DOI: 10.1002/cjoc. 201600867

# Preparation and Stability Evaluation of Size-Controllable PDHCA-β-CD Nanoparticles as Drug Carrier

Hong Chu,[a] Xue Zhao,[a] Shirong Liu,[a] Zhongbin Ni,[a] Dongjian Shi,[a,b] and Mingqing Chen*,[a,b]

[a] *School of Chemical and Material Engineering, Jiangnan University, Wuxi, Jiangsu 214122, China*
[b] *The Key Laboratory of Food Colloids and Biotechnology, Ministry of Education, Jiangnan University, Wuxi, Jiangsu 214122, China*

A novel biocompatible polymer was prepared by grafting the derivate of β-cyclodextrin (6-SH-β-CD) onto poly(3,4-dihydroxycinnamic acid) (PDHCA) via Michael addition. PDHCA-β-CD nanoparticles were prepared by the self-assembly of amphiphilic PDHCA-β-CD polymer with *N,N*-dimethylformamide (DMF) as good solvent and water as poor solvent. The PDHCA-β-CD nanoparticles were monodispersed with spherical morphology as shown in the scanning electron microscopic (SEM) images in accord with the result of dynamic light scattering (DLS) measurement. The size of the nanoparticles could be controlled from 60 to 180 nm by tuning the grafting degree (GD) of PDHCA-β-CD polymer and also significantly influenced by the amount of water used during the process. These as-prepared nanoparticles were stable without any significant change in the particle size after six-months' storage and even after being irradiated by UV at $\lambda > 280$ nm for hours. The formation mechanism of PDHCA-β-CD nanoparticles was explored. The content of doxorubicin (DOX) loaded onto the nanoparticles was up to 39% with relatively high loading efficiency (approximately 78.8% of initial DOX introduced was loaded). In vitro release studies suggested that DOX released slowly from PDHCA-β-CD nanoparticles. These features strongly support the potential of developing PDHCA-β-CD nanoparticles as carriers for the controlled delivery of drug.

**Keywords** PDHCA-β-CD nanoparticles, controllable and desirable size, high stability, drug carrier

## Introduction

Cyclodextrins (CDs) are donutlike oligosaccharides commonly used as excipients in numerous drug formulations. The center of CDs is lined by the skeletal carbons and ethereal oxygen of the glucose residues. Such a hydrophobic cavity imparts CDs ability to form inclusion complexes with various hydrophobic chemicals. While the abundant OH groups on its exterior impart CDs a hydrophilic outer surface, which helps dissolve CDs or CD complexes due to the CD-water H-bonds formation. In some cases, CDs can be induced to self-assemble to form aggregates of nanoscale when CD-CD H-bonds were formed.[1] The β-CD aggregates reported by Bonini *et al*. were polydispersed, nearly spherical with size about 100 nm at lower concentrations and micrometer planar aggregates at higher concentrations.[2,3] The CD aggregates reported by Polarz *et al*., however, were wormlike, where CD molecules line up in ideally parallel or staggered parallel arrangement.[4] In recent decades, many amphiphilic CDs were developed via attaching CD to a hydrophobic moiety by chemical bonds or host-guest interaction, where the CD outer surface acts as a hydrophilic moiety.[5-9] Such amphiphilic CD-based aggregates provide macrocyclic hosting sites on the surface, creating new possibilities for host-guest interaction and recognition. Although CD complexes usually form aggregates with diameter of about 50—200 nm, in general, these self-assembled aggregates are not stable enough for drug delivery systems.[10] They tend to fall apart upon dilution, filtration, mixing or heating and need to be stabilized before they can be used as drug carriers. One of the approaches for obtaining stable CD nanoparticles is to form water-soluble CD polymers. It is well known that the cohesive forces of water-soluble polymers increase with increasing molecular weight.[11] This increment of cohesion can result in an enhancement of the ability to self-assemble to form nanoparticles. CD grafting versatile polymers therefore receive much attention for representing a unique class of host materials with tunable inclusion properties combined with the advantage of function polymer.[12-16] Doxorubicin (DOX) is one of the first line treatments used for a wide range of cancers. The cardiotoxicity and nephrotoxicity associated with unformulated doxorubicin has called researchers' interests to develop innovative strategies to entrap this drug in different nanocarriers including CD composite nano-

* E-mail: mqchen@jiangnan.edu.cn
Received December 6, 2016; accepted January 19, 2017; published online XXXX, 2017.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201600867 or from the author.

particles.[17]

Herein, PDHCA-*β*-CD polymers were prepared with PDHCA and *β*-CD as start materials by Michael addition (Scheme 1). PDHCA-*β*-CD nanoparticles were prepared by mixed solvent method with DMF and water employed as good/poor solvents pair. DOX was used as a model drug to test the drug loading capability of PDHCA-*β*-CD nanoparticles. Besides the advantages of mild conditions and averting the use of emulsifiers and co-stabilizers, the collection of pure products and recovery of solvents can be achieved easily by distillation. Furthermore, this technique allows the formation of NPs along with bioactive molecule immobilization. Such prepared *β*-CD based nanoparticles can be considered as an alternative biodegradable material applied as a carrier in drug delivery system.

## Experimental

### Materials

*β*-Cyclodextrin, acetyl chloride (AR), *p*-methyl benzene sulfonyl chloride (TsCl), thiourea, trichloroethylene (AR) were purchased from Shanghai Jingchun Biological Technology Co., Ltd. 3,4-Dihydroxycinnamic acid (DHCA) was kindly supplied by Huzhou Enbeixi Biological Material Co., Ltd. Acetic anhydride and sodium pyrosulfite ($Na_2S_2O_5$) were obtained from Shanghai Chemical Reagent Co., Ltd. Anhydrous ethanol, anhydrous diethyl ether, acetone, *N,N*-dimethylformamide (DMF), trifluoroacetic acid (TFA), triethylamin, hydrochloric acid, sodium hydroxide and sodium acetate were purchased from Sinopharm Chemical Reagent Co., Ltd and used without further purification. Doxorubicin (DOX) and adriamycin hydrochloride (DOX•HCl) were supplied by Kameishu Shanghai Biological Technology Co., Ltd.

