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ARTICLE TYPE

Facile synthesis of well-defined cyclodextrin-pendant polymer *via* ATRP for nanostructure fabrication

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Preparation of *mono*-vinyl substituted cyclodextrin (CD) monomers are particularly challenging due to the presence of numerous equally reactive hydroxyl groups on CD, which limits the synthesis of CD-pendant polymers with well-defined structure, high CD density and flexible functionality. In this work, a new *mono*-methacrylate substituted cyclodextrin (MCD) was successfully prepared in a mild reaction condition. Thus, well-defined hydrophilic diblock copolymer poly(ethylene glycol)-*b*-poly(cyclodextrin) (PEG-*b*-PCD) can be easily synthesized *via* atom transfer radical polymerization of MCD from poly(ethylene glycol) macroinitiator. The block copolymer was able to include a variety of guest molecules and self-assembled into advanced nanostructures due to the synergistic effect of CD moieties. By altering the type of guest molecules and the ratio of PEG-*b*-PCD to guests, the self-assembled nanostructures showed different size and morphology. The strategy developed in this study provides a facile and general method for the design of nanostructures based on well-defined CD-pendant polymer, and these nanostructures may find applications in the fields of drug and gene delivery, self-healing materials, catalysts and coatings.

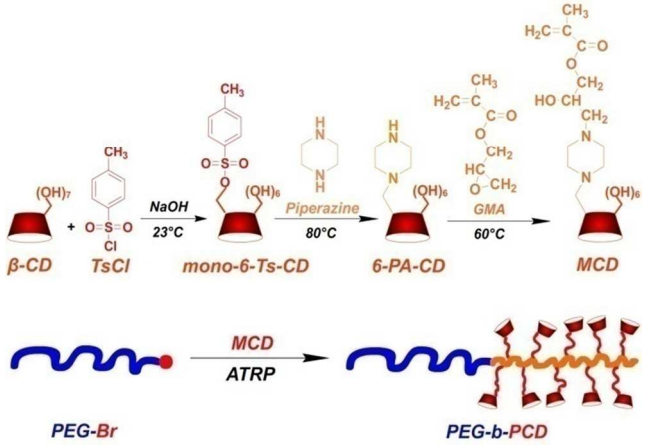
Introduction

Cyclodextrin-based polymers, the polymers composed of multiple cyclodextrin (CD) rings threaded or tethered on a polymer chain, are able to bind substrates more efficiently than single CD molecule, due to the cooperation of adjacent CD moieties.[1, 2] In recent years, they have inspired interesting developments of novel supramolecular structures [3-7] and potential biomedical applications.[8-11] Polymers with pendant CD groups on the side chains often have improved physicochemical properties and possess macromolecular hosts with multiple binding sites. Host-guest polymer assemblies across nano, micro, and macro-scales originated from these CD-pendant polymers have aroused many interests in the fields of nanostructure fabrications, pharmaceutics and biomedicine.[12-14] Jiang and coworkers prepared a hydrophobic linear poly(*tert*-butyl acrylate) with pendant adamantyl groups (P*t*BA-ADA), and a hydrophilic linear poly(glycidyl methacrylate) with β-CD on the side chain (PGMA-CD). Micelles were formed by the inclusion complexation between β-CD and ADA.[15] Zhang and coworkers synthesized a kind of highly efficient nanomedicines, which was fabricated by direct self-assembly of the indomethacin (IND) and β-CD-conjugated polyethyleneimine (PEI-CD).[8] Fan and Tian prepared β-CD polymer brushes based on polycarbosilane particles. The CD-containing polymer brushes possess molecular inclusion capability, and can control the release behaviors of two model drugs.[16, 17]

Generally, approaches to obtain CD-pendant polymers can be classified into two groups. One is carried out by substitution reaction between CD derivatives and the target polymers.[18-21] The other is the direct polymerization of CD-based monomers alone or together with other monomers.[15, 17, 22, 23] For the first strategy, it is difficult to achieve high grafting density because of steric crowding of reactive sites by already modified CDs. Alternatively, controlled radical polymerization of CD monomer is a powerful strategy to achieve CD-pendant polymer with well-defined structure, high CD density and flexible functionality. However, the preparation of *mono*-vinyl substituted CD monomers is particularly challenging, due to the presence of numerous equally reactive hydroxyl groups on the CD. To our knowledge, various CD monomers have been described, but most of them are *multi*-vinyl substituted monomers.[24] A common approach to achieve *mono*-vinyl substituted CD is to prepare *mono*-tolylsulfonyl-CD (Ts-CD) first, then convert the tolylsulfonyl group into vinyl group by a series of reactions. In some cases, Ts-CD is derived into alkyl diamine substituted CD (DA-CD) and then CD monomer is produced by ring-opening reaction between glycidyl methacrylate (GMA) and DA-CD in a mild condition. However, a mixture of *multi*- rather than *mono*-GMA substituted CD was usually obtained, since the primary amino group on the DA-CD can simultaneously react with two GMA molecules.

