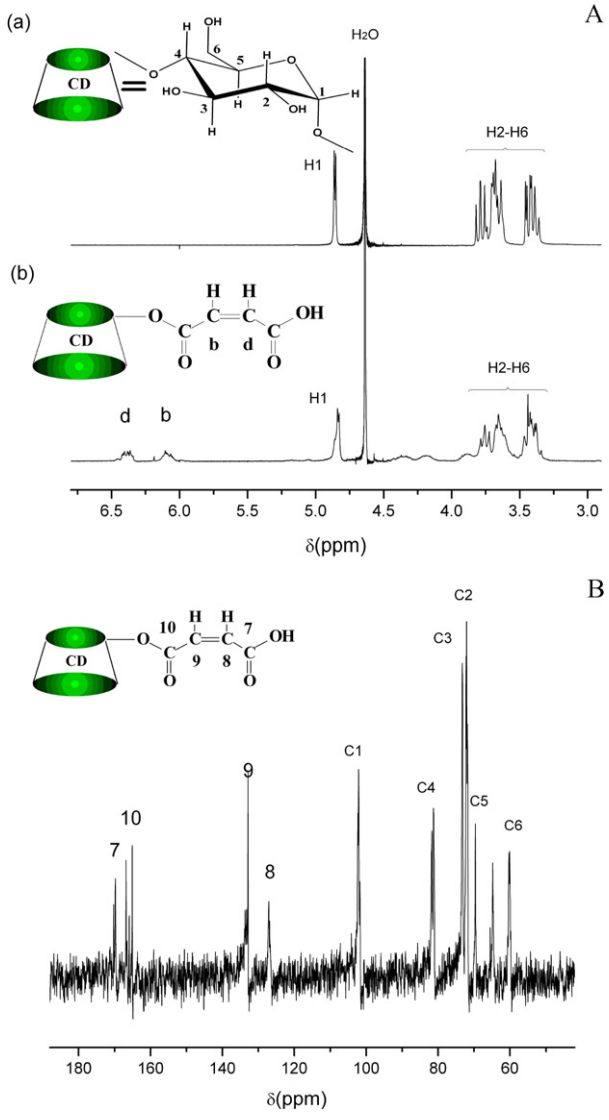


Fig. 3. ^{1}H NMR spectra of pure α-CD (A-a) and MAH-α-CD (A-b) in D_2O, and ^{13}C NMR spectrum of MAH-α-CD (B) in D_2O at room temperature.