### Synthesis of 6-OTs-*β*-CD

*β*-CD (5 g, 4.4 mmol) was added in aqueous NaOH solution (0.4 mol/L, 100 mL). TsCl (5 g, 26 mmol) was slowly added into the mixture under violent mixing and stirred for 3.5 h at 0—5 ℃. The reaction mixture was suction filtrated to remove unreacted TsCl. Aqueous HCl solution (0.1 mol/L) was added for neutralization and the reaction solution was kept in the refrigerator overnight. The white solids were obtained by suction filter, and then recrystallized twice with water. 2.537 g white powder was collected after being dried (yield 42.71%).

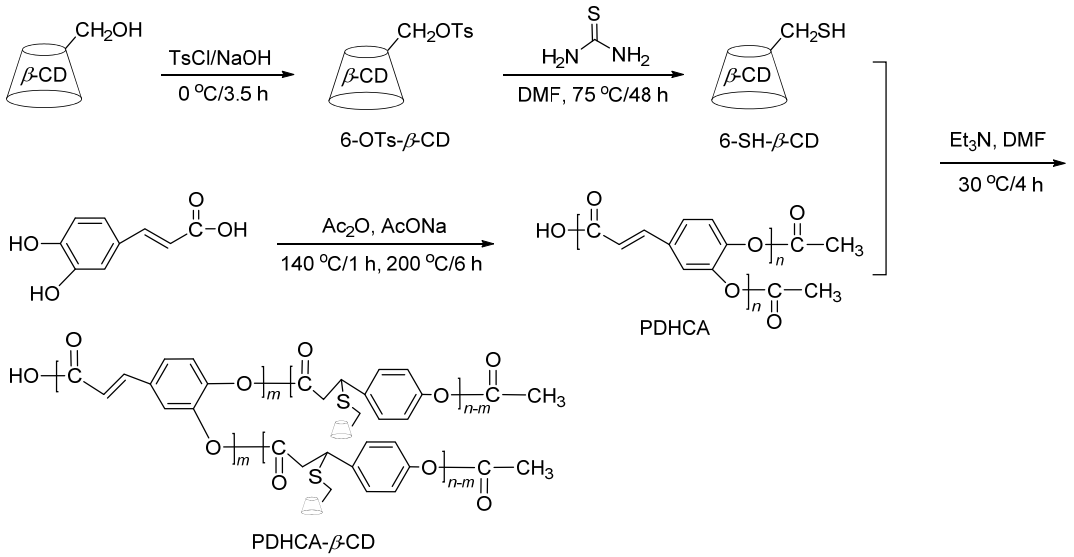
### Synthesis of 6-SH-*β*-CD

6-OTs-*β*-CD (1.2 g, 0.93 mmol) and thiourea (1.2 g, 15.8 mmol) were dissolved in 48 mL anhydrous DMF. The mixture solution was allowed to react for 48 h at 75 ℃, and then the reaction solution was cooled down to ambient temperature. After that, 36 mL anhydrous diethyl ether was added into the solution with stirring and the mixture was washed with acetone twice. The reaction mixture and 48 mg of $Na_2S_2O_5$ were dissolved in 40 mL aqueous NaOH solution (1 mol/L) and then stirred for 30 min at 25 ℃. Then aqueous HCl solution (1 mol/L) was dropped into the reaction solution to regulate the pH value to 3 before 2 mL of trichloroethylene was added in and treated by ultrasonic for 10 min. The precipitation was recrystallized twice with water. A white precipitate was recovered and dried in Blast Oven at 50 ℃ for 12 h to obtain 0.6988 g powder (yield 64.29%).

### Synthesis of PDHCA

PDHCA homopolymer was prepared from DHCA monomers by thermal polycondensation. DHCA (4.3 g, 23.9 mmol) and sodium acetate (0.4 g, 4.88 mmol) were dissolved in 10 mL acetic anhydride. The mixture solu-

**Scheme 1** Syntheses of PDHCA-*β*-CD polymer



tion was maintained stirring for 1 h at 140 ℃ and subsequent 6 h at 200 ℃ with $N_2$ purging. Then the reaction mixture was washed with ethanol and deionized water twice, respectively. A brown precipitate was recovered and dried in blast oven at 50 ℃ for 12 h to obtain 2.967 g powder (yield 69%).

### Synthesis of PDHCA-β-CD

Various amounts of 6-SH-β-CD were dissolved in 30 mL DMF respectively. And then 1 g PDHCA was added into the solution with ultrasonic-assistant dissolving. With 0.5 mL triethylamine as catalyst, the reaction was carried on at 30 ℃ for 4 h. The reaction solution was treated by vacuum distillation to remove the solvent and then dried at 60 ℃.

### Preparation of PDHCA-β-CD nanoparticles

The obtained PDHCA-β-CD polymers were dissolved in 2 mL DMF at a concentration of 1 mg/mL. A certain amount of ultrapure water was dropped into the solution with stirring and then stirred for another 24 h. After purified by dialysis in distilled water for 4—5 d, PDHCA-β-CD nanoparticles were then collected by lyophilization.