To improve this convenient approach and obtain *mono*-vinyl substituted CD monomer, a facile method was developed in this

study. By only replacing alkyl diamine with piperazine, a new *mono*-methacrylate substituted CD monomer was easily prepared in a mild reaction condition (Scheme 1). Atom transfer radical polymerization (ATRP) of the CD monomer was conducted from poly(ethylene glycol) macroinitiator (PEG-Br) and the reaction condition was studied in detail. Then the self-assembly behavior of the block copolymer was evaluated *via* host-guest interactions between CD moieties and a variety of guest molecules. Numerous advanced nanostructures with different size and morphology were obtained. The strategy developed in this work provides a facile and general method for the design of well-defined nanostructures based on CD-pendant polymers, which have potential applications in nano-fabrications, drug delivery, self-healing materials, and coatings.



Scheme 1. Synthesis of *mono*-methacrylate substituted cyclodextrin (MCD) and atom transfer radical polymerization of MCD from PEG-Br initiator.

Experimental

Materials

β-cyclodextrin (β-CD) was purchased from Sinopharm Chemical Regent Co., Ltd and recrystallized twice from water. Glycidyl methacrylate (GMA, Fluka, ≥97%) and 2-(dimethylamino) ethyl methacrylate (DMAEMA, Aldrich, 98%) was purified by passing through a basic alumina column. CuCl (Tianjin, P. R. China, AR) was purified by dissolving in concentrated HCl, precipitating in water, washing with ethanol and ethyl ether for three times, and then drying under vacuum. $CuCl_2$ (Tianjin, P. R. China, AR) was baked at 120˚C to remove the crystal water. Pyrene (Fluka, ≥97%) was recrystallized from ethanol twice. Piperazine hexahydrate (Alfa Aesar, 98%), 2-bromoisobutyryl bromide (BriBB, Aldrich, 98%), *N,N,N′,N″,N‴*-pentamethyldiethylenetriamine (PMDETA, Aldrich, 99%), bipyridine (bpy) (Sinopharm Chemical Reagent Co., Ltd), Rhodamine B (RhB, Solarbio), Poly(*D,L*-lactide) (PLA, M_n=10,000, Shandong Institute of Medical Instrument), anhydrous dimethyl formamide (DMF, Aldrich, 99.8%), tetrahydrofuran (THF, Tianjin, P. R. China, AR) and *N*-methyl-2-pyrrolidone (NMP, Tianjin, P. R. China, AR) were used without further purification. *Mono*-6-(*p*-tolyl sulfonyl)-β-cyclodextrin (*Mono*-6-Ts-CD) was synthesized according to the reference[25] as described in ESI. Poly(ethylene glycol) macroinitiator (PEG-Br) was synthesized by the esterification of poly(ethylene glycol) monomethyl ether (PEG, M_n=5,296 based on ^{1}H NMR result) and BriBB according to the literature.[26] 1-Adamantylmethyl methacrylate (AdMMA) and poly(1-adamantylmethyl methacrylate) (PAdMMA) are synthesized according to the literature.[27] ADA-PDMAEMA is synthesized by ATRP of DMAEMA from 1-adamantyl 2-bromoisobutyrate (ABiB) initiator as described in ESI.

Synthesis of 6-piperazine-β-cyclodextrin (6-PA-CD)

Mono-6-Ts-CD (9.5 g) was added to 15 g of molten piperazine and reacted at 80˚C for 24 h. After the reaction was completed, the mixture was diluted by water and precipitated into acetone. The product was dissolved in water and poured into acetone several times for the removal of unreacted piperazine and then recrystallized from water. The sample obtained was dried under vacuum to give a white powder (6.5 g, 73%). ^{1}H NMR (D_2O, ppm) (Fig. S4†): 5.1 ppm (7 **H**, C1-**H** on CD rings), 2.5-3.0 ppm (8 **H**, -N(C**H**$_2$C**H**$_2$)$_2$N-). ESI-MS (Fig. S5†): m/z 1203. 6, calcd 1203.10.

