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Biopolymer-based supramolecular micelles from β-cyclodextrin and methylcellulose

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ABSTRACT

Supramolecular polymer micelles (SMPMs) were constructed from natural and natural-derived polymers: β-cyclodextrin (β-CD)/maleic anhydride modified β-cyclodextrin (MAh-β-CD) and methylcellulose (MC) in aqueous solution by one-pot self-assembly procedure, in which, β-CD and MAh-β-CD inclusion complexes were used as the hydrophilic shell and the free MC as the core. The shapes of the SMPMs were regular spheres with diameters of 25 ± 5 nm. The critical micelle concentrations, calculated from steady-state fluorescence emission spectra, were around 15.13 and 20.89 mg/L for MC/β-CD and MC/MAh-β-CD SMPMs, respectively. The *in vitro* drug release behaviors of the micelles were studied using prednisone acetate as a model drug, and the results showed that the MC/MAh-β-CD micelle had a drug-enrichment core and excellent drug released behaviors with a sustaining release time of 700 h.

1. Introduction

Nowadays, a remarkable trend in chemistry is supramolecular chemistry (Araki & Ito, 2007; Hunter & Anderson, 2009; Zhang, 2003). In the past decade, pioneering studies have provided various supramolecular systems by self-assembly of amphiphilic polymers derived from secondary forces of non-covalent interactions, such as ionic bonds, hydrogen bonds, hydrophobic interactions, and π–π interactions (Guo & Jiang, 2009; Lehn, 1985; Schneider, 2009; Wooley, 2000). It is desirable that these supramolecular systems are renewable, biodegradable, and recyclable (Edgar et al., 2001). So the blocks to assemble polymer micelle systems are called for a development from artificial polymers to natural polymers (Burda, Chen, Narayanan, & Sayed, 2005; Jawaid & Khalil, 2011; Kataoka, Harada, & Nagasaki, 2001; Riess, 2003; Wu et al., 2011; Yuan et al., 2001).

As an important kind of natural molecule in supramolecular chemistry, cyclodextrin (CD) has attracted much attention because of its novel rigid, well-defined ring structure, and marvelous hydrophobic cavity. The above properties of CD make it a favorable species for the design of supramolecular systems with hydrophobic molecules by hydrophobic host–guest interactions (Banerjee, Yu, & Matsui, 2003; Dong, Li, et al., 2008; Harada, Hashidzume, & Takashima, 2006; Hunt, Tonelli, & Balik, 2007; Li et al., 2011; Ritter & Tabatabai, 2002; Song, Bai, Xu, He, & Pan, 2009; Szejtli, 1998; Xing, Lin, & Xiao, 2010). At the same time, cellulose and its derivatives, especially cellulose ethers and esters, have been attracting considerable interest since the term "cellulose" was first reported by French chemist Anselme Payen in 1839 (Brogniart, Pelonze, & Dumas, 1839). Recently, the researches of them have extended to the design of novel supramolecular systems for controlled drug release application (Buchholz, Wegmer, Strainmeand, & Odberg, 1996; Loescher, Ruckstuhl, Jaworek, Wegner, & Seeger, 1998; Schaub, Wenz, Wegner, Stein, & Klemm, 1993; Wegner, 2003). For instance, micelles with cellulose as the hydrophilic shell and poly(L-lactide) as the hydrophobic core have been constructed from cellulose-*graft*-poly(L-lactide) graft copolymer (Dong, Xu, et al., 2008).

Our group previously prepared supramolecular polymer micelles (SMPMs) by the self-assembly of amphiphilic polyrotaxanes which were formed through the hydrophobic host–guest interaction with α-cyclodextrin (α-CD) as host molecule and poly(ε-caprolactone) (PCL) as the guest molecule (Dong, Li, et al., 2008). The micelles were constructed directly from α-CD and PCL by one-pot procedure and the chemical synthesis of amphiphilic polymer blocks was avoided. However, the guest molecule PCL still needs to be produced from oil resource, it is necessary to construct the micelles from bio-based resources without tedious polymerization procedure.