### Drug loading onto the PDHCA-β-CD nanoparticles

The DOX-loading nanoparticles were prepared by the similar method as described above. In a typical experiment, 2.5 mg DOX and 5mg polymer were dissolved in 5 mL DMF with stirring overnight. Then a certain amount of ultrapure water was dropped into the solution at room temperature followed by violent stirring for 24 h. The solution was then dialyzed against distilled water for 4—5 d. The sample was then subjected to UV analysis at $\lambda$=80 nm where the nanoparticles alone did not absorb (Figure S5). Quantification was performed from the calibration curve of DOX•HCl aqueous solution (Figure S6). Quantification of the DOX loading will be given through the loading content (%) (mass of DOX in vesicle/mass of polymer) and loading efficiency (%) (mass of DOX in vesicles/mass of DOX in the initial solution).

### In vitro drug release from the PDHCA-β-CD nanoparticles

To determine the drug release from the drug loaded nanoparticles, 1 mL of drug-loaded nanoparticle (1 mg) suspension was transferred to a dialysis bag (MWCO 8000—12000), and dialyzed against 25 mL of phosphate buffered saline (PBS, pH 6.4) in dark with the shaking rate of 120 r/min at 37 ℃ for 68 h. Then, at different time intervals, samples of 4 mL were taken from the medium outside of the dialysis bag at predetermined times and replenished the same volume fresh medium. The amount of released DOX in the collected samples was determined by measuring the absorbance of the samples at 480 nm by an ultraviolet and visible spectrophotometer. The drug concentration could be directly calculated from the measured absorbance based on calibration curve. Each experiment was carried out in triplicate and the average values were plotted.

### Measurements

Fourier transform infrared spectroscopy (FT-IR) spectrum was recorded with KBr disc technique on an FT-IR2000-104 spectrometer (ABB, USA). $^1$H NMR spectrum was recorded using an AVANCE Ⅲ NMR spectrometer (400 MHz, Bruker, Switzerland) with TMS as an internal standard. UV-vis spectrum was performed on a UV-1100 spectrometer (Rayleigh, China) at room temperature. Gel permeation chromatography (GPC, Agilent 1515, HP, USA) was performed using DMF as moving phase and calibrated with monodispersed polystyrene (PS) standards at a flow rate of 1.0 mL/min at 35 ℃. The glass transition temperature ($T_g$) was determined by differential scanning calorimeter (DSC822e, Mettler Toledo, Switzerland) with nitrogen atmosphere flow rate of 50 mL/min and heating rate of 10 ℃/min within 0—150 ℃. The weight loss was measured by thermogravimetric analyzer (TGA1100SF, Mettler Toledo, Switzerland) with a heating rate of 15 ℃/min from 25 to 800 ℃. OCA 40 optical contact angle measuring device (Eastern-Dataphy, China) was used to study the hydrophobicity of the resulting polymer. The size and morphology of polymer nanoparticles were observed by scanning electron microscopy (SEM, S-4800, HITACHI, Japan). Dynamic light scattering (DLS, ALV/DLS/SLS-5022F, HOSIC Ltd, Germany) was also applied to measure the size and size distribution of nanoparticles.

## Results and Discussion

### Synthesis of PDHCA-β-CD polymers

PDHCA-β-CD polymer was synthesized by Michael addition between PDHCA and 6-SH-β-CD. The structures of intermediate products of each step were identified by FT-IR (Figure S1, Figure S2). By tuning the feeding molar ratio of PDHCA to β-CD, a series of PDHCA-β-CD polymers with different composition were prepared (Table 1). The average molecular weight of PDHCA obtained from the GPC measurements was 32000 g/mol.

**Table 1** Synthesis of PDHCA-β-CD polymer

| $n_{PDHCA}$ : $n_{\beta\text{-CD}}$ | PDHCA/g | 6-SH-β-CD/g | Grafting degree[a]/% | $T_g$/℃ |
|---|---|---|---|---|
| | 1.0 | 0 | 0 | 117.4 |
| 100∶1 | 1.0 | 0.0714 | 4.90 | 93.1 |
| 50∶1 | 1.0 | 0.1427 | 30.2 | 90.1 |
| 25∶1 | 1.0 | 0.2854 | 45.1 | 74.2 |
| 5∶1 | 1.0 | 1.4272 | 74.9 | 60.5 |

[a] The grafting degree (GD) referring to the amount of β-CD attached to PDHCA polymers was estimated from $^1$H NMR measurements.

As shown in the FT-IR (KBr) spectra of PDHCA-*β*-CD polymers (Figure 1), the peak at the position of 1632—1634 $cm^{-1}$ was caused by the stretching vibration of C=C of the cinnamate groups in the PDHCA segments. Comparing with PDHCA, the strength of the peak was remarkably weakened along with the increased *β*-CD grafting degrees, indicating successful substitution of the double carbon bond (CH=CH) by S—CH bond. On the other hand, the strength of the peak at 3375 $cm^{-1}$ caused by the stretching vibration of hydroxy group in the *β*-CD moiety was enhanced gradually when the content of *β*-CD in the polymer increased.

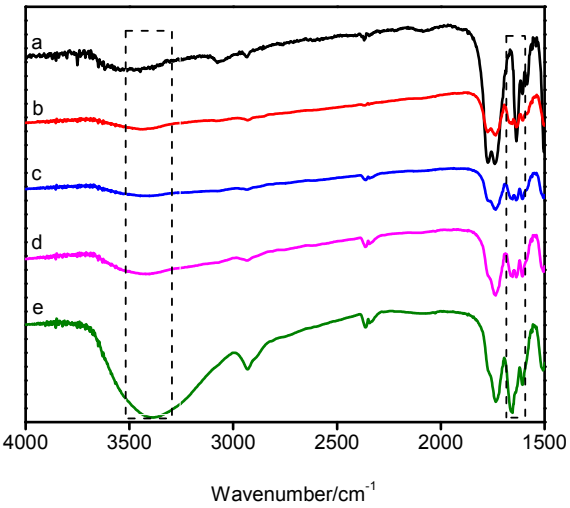



**Figure 1** FT-IR spectra of PDHCA-*β*-CD polymer with different composition: (a) PDHCA, (b) GD-5, (c) GD-30, (d) GD-45, (e) GD-75.