Synthesis of *mono*-methacrylate substituted cyclodextrin monomer (MCD)

6-PA-CD (6.015 g, 5 mmol) was dissolved in 62.5 mL of dry DMF and then excess GMA (2 mL, 15 mmol) was added. After purging with Ar for 30 min, the mixture was stirred at 60°C for 24 h. The product was precipitated in excess acetone, recovered by filtration, washed by acetone for several times and dried under vacuum (6.7 g, 99%). ^{1}H NMR (DMSO-d_6, ppm) (Fig. S6†): 6.1 ppm (1 **H**, one proton of C**H**$_2$=), 4.8 ppm (7 **H**, C1-**H** on CD rings). ESI-MS (Fig. S7†): m/z 1345.8, calcd 1345.25.

Preparation of PEG-*b*-PCD diblock copolymer *via* ATRP

CuCl (0.0025 g, 0.025 mmol), $CuCl_2$ (0.0017 g, 0.0125 mmol) and PMDETA (15.66 μL, 0.075 mmol) were dissolved in dry DMF (0.5 mL) in a 10 mL two-neck flask and degassed with three freeze-pump-thaw cycles. A solution of PEG-Br (0.1376 g, 0.025 mmol) and MCD (1.0088 g, 0.75 mmol) in dry DMF (2.0 mL) was added into the solution through a syringe under Ar atmosphere, and the mixture was degassed with another two freeze-pump-thaw cycles. The reaction mixture was then stirred at 90°C for 48 h. The polymer was further purified by dialysis against deionized water for 48 h and recovered by lyophilization.

Preparation of complexes by host-guest interactions between PEG-*b*-PCD diblock copolymer and guest molecules

Complexes based on PEG-*b*-PCD diblock copolymer were prepared by dialysis method. For RhB guest, a mixture of the PEG-*b*-PCD copolymer and RhB molecules was dissolved in water and stirred over night. Then the mixture was transferred into dialysis bags (MWCO 7000 Da) and dialyzed against deionized water for 60 h. For ADA-PDMAEMA and PLA polymers, mixtures of the PEG-*b*-PCD copolymer and guest polymers dissolved in DMSO were stirred at 50˚C over night, and then dialyzed against deionized water for 48 h at room temperature for complexation. For PAdMMA polymer, a mixture of the PEG-*b*-PCD copolymer and PAdMMA polymer dissolved in THF/NMP (1:1, v/v) was stirred at 50˚C over night, and then dialyzed against deionized water for 48 h at room temperature for complexation.

Characterization

^{1}H NMR analysis was carried out on a Varian UNITY-plus 400M spectrometer. The mass spectrum measurement was performed on 6510 Q-TOF LC/MS instrument. The apparent molecular weight and polydispersity of the PEG-*b*-PCD diblock copolymers were determined by gel permeation chromatography (GPC) with a CoMetre 6000 LDI pump and a Schambeck SFD GmbH RI2000 refractive index detector. DMF with 0.01 M LiBr was used as mobile phase at a flow rate of 1 mL min^{-1}. Polymer solution was injected through PLgel 10 μm 10^3 Å and 10^4 Å columns at 70°C. Poly(methyl methacrylate) calibration kit was used as the calibration standard. The size and size distribution of complexes were measured by a Malvern Zetasizer Nano ZS instrument at 25°C. Transmission electron microscopy (TEM) images were obtained on a Tecnai G2 20 S-TWIN electron microscope equipped with a Model 794 CCD camera. All TEM images were obtained at an operating voltage of 200 kV. Atomic force microscopy (AFM) images were collected on a Nanoscope V atomic force microscope (Digital Instruments Inc.). Using pyrene as a fluorophore, steady-state fluorescence spectra were recorded on HITACHI F-4500 fluorescence spectrophotometer. β-CD or polymer solutions of various concentration containing pyrene (6.0×10^{-7} M) were incubated at 50°C overnight and subsequently allowed to cool to room temperature. The excitation and emission slit opening were 10 and 2.5 nm, respectively. The excitation wavelength was set at 335 nm. All tests were carried out at 25°C with scanning rate setting at 60 nm min^{-1}. Competitive inclusion behaviour of the complexes based on PEG-*b*-PCD was measured by UV-*vis* spectroscopy from 350 to 650 nm. Methyl orange (MO) (4×10^{-5} M) was used as a competitive guest molecule and dissolved in a PBS solution (0.01 M，pH 5.8) or PBS solutions containing free β-CD, PEG-*b*-PCD or complexes with same CD concentration, respectively.