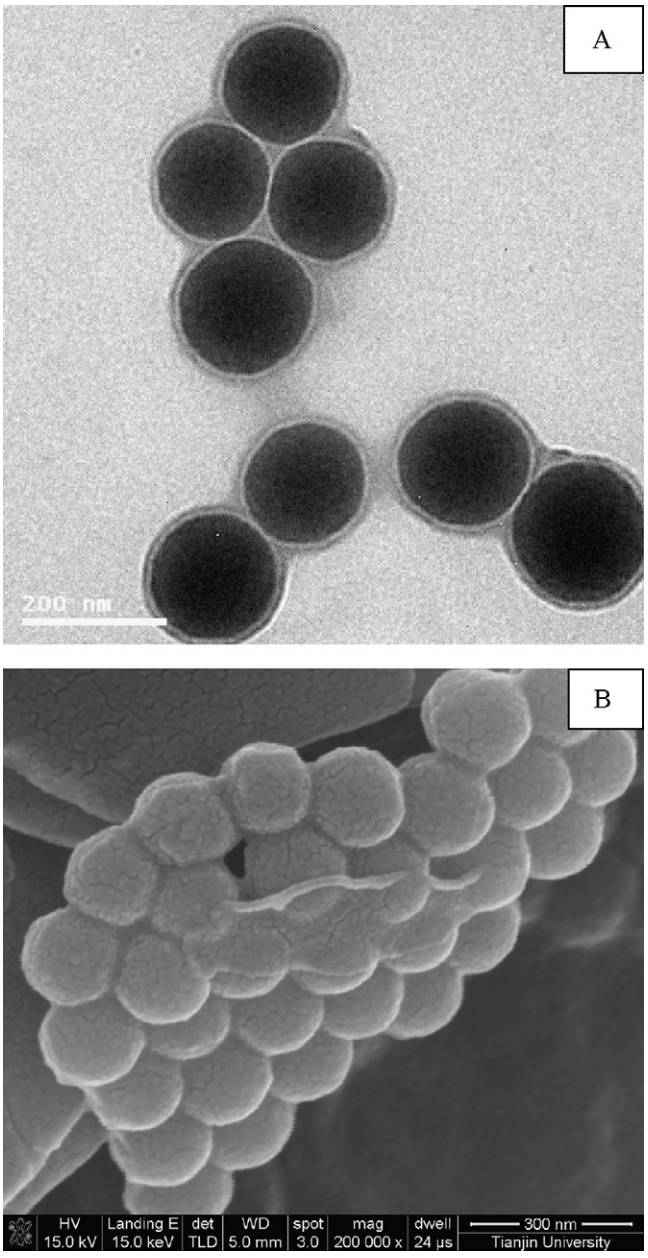


Fig. 4. TEM (A) and EF-SEM (B) images of SiO_2–polypseudorotaxane nanoparticles.

Hydroxyl groups of α-CDs have been modified into vinyl carboxylic acid groups by maleic anhydride (MAH). The carboxylic acid groups were then activated by NHS with DCC and then conjugated with ethylene diamine for the purpose of crosslinking adjacent α-CD nanotubes. Through amide formation, adjacent α-CD nanotubes were firmly crosslinked, leading to substantial network of α-CD nanotubes. After template removal, hollow sphere with crosslinked α-CD nanotube assembled shell was obtained. Firstly, the inner silica core was etched by 10 wt.% HF, giving a large cavity volume of hollow sphere. Secondly, PEG chains that included in the α-CD nanotubes were removed by heating and dialysis. TEM image of the resultant hollow sphere is shown in Fig. 6. Monodisperse hollow sphere with white center and dark shell could be clearly seen. The thickness of the shell is about 12 nm, which is very coherent with the polypseudorotaxanes that formed by MAH-α-CDs and the grafted PEG (light ring area with thickness of 15 nm in Fig. 4(A)). The tubular structure of α-CD nanotubes could be preserved in good condition during template-removal process because adjacent α-CD

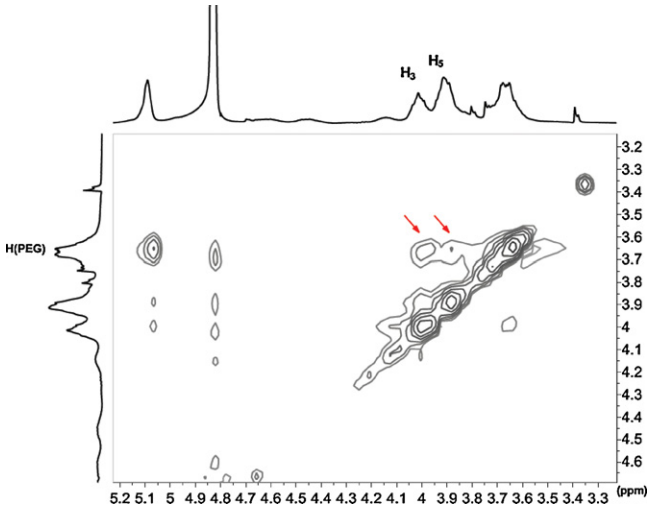


Fig. 5. Portion of 400 MHz NOESY spectrum of SiO_2–polypseudorotaxane nanoparticles in D_2O at room temperature.