The structure of PDHCA-*β*-CD polymers was further confirmed by $^1$H NMR spectra (Figure 2). The peak at *δ* 2.40 was corresponding to the —$CH_3$ proton of acetyl group in PDHCA. The peaks at *δ* 7.06—7.59 were caused by CH proton in benzene ring. The peaks at *δ* 6.70 and *δ* 8.01 were assigned to —CH=CH— protons of the cinnamate groups in PDHCA. A new peak appearing at approximately *δ* 4.3 was assigned to the proton of —SCH group, indicating the *β*-CD was successfully introduced into PDHCA. The peaks at *δ* 2.69—3.19 and *δ* 4.82 were corresponding to the protons of $CH_2$ group at C6 and C1 position in cyclodextrin pyran saccharide moiety, respectively. The peak appearing at the position of *δ* 3.32—3.43 was corresponding to the proton of C*H*OH in cyclodextrin pyran saccharide moiety. The other new peak observed at *δ* 4.59 was assigned to the proton of CH located at the position where cyclodextrins grafted onto cinnamic acid. The grafting degree (GD) was calculated by comparing the peak area between cinnamate groups at *δ* 8.01 and —SCH at *δ* 4.3 as listed in Table1.

The PDHCA-*β*-CD sample solution in TMF was scanned by UV-vis instrument within 200—500 nm.

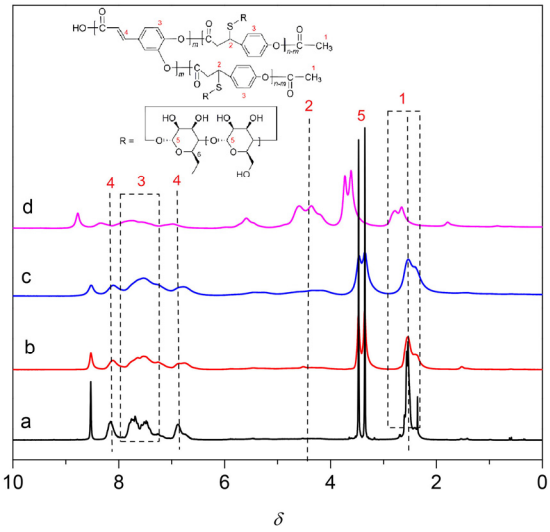



**Figure 2** $^1$H NMR (TFA, 400 MHz) spectra of PDHCA-*β*-CD polymer with different composition: (a) GD-5, (b) GD-30, (c) GD-45, (d) GD-75.

The maximum adsorption wavelength was closed to 298 nm (Figure 3), similar to that of PDHCA, which was the char acteristics absorption of the C=C double bond from cinnamic acid moiety. However, the absorbance of PDHCA-*β*-CD polymers was lower than that of PDHCA, which implied that a number of C=C double bonds were broken when 6-SH-*β*-CD grafted onto PDHCA, also supporting the formation of the PDHCA-*β*-CD polymers.

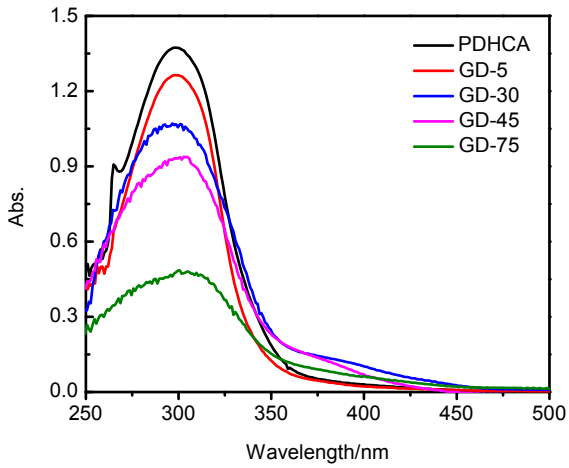



**Figure 3** UV-vis spectra of PDHCA and PDHCA-*β*-CD polymers.

## Hydrophilic-hydrophobic property of PDHCA-*β*-CD polymers

The contact angles of PDHCA-*β*-CD polymer with various compositions were measured by tabletting method to investigate the hydrophilic-hydrophobic property. As shown in Figure 4, the contact angles of PDHCA-*β*-CD polymers with higher grafting degree were smaller, which means the polymers became more

and more hydrophilic. Such a change was reasonable for there are a large number of hydroxyl groups located in the external structure of β-CD. The more β-CDs were contained in the PDHCA-β-CD polymers, the more hydrophilic the polymers would be. Thus, the hydrophilic-hydrophobic property of PDHCA-β-CD polymers could be controlled by adjusting the grafting degree of β-CD. In another word, amphiphilic PDHCA-β-CD polymers were successfully obtained with PDHCA as hydrophobic moiety and β-CD as hydrophilic moiety, which made it possible for PDHCA-β-CD polymers to self-assemble to aggregates under appropriate conditions.