Results and discussion

Polymerization of PEG-*b*-PCD block copolymer

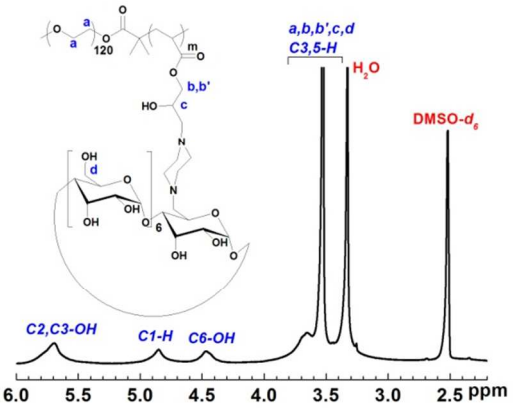


Fig. 1 ^{1}H NMR spectrum of PEG-*b*-PCD diblock copolymer in DMSO-d_6.

Table 1 ATRP of MCD using CuCl/$CuCl_2$/PMDETA as catalyst system and DMF as solvent.

Entry	$[M]_0$ [a] (mol L^{-1})	Cu^{2+}/Cu^{+} (mol%)	Time(h)	DP_n [b]	Conversion of monomer (%)	*f* (%) [c]	M_n [d]	PDI (M_w/M_n) [d]
1	0.20	0	48	6.2	31	91	25080	1.12
2	0.35	0	48	16.9	48	72	34875	1.24
3	0.35	50	48	12.0	34	79	28723	1.15
4	0.35	100	48	13.9	40	78	27232	1.15
5	0.30	0	24	13.4	45	82	31128	1.11
6	0.30	50	24	11.2	37	84	27898	1.17
7	0.30	100	24	11.4	38	95	28323	1.15

[a] $[M]_0$ represents monomer concentration at the beginning of the reaction. [b] The experimental degree of polymerization calculated by ^{1}H NMR. [c] *f*=initiator efficiency={(Weight of polymer/Molecular Weight of polymer calculated by NMR)/molar of initiator} × 100% . [d] M_n, M_w/M_n of the PEG-*b*-PCD measured by GPC.

On the basis of the convenient method mentioned above, a new CD monomer was synthesized. Firstly, *mono*-6-Ts-CD was successfully prepared to ensure single chain derivations in the following steps. It derived into a single-piperazine substituted CD (6-PA-CD) by reacting with piperazine. Subsequently, methacrylate group was introduced into the CD after a ring-opening reaction of GMA by 6-PA-CD. Since the secondary amine on 6-PA-CD can only react with one epoxy group, *mono*- rather than *multi*-GMA substituted CD (MCD) was obtained.

ATRP is one of the frequently used controlled/'living' polymerization method to prepare well-defined polymers with various topology architectures (linear, branched, hyperbranched, stars, etc.) because of its tolerance to a wide range of monomers such as styrenes, acrylates, and methacrylates including numberous functional monomers.[28, 29]. Based on a copper hilide/nitrogen based ligand catalyst, a rapid dynamic equilibration between a minute amount of growing free radicals and a large majority of the dormant species can be established, and thus the controlled polymerization is achieved. In this study, well-defined PEG-*b*-PCD block copolymers was synthesized by ATRP of MCD monomer from PEG-Br, using CuCl/$CuCl_2$/PMDETA as catalyst system and DMF as solvent. ^{1}H NMR was first employed to analyze the structure of the PEG-*b*-PCD block copolymer (Fig. 1). The signal at 4.8 ppm (signal *C1-H*) corresponds to the protons on C1 in CD moieties. The peak at about 3.4-3.9 ppm represents the methylene protons in PEG, the protons on C3 and C5 in CD moieties and the methylene protons on GMA groups. ^{1}H NMR analysis result confirms the successful polymerization of MCD on the PEG chains. Table 1 summarizes the polymerization results under a variety of conditions. GPC results show the evidence for the controlled nature of the polymerization of MCD (**Fig. S8**†). As displayed in Entry 1 and 2, when polymerization is carried out in a condition of high monomer concentration ($[M]_0$=0.35 mol L^{-1}),

low initiator efficiency (*f*) and broad polydispersity index (PDI) are obtained, which is due to a relatively large proportion of termination. However, with the addition of external Cu^{2+} at the beginning of the polymerization, the initiator efficiency is enhanced (as shown in Entry 2 to 4 and 5 to 7) and the PDI of the copolymer decreases to less than 1.20. Therefore, the addition of external Cu^{2+} complex leads to a better control of the polymerization process. It is important that deactivation occurs quickly to prevent a high radical concentration and then termination at the beginning of the reaction. Adding Cu^{2+} to the reaction media favors the deactivation rate and suppresses the radical termination at the early stage.[30-32] Thus, the polymerization can proceed smoothly with a constant radical concentration, and well-defined polymers with low PDI can be obtained.