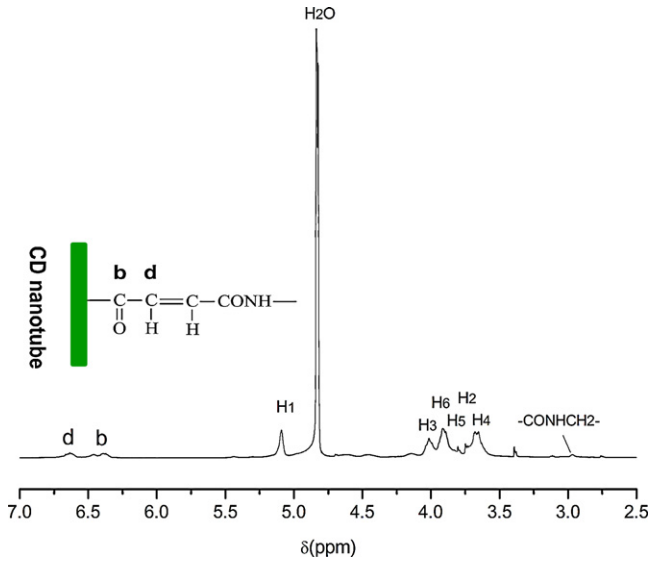


Fig. 7. ^1H NMR spectrum of hollow spheres with α-CD nanotube assembled shells.

nanotubes have already been firmly fixed by crosslinking. Nevertheless, the diameters of hollow spheres shrink a lot compared with that of the nanoparticles before etching as measured by the TEM measurement. It is possible that the shell of the crosslinked α-CD nanotubes is not dense enough to withstand the contraction when the solid silica support is removed.

Fig. 7. displays ^1H NMR spectrum of the final hollow spheres (freeze drying followed by dispersing in D_2O). Besides the typical absorptions of α-CDs, we can also find that these peaks were broadened compared with pure MAH-CD because of the restriction of molecular motion by the cross-linking and chain interlocking. And no typical signal of PEG chains is found in the ^1H NMR spectrum, indicating that included PEG chains have been removed completely after dialysis against neutral water at 50 °C for 1 week.

Folate has been vastly employed as targeting moiety of various anticancer drug-delivery agents to avoid their non-specific attack on normal tissue as well as to increase their cellular uptake at target tumor cells (Lu & Low, 2002). Folate-conjugated polymer micelles also have been widely researched for tumor treatment (Zhao, Duong, & Yung, 2010). Since α-CD nanotubes have a function of molecular recognization with PEG, the as-synthesized hollow nanospheres with α-CD nanotube assembled shell could form inclusion complexes with end-functionalized PEG, such as folate-functionalized PEG, making them promising target drug delivery vehicles for tumor therapy. Endeavors to explore their applications are actually under progress.

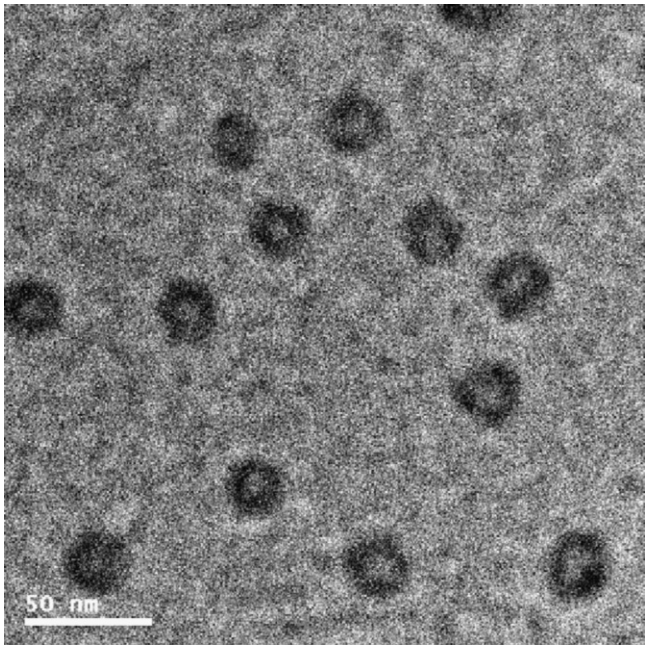


Fig. 6. TEM image of hollow spheres with α-CD nanotube assembled shells.

4. Conclusions

In summary, a novel hierarchical hollow sphere with shell composed of radially aligned and crosslinked α-CD nanotubes was constructed using PEG-grafted silica as template. The products were composed of intact and dispersed hollow spheres with uniform shell thickness of 12 nm as confirmed by transmission electron microscopy (TEM) measurement. This hollow nanosphere is promising to be used as target drug delivery vehicle.

Acknowledgements

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