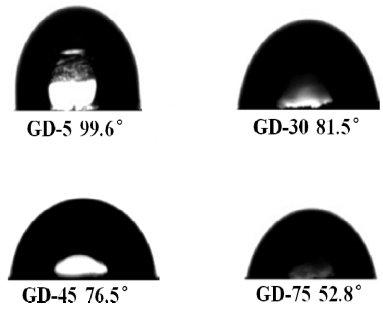



**Figure 4** Contact angles of PDHCA-β-CD polymers with various grafting degrees.

### Effect of polymer composition on size and size distribution of PDHCA-β-CD nanoparticles

PDHCA nanoparticles with average diameter of 50 nm have been successfully obtained by self-assembly of PDHCA polymers (Figure S3). Furthermore, various PDHCA-β-CD nanoparticles were obtained from PDHCA-β-CD polymers with varying β-CD content. The obtained nanoparticles were monodispersed, spherical with smooth surface as observed from SEM images (Figure 5). The sizes of nanoparticles ranged from 60 to 180 nm, however unlike other cases, they did not depend on the grafting degree of β-CD. It is known that increasing the hydrophilic unit number will induce a size decrement in the obtained particles. According to the contact angle, the size of nanoparticles should be smaller and smaller when more and more β-CDs were grafted onto PDHCA. Such a general law does not work in this extremely complicated case since both PDHCA and β-CD possess hydrophilic and hydrophobic moieties inside their structures. As mentioned before, the volume of β-CD's hydrophobic region is very large. With the introduction of β-CD to PDHCA polymer, the hydrophilic-hydrophobic balance of the polymer was broken and then rebulit. In the case of lower grafting degree, β-CD makes more significant contribution to hydrophobic moiety resulting in an increase in particle size.

Continuously increasing the grafting degree, β-CD makes more significant contribution to hydrophilic moiety, resulting in a decrease in particle size. The average diameters of PDHCA-β-CD nanoparticles calculated from SEM images were smaller than the results of DLS measurement, probably due to shrinkage during the drying process.

### Effect of solvent composition on size and size distribution of PDHCA-β-CD nanoparticles

When water was added to the polymer solution as a poor solvent, classic amphiphilic self-assembly is mainly governed by a delicate balance between two opposite effects: the hydrophobic effect, which drives the hydrophobic moiety to aggregate to minimize contact with water, and the solvation of the hydrophilic moiety, which tends to maintain contact with water. In this paper, the particle size changes were investigated in 1/1, 1/2.5, 1/5,1/7.5 and 1/10 of DMF/water (*V*/*V*) at a 1 mg/mL concentration (Figures 6a—6e). The SEM observation suggested the diameter firstly increased from

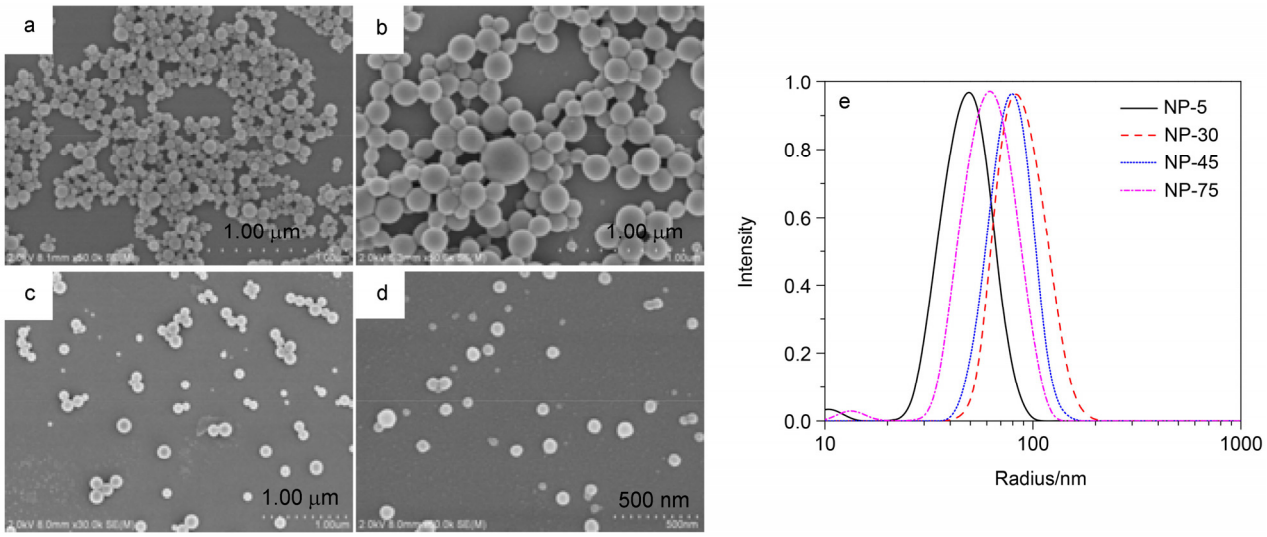



**Figure 5** SEM images of PDHCA-β-CD nanoparticles: (a) NP-5, (b) NP-30, (c) NP-45, (d) NP-75; (e) size and size distributions measured by DLS.