Fluorescence study of PEG-*b*-PCD block copolymer

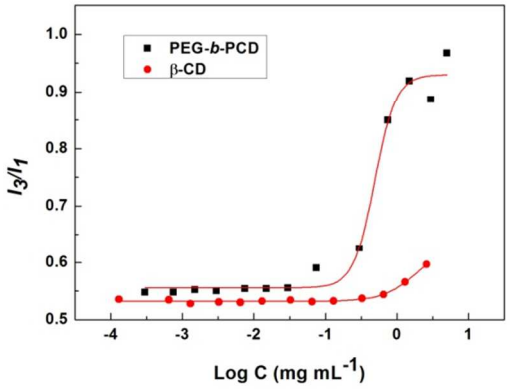


Fig. 2 Plot of I_3/I_1 as a function of the PEG-*b*-PCD and β-CD concentration. [Pyrene] = 6.0×10^{-7} M.

Fluorescence techniques have been successfully used in the study of polymeric assemblies. In this research, pyrene molecule was employed as fluorescent probe to investigate the self-assembly behavior of PEG-*b*-PCD copolymer. The intensity ratio of the third to the first vibration band of pyrene monomer emission (I_3/I_1) is employed to monitor the polarity of the environment.[33] Fig. 2 displays the influence of the block copolymer concentration and free β-CD concentration on the value of I_3/I_1. It is obvious that no significant changes of I_3/I_1 are observed in free β-CD solution, which demonstrates that pyrene molecules do not enter the apolar environment. However, the value of I_3/I_1 is significantly enhanced when the concentration of the block copolymer reaches a critical value, suggesting that pyrene molecules transfer from a hydrophilic to a more hydrophobic environment in the PEG-*b*-PCD copolymer solution. The result is attributed to the synergistic effect of CD moieties that favors pyrene molecules entering the cavity composed of several CD molecules, which indicates the block copolymer is able to bind guest molecules *via* host-guest interactions and form advanced nanostructures (self-assembled nanoparticles), such as spheres, rods, vesicles and so on.[14, 34]

Polymer assemblies driven by host-guest interactions

To further investigate the self-assembly behaviors of PEG-*b*-PCD copolymer, it was used as "host" polymer to complex with several "guest" molecules. Before inclusion study, the morphology and size of the PEG-*b*-PCD copolymer was characterized by TEM and DLS. Light gray nanoparticles can be observed in the TEM image with the average size less than 10 nm (Fig. S9†), and in aqueous solution the size of the block copolymer is about 8 nm.

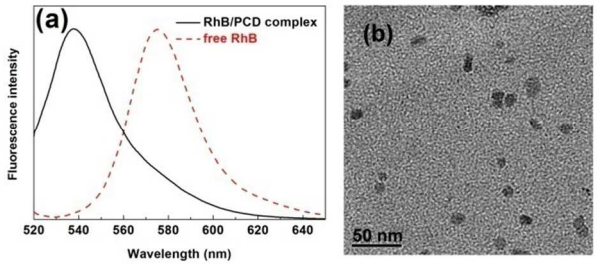


Fig. 3 Fluorescent emission spectra of RhB/PCD complex and free RhB in aqueous solution (λ_{ex} = 520 nm) (a), and TEM image of RhB/PCD complex in aqueous solution (b). Scale bar: 50 nm.

Rhodamine B (RhB) was first used as a guest molecule to evaluate the inclusion capability of PEG-*b*-PCD block copolymer. The complex (named as RhB/PCD) was prepared with the molar ratio of RhB to CD moiety as 2:1. The fluorescent emission spectra of RhB/PCD complex and free RhB in aqueous solution were investigated and the results are shown in Fig. 3a. Comparing with that of free RhB, the fluorescence of the RhB/PCD complex displays an obvious blue shift from 575 to 538 nm, which indicates RhB has successfully included into the cavity of CD. The morphology and size of the RhB/PCD complex was further investigated by TEM and DLS. Irregular spheres are observed in the TEM image (Fig. 3b). Comparing to the PEG-*b*-PCD copolymer, the image contrast of the spheres is significantly enhanced, indicating the successful inclusion of RhB by PEG-*b*-PCD copolymer. DLS study displays that in aqueous solution the size of RhB/PCD complex is 41 nm.

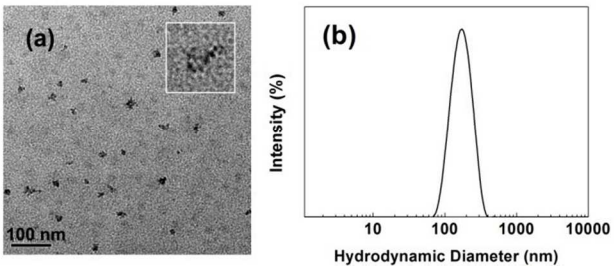


Fig. 4 TEM image (a), size and size distribution (b) of PAdMMA/PCD complex. The inset of the part is a magnified image of a specific PAdMMA/PCD complex. Scale bar: 100 nm.