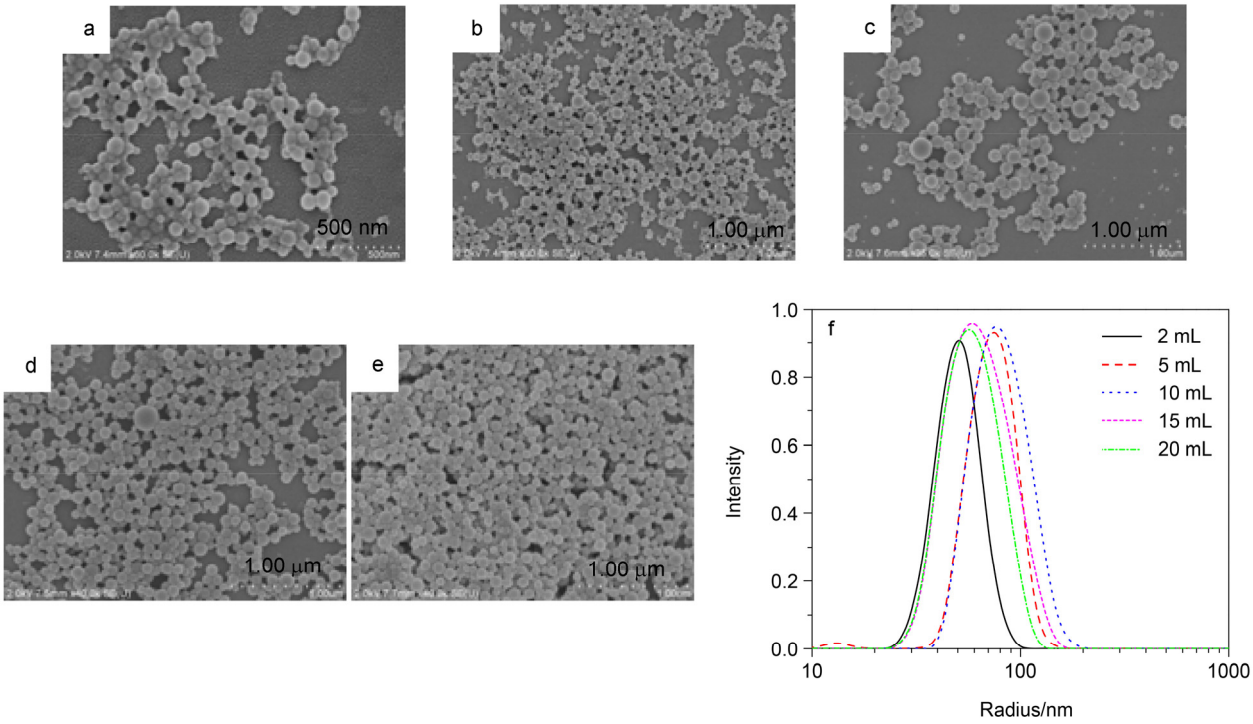



**Figure 6** SEM images of PDHCA-*β*-CD nanoparticles (NP-30) prepared by adding various amount of water: (a) 2 mL, (b) 5 mL, (c) 10 mL, (d) 15 mL, (e) 20 mL; (f) size and size distributions measured by DLS.

80±15 nm ($n$=50) to 125±40 nm ($n$=50) when the feeding amount of water changed from 2 mL to 10 mL and then decreased in case of more water added. The trend was further confirmed by DLS measurement results (Figure 6f). Although an increment in water content causes higher interfacial tension, PDHCA-*β*-CD nanoparticles did not show an increment in the diameter as classical amphiphilic polymers did. As the driving force of self-assembly, the hydrophobic effect, however, appears to be relatively weak and nondirectional, which is easily influenced by *β*-CD due to its hydrophobic cavity. Besides, the lower interfacial tension caused by the H bond formed between *β*-CD and water also interferes the further growth of nanoparticles.

### Stability evaluation of PDHCA-*β*-CD nanoparticles

Physicochemical stability studies provide information required for the development of the preformulation, highlighting particular requirements regarding unstable drugs. Cinnamic acid and its derivates show well-known [2＋2] cycloaddition (crosslinking) formation induced by UV irradiation at $\lambda$>280 nm. Several kind of photo-reactive nanoparticles containing cinnamic acid and its derivates were fabricated in our previous reports.[18,19] Those particles showed remarkable change in size after UV irradiation at $\lambda$>280 nm. In our research, the effects of UV-irradiation on particle size were also investigated by SEM and DLS measurements, respectively. Comparing with Figure 5c, the diameter of the PDHCA-*β*-CD nanoparticles changed slightly after UV irradiation for 24 h (Figure 7a), which is quite different from the fore-mentioned phenomenon. It was implied that the *β*-CD located on the surface of particles might prevent the PDHCA moiety from UV irradiation.

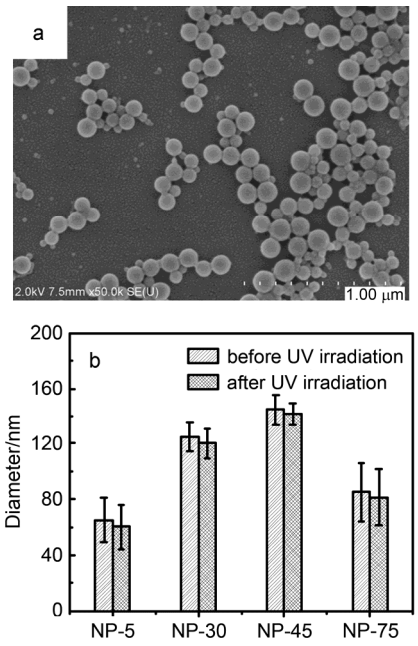



**Figure 7** (a) SEM image of PDHCA-*β*-CD nanoparticles (NP-45) after UV irradiation at λ>280 nm for 24 h; (b) The size change of PDHCA-*β*-CD nanoparticles caused by UV irradiation for 24 h.

As a matter of fact, when a DMF solution of PDHCA-*β*-CD polymer (GD-5) was placed under UV lamp light for a certain time, the absorbance was gradu-

ally reduced along with the light-induced time (Figure S4), which indicated that the isomerization of cinnamic acid groups occurred first and when such structural transformation proceeded to a certain extent, some of the C=C double bonds were open and [2+2] cycloaddition reaction was carried on next. Thus, four-member rings were generated and the crosslinking reaction was accomplished. In another word, the photo-reactivity of PDHCA was maintained in PDHCA-β-CD polymer. Interestingly, photo-stable nanoparticles were obtained via the self-assembly of photo-reactive polymers in this case.

After six months of storage at ambient temperature and humidity, the prepared particles, as observed in SEM images (Figures 8a, 8b) almost kept the same morphology, size and size distribution. According to the DSC analysis, a sharp weight loss occurred after the particle was heated above 300 ℃. The ζ-potential of the particles in PBS (pH=7.1) was around −70—−20 mV of negative charge (Figure 8d), implying a favorable thermodynamic stability and on the other hand, supporting the presence of hydroxyl groups on the particle surface. In other words, the DHCA units were arranged in the core of the particle probably due to their higher hydrophobicity than β-CD, while the surface of the nanoparticles seemed to be filled with hydrophilic β-CD chains (Figure 9). The nanoparticles became well dispersed in water due to the hydroxyl groups distributed in their surface resulting from the grafting of β-CD. Classic amphiphilic self-assembly is mainly governed by a delicate balance between two opposite effects: the hydrophobic effect, which drives the hydrophobic moiety to aggregate to minimize contact with water, and the solvation of the hydrophilic moiety, which tends to maintain contact with water. As the driving force of amphiphilic assembly, the hydrophobic effect, however, appears to be relatively weak and nondirectional, which is easily influenced by β-CD's hydrophobic cavity.

### Drug loading and release from PDHCA-β-CD nanoparticles

The self-assembly of amphiphilic PDHCA-β-CD polymer made it possible to immobilize drugs along with the formation of nanoparticles. As can be seen in SEM image, the DOX-loaded nanoparticles were spherical with a smooth surface (Figure 10). The diameter was much larger than that of neat nanoparticles (Figure 5b), which was coincide with the DLS measurement result. The DOX loading content calculated from the calibration curve was up to 39%. Approximately 78.8% of initial DOX was loaded onto the nanoparticles.

In vitro release profiles of DOX from nanoparticles were evaluated at 37 ℃ in PBS buffer solution. As shown in Figure 11, The accumulative amount of DOX released was 20% within 68 h, which implied that the DOX loaded onto PDHCA-β-CD nanoparticles would have longer-term therapeutic effect.

## Conclusions

A novel PDHCA-β-CD nanoparticle composed of a photoreactive DHCA unit and β-CD moiety was designed. The diameter of the PDHCA-β-CD nanoparticles could be controlled and maintained almost the same

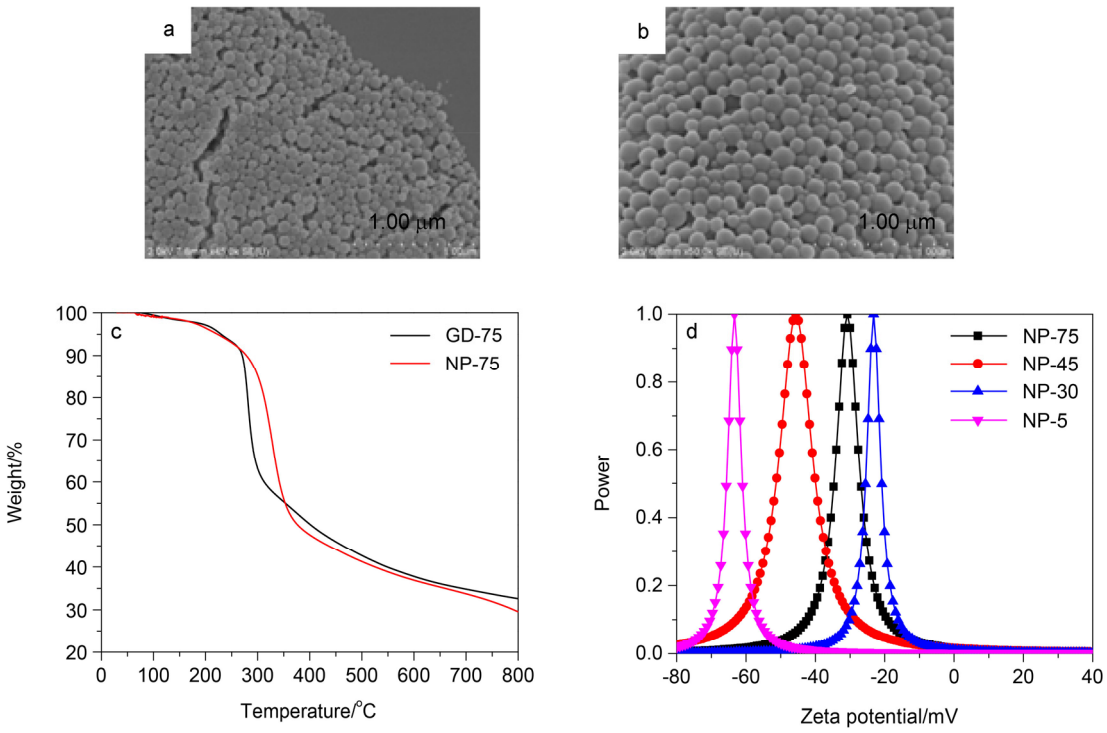



**Figure 8** SEM images of PDHCA-β-CD nanoparticles (NP-30): (a) fresh, (b) stored for six months; (c) weight lose curve of PDHCA-β-CD polymer and nanoparticles; (d) Zeta potential of nanoparticles.

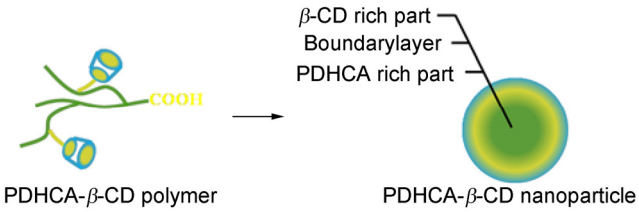



**Figure 9** Schematic representation of PDHCA-*β*-CD nanoparticles formation.

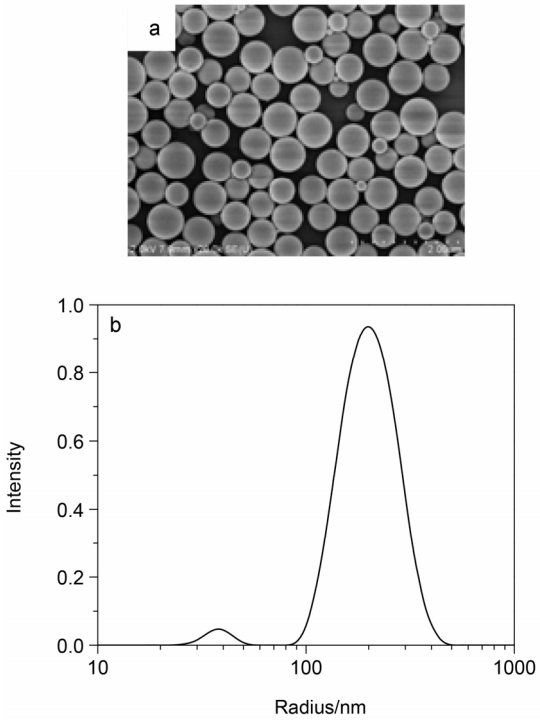



**Figure 10** (a) SEM image of DOX-loading PDHCA-*β*-CD nanoparticles (NP-30); (b) size and size distribution measured by DLS.