Since β-CD has strong association capability with adamantane derivatives,[35] polymers with pendant adamantane and cyclodextrin groups were usually used as building block to construct micelles [15] and gels.[36, 37] In this research, poly(1-adamantylmethyl methacrylate) (PAdMMA) was synthesized and used as "guest polymer" to investigate the formation of complex. The complex named as PAdMMA/PCD was prepared with the molar ratio of adamantyl group to CD moiety as 0.5:10. During the dialysis procedure opalescence appeared immediately, indicating the formation of complex. The

shape, size and size distribution of PAdMMA/PCD complex were then characterized by TEM and DLS. TEM image in Fig. 4a shows that PAdMMA/PCD complex self-assembles into irregular shaped nanoparticles. A magnified image of a specific structure clearly displays that the nanoparticle is composed of small black spheres, which represent the nano-complex-units formed by adamantyl groups and CD moieties. The size of nanoparticles in aqueous solution was further identified by DLS analysis (Fig. 4b), giving an average D_h of 200 nm with a sharp size distribution. This indicates the uniform nanoparticles are ubiquitous in the solution.

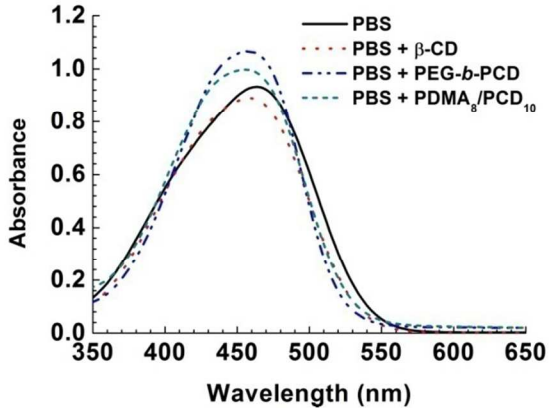


Fig. 5 UV-*vis* spectra of MO in PBS solution, or PBS solution containing β-CD, PEG-*b*-PCD or $PDMA_8/PCD_{10}$ complex.

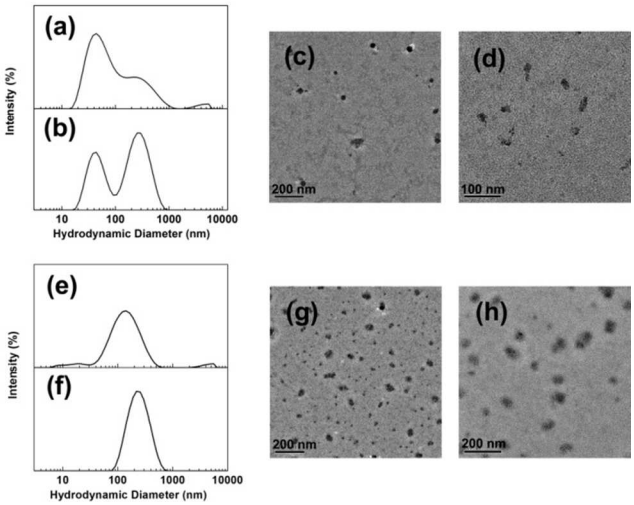


Fig. 6 Size and size distribution histograms of $PDMA_2/PCD_{10}$ complex in aqueous solution (a) and at pH 10.0 (b), TEM images of $PDMA_2/PCD_{10}$ complex in aqueous solution (c) and at pH 10.0 (d). Size and size distribution histograms of $PDMA_8/PCD_{10}$ complex in aqueous solution (e) and at pH 10.0 (f), TEM images of $PDMA_8/PCD_{10}$ complex in aqueous solution (g) and at pH 10.0 (h). Scale bars: 200 nm for (c), (g), (h) and 100 nm for (d).