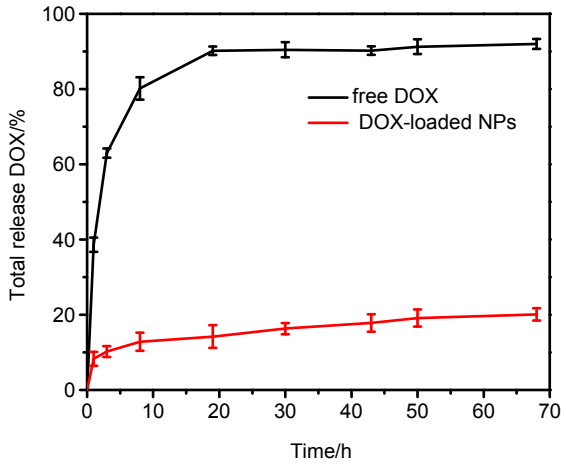



**Figure 11** In vitro DOX-release profiles of free DOX and loaded DOX NP-30 at pH 6.4.

without being affected by UV irradiation. Compared with other polymer aggregates, this kind of CD-based nanoparticles provide macrocyclic hosting sites on the surface, creating new possibilities for host-guest interaction and recognition. The model drug loading and release tests also give empirical evidence that these biocompatible, water-dispersible and highly stable PDHCA-*β*-CD nanoparticles can be promisingly used for drug delivery systems as a specific carrier.

## Acknowledgement

This research was supported by the National Natural Science Foundation of China (No. 51173072), the Fundamental Research Funds for the Central Universities (JUSRP51408B) and Jiangsu Province Joint Innovation Funds (BY2014023-12).

## References

[1] Messner, M.; Kurkov, S. V.; Jansook, P.; Loftsson, T. *Int. J. Pharm.* **2010**, *387*, 199.
[2] Bonini, M.; Rossi, S.; Karlsson, G.; Almgren, M.; Lo Nostro, P.; Baglioni, P. *Langmuir* **2006**, *22*, 1478.
[3] Rossi, S.; Bonini, M.; Lo Nostro, P.; Baglioni, P. *Langmuir* **2007**, *23*, 10959.
[4] Polarz, S.; Smarsly, B.; Bronstein L.; Antonietti, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4417.
[5] Silva, O. F.; Fernández, M. A.; Pennie, S. L.; Gil, R. R.; de Rossi, R. H. *Langmuir* **2008**, *24*, 3718.
[6] Nalluri, S. K.; Ravoo, B. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5371.
[7] Versluis, F.; Tomatsu, I.; Kehr, S.; Fregonese, C.; Tepper, A. W.; Stuart, M. C.; Ravoo, R. J.; Koning, R. I.; Kros, A. *J. Am. Chem. Soc.* **2009**, *131*, 13186.
[8] Baâzaoui, M.; Béjaoui, I.; Kalfat, R.; Amdouni, N.; Hbaieb, S.; Chevalier, Y. *Colloid Surf. A-Physicochem. Eng. Asp.* **2015**, *484*, 365.
[9] Aktaş, Y.; Yenice, İ.; Bilensoy, E.; Hincal, A. A. *J. Drug. Sci. Tec.* **2015**, *30*, 261.
[10] Messner, M.; Kurkov, S. V.; Jansook, P.; Loftsson, T. *Int. J. Pharm.* **2009**, *387*, 199.
[11] Messner, M.; Kurkov, S. V.; Flavià-Piera, R.; Brewster, M. E.; Loftsson, T. *Int. J. Pharm.* **2011**, *408*, 235.
[12] Yuan, Z.; Ye, Y.; Gao, F. *Int. J. Pharm.* **2013**, *446*, 191.
[13] Zhou, Y.; Wang, C.; Wang, F.; Li, C.; Dong, C.; Shuang, S. *Chin. J. Chem.* **2016**, *34*, 599.
[14] Sajomsang, W.; Nuchuchua, O.; Gonil, P.; Saesoo, S.; Sramala, I.; Soottitantawat, A.; Ruktanonchai, U. R. *Carbohyd. Polym.* **2012**, *89*, 623.
[15] Nuvoli, D.; Alzari, V.; Nuvoli, L.; Rassu, M.; Sanna, D.; Mariani, A. *Carbohyd. Polym.* **2016**, *150*, 166.
[16] Li, Y.; Guo, H.; Gan, J.; Zheng, J.; Zhang, Y.; Wu, K.; Lu, M. *J. Polym. Res.* **2015**, *22*, 1.
[17] Chen, J. C.; Li, J. Z.; Liu, J. H.; Xu, L. Q. *Chin. Chem. Lett.* **2015**, *26*, 1319.
[18] Shi, D. J.; Matsusaki, M.; Akashi, M. *Macromol. Biosci.* **2009**, *9*, 248.
[19] Shi, D. J.; Matsusaki, M.; Chen, M. Q.; Akashi, M. *Macromol. Chem. Phys.* **2012**, *213*, 2157.

(Pan, B.; Fan, Y.)