PDMAEMA is a pH sensitive polymer with the pK_a at about 7.1. Above pH 7.1, the chain conformation of PDMAEMA turns to be hydrophobic, although they remain soluble.[38] On the basis of this character, a PDMAEMA homopolymer with an adamantyl group at the end of the chain was employed as the guest polymer, and pH-responsive complexes were successfully prepared with the molar ratio of adamantyl group to CD moiety as 2:10 and 8:10 (named as $PDMA_2/PCD_{10}$ and $PDMA_8/PCD_{10}$), respectively. Competitive inclusion method was firstly employed to investigate the formation of the PDMA/PCD complex. Methyl orange (MO) was used as a competitive guest molecule, since the absorption of MO would decrease when it was included by free β-CD. Fig. 5 shows the UV absorption spectra of MO in PBS solution, PBS solution containing free β-CD, PEG-*b*-PCD and $PDMA_8/PCD_{10}$ complex. Interestingly, unlike the case in free β-CD-containing solution, the absorption intensity of MO in PEG-*b*-PCD-containing solution significantly enhanced compared to that in aqueous solution. This result is attributed to the unique structure of PEG-*b*-PCD. It is well known that the absorption intensity of MO molecules increase with the significant decrease of the polarity of environment. Thus, this result indicates MO molecules transfer to a more apolar domain composed of several CD moieties due to the synergistic effect of CD moieties, which is different to the complexation with free β-CD. Compared to the PEG-*b*-PCD, the decrease of absorption intensity of MO in $PDMA_8/PCD_{10}$ complex-containing solution indicates that the formation of PDMA/PCD complex is driven by host-guest interactions between CD and adamantyl group, since MO cannot drives the adamantyl group out of the cavity of CD in the complex solution. Furthermore, the complexes were characterized by GPC as shown in Fig. S10†. Both of the complexes with two feed ratios have larger molecular weight than PEG-*b*-PCD copolymer, indicating the formation of inclusion compounds. DLS was used to monitor the pH sensitivity of the complexes in the solution. As a control, the D_h of ADA-PDMAEMA homopolymer in aqueous solution and at pH 10 is measured to be 90 nm and 15 nm, which have remarkable difference with the PDMA/PCD complexes. As shown in Fig. 6a, $PDMA_2/PCD_{10}$ shows a broad size distribution in aqueous solution, meaning that the complex is in random coil state.[37] This is due to the good solubility of both of the PEG-*b*-PCD copolymer and PDMAEMA chains in aqueous solution.The size increases with increasing the pH value of solution to 10.0. This is obviously attributed to the fact that the hydrophilic PDMAEMA turns to hydrophobic at pH 10.0, which further causes the complexes to combine each other to form larger compounds. As displayed in Fig. 6b, the peak at about 290 nm increases at pH 10.0 comparing to that in aqueous solution, demonstrating the formation of larger compounds. However, the broad size distribution reveals that the compounds are in dynamic equilibrium between association and dissociation, since the proportion of hydrophobic PDMAEMA is too low to "freeze" the compounds. The morphology of $PDMA_2/PCD_{10}$ complex was further investigated by direct observation with TEM. Images in Fig. 6c and 6d show that the complex prepared in aqueous solution is in irregular spherical shape with the average size about 30 nm, and some of them aggregate into rod-like shape at pH 10.0 due to the combination of hydrophobic PDMAEMA chains. In order to achieve complex with uniform structure, the feed ratio of ADA-PDMAEMA to PEG-*b*-PCD copolymer was increased to 8:10. Complexes with the average D_h of 107 nm are obtained in aqueous solution, and they further self-assemble into advanced nanostructures with D_h of 195 nm at pH 10.0. Moreover, the size distribution of the $PDMA_8/PCD_{10}$ complexes at pH 10.0 (Fig. 6f)

becomes narrower than that in aqueous solution (Fig. 6e). This indicates the self-assembled nanostructures are effectively frozen due to the large proportion of hydrophobic PDMAEMA, and thus, uniform nanoparticles are formed. The morphology of the $PDMA_8/PCD_{10}$ complex was also investigated by TEM. Images show that $PDMA_8/PCD_{10}$ complex forms irregular spherical particles in aqueous solution (Fig. 6g), and it further self-assembles into larger spherical particles at pH 10.0 (Fig. 6h).

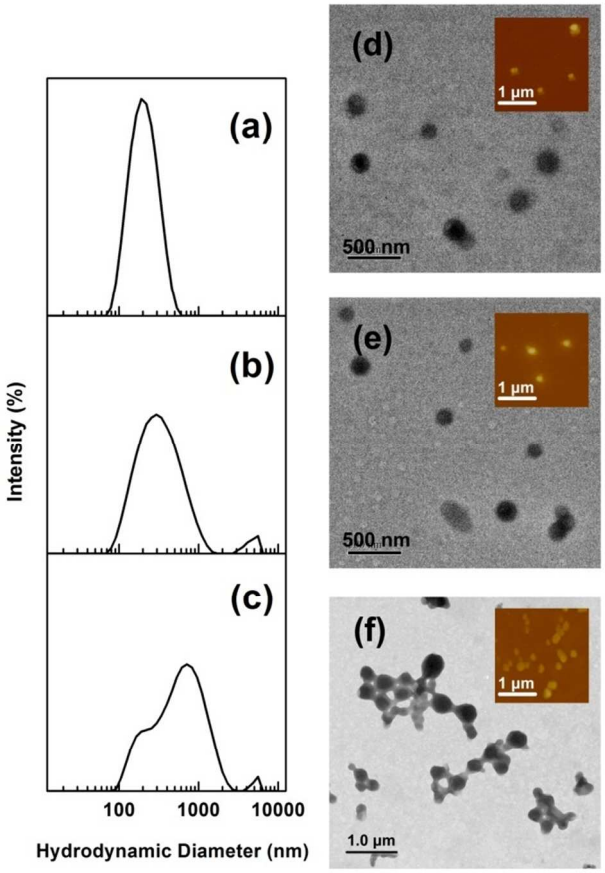


Fig. 7 Size and size distribution histograms of $PLA_{0.5}/PCD_{10}$ (a), $PLA_{1.0}/PCD_{10}$ (b) and $PLA_{2.0}/PCD_{10}$ (c) nanoparticles. TEM images of $PLA_{0.5}/PCD_{10}$ (d), $PLA_{1.0}/PCD_{10}$ (e) and $PLA_{2.0}/PCD_{10}$ (f) nanoparticles. Scale bars: 500 nm for (d) and (e), and 1 μm for (f). The insets of parts are AFM images of self-assembled nanoparticles.

To study the feasibility of the assemblies formation based on the PEG-*b*-PCD diblock copolymer with other guest molecules, poly(lactic acid) (PLA), which can be included by α- [39] or β-CD [40] to form complex, was selected as a guest polymer. The self-assembled nanoparticles were prepared with the weight ratio of PLA to PEG-*b*-PCD copolymer as 0.5:10, 1.0:10 and 2.0:10 (named as $PLA_{0.5}/PCD_{10}$, $PLA_{1.0}/PCD_{10}$ and $PLA_{2.0}/PCD_{10}$, respectively). During the dialysis procedure bluish opalescence appeared immediately for all samples, suggesting the formation of assembled nanoparticles. Competitive inclusion method was also employed to investigate the formation of the PLA/PCD complex. As shown in Fig. S11†, the absorption intensity of MO in $PLA_{0.5}/PCD_{10}$ complex-containing solution significantly decreases compared to that in PEG-*b*-PCD-containing solution, which suggests the formation of PLA/PCD complex is driven by inclusion interactions between CD moieties and hydrophobic PLA. DLS was employed to measure the size and size distributions of the nanoparticles. As shown in Fig. 7, the size of the nanoparticles increases with increasing PLA to PEG-*b*-PCD ratio from 0.5:10 to 1.0:10. The average D_h is 187 nm for $PLA_{0.5}/PCD_{10}$ nanoparticles and 284 nm for $PLA_{1.0}/PCD_{10}$ nanoparticles, respectively. With further increasing PLA content, the nanoparticles become aggregate, as a bimodal particle size distribution is observed. Besides, it is known that PLA itself can self-assemble into nanoparticles by the same procedure. In this work, we find that obvious aggregates are observed in pure PLA nanoparticles solution soon after one day. On the contrary, the PLA/PCD complexes keep stable in the solution, which further suggests PLA chains are included into the CD moieties. TEM was then used to exam the morphology of the nanoparticles. Fig. 7 shows that spherical nanoparticles are formed in all cases and significant agglomeration is observed in $PLA_{2.0}/PCD_{10}$ nanoparticles. These results are in accordance with those given by DLS measurement. A close examination of AFM further clarified the morphology of the nanoparticles. The height images show round shapes of all samples and the horizontal distance is similar to the diameters observed by TEM. These results also confirm the successful inclusion of PLA in PEG-*b*-PCD copolymer.

Conclusions

In summary, we have successfully synthesized a new *mono*-methacrylate substituted cyclodextrin monomer in a mild reaction condition. ATRP of the new CD monomer was conducted using PEG-Br as initiator, $CuCl/CuCl_2$/PMDETA as catalyst system and DMF as solvent. Well-defined PEG-*b*-PCD double hydrophilic block copolymer was obtained by increasing Cu^{2+} concentration. The block copolymer could self-assemble into advanced nanostructures *via* host-guest interactions with a variety of guest molecules, which is attributed to the synergistic effect of CD moieties. The strategy developed in this study provides a facile and general method for the fabrication of nanostructures based on well-defined CD-pendant polymers, and these nanostructures may find applications in the fields of drug and gene delivery, self-healing materials, catalysts and coatings.

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PEG-*b*-PCD block copolymer could be synthesized by ATRP of new methacrylate-CD monomer, and self-assemble into advanced nanostructures with various guest molecules.