In this work, methylcellulose (MC), which is generally considered as a hydrophilic macromolecule, was used as guest molecule and β-cyclodextrin (β-CD)/maleic anhydride modified β-cyclodextrin (MAh-β-CD) as host molecule. In such supramolecular system, the host and guest molecules were biopolymers or their derivatives and the micelles were constructed in aqueous solution by one-pot self-assembly merely. As a potential drug delivery

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vehicle, hydrophobic drugs can be loaded into the supramolecular polymer micelles owing to the hydrophobic core of the micelles. Prednisone acetate, an anti-inflammatory drug with a very low solubility in water, was used as a model drug to evaluate the drug release behaviors of the micelles.

2. Experimental

2.1. Formation of supramolecular micelles

The solution of β-CD/urea (or MAh-β-CD) in distilled water was added dropwise to a stirred solution of MC in DMSO at 60 °C, and the resulting mixture was stirred continuously for 24 h, precipitates were removed by centrifugation after cooling the mixture to room temperature. The solvent and excess small molecules in the mixture were removed by dialysis in distilled water. The solution was freeze-dried before characterization. The yield of the supramolecular micelles was calculated based on the following equation:

$$\text{Yields } (\%) = \frac{W_t}{W_o} \times 100$$

where W_t represents the weight of obtained micelles, and W_o is the weight of fed β-CD or MAh-β-CD.

2.2. Drug loading of supramolecular micelles

The solution of β-CD/urea (or MAh-β-CD) in distilled water was added dropwise to a stirred solution of MC/prednisone acetate in DMSO at 60 °C. And the other procedure is the same as the formation of SMPMs above.

2.3. Measure of dynamic contact angles

The powders of tested polymers were pressed into slices, respectively, and distilled water was dropped on their surfaces, the dynamic water contact angles (DWCAs) were recorded synchronously. Dynamic poly(L-lactide) contact angles (DPLACAs) of MC, β-CD and MAh-β-CD were also measured to evaluate their hydrophobic properties. The samples were dissolved in distilled water and the solutions (c = 5 mg/mL) were dropped on to the surface of PLLA slice.

2.4. Fluorescence measurements

The fluorescence experiment used pyrene as a hydrophobic probe, which can preferentially getting into hydrophobic domains with a concurrent change in photophysical properties. Equivalent to 500 μL pyrene solutions (in acetone) with a concentration of 6×10^{-6} mol/L were added into a series of volumetric flasks, thereafter the acetone was volatilized completely. The solution of redissolved freeze-dried micelles were added into the volumetric flasks and diluted till the calibration mark using distilled water to achieve the desired concentrations ranging from 1 mg/L to 500 mg/L. The samples were ultrasonic for 5 min, and stored at room temperature for 24 h. Steady-state fluorescence emission spectra were recorded at 337 nm excitation wavelength and 10 nm slit width.

2.5. In vitro drug release

2 mL dialyzate was transferred to a new dialysis bag and immediately immersed into 80 mL distilled water at 37 °C. 2 mL aliquots were removed periodically from the solution as well as the volume of solution was preserved constantly by adding 2 mL distilled water. The quantities of drug released from the micelles were calculated from the UV absorbance of the solution at 242 nm. As shown behind, the concentration of prednisone acetate in distilled water (c) was calculated from the calibration curve:

$$c(\text{g/mL}) = \frac{A}{0.04762}$$

where A represents the UV absorbance at 242 nm. The cumulative drug release was calculated from the following relationship:

$$\text{Cumulative drug release}\,(\%) = \left(\frac{M_t}{M_0}\right) \times 100$$

where M_t represents the amount of drug released from micelles at time t, and M_0 is the amount of drug loaded by the micelles.

2.6. Apparatus

^{1}H NMR spectra were recorded on a Mercury VX-300 spectrometer using DMSO-d_6 as solvents. FT-IR spectra were recorded on ThermoFisher IS10 spectrometer. Steady-state fluorescence emission spectra were recorded on RF-5301PC (Shimadzu Corp.) spectrofluorophotometer. TEM images were recorded on JEM-2100 transmission electron microscope at an acceleration voltage of 200 kV, using 0.01% (w/v) phosphotungstic acid as negative staining reagent. The UV absorbance was recorded on SP-752 UV spectrophotometer (Shanghai spectrum Corp.). The X-ray diffraction patterns were obtained from D8-XRD (Bruker Corp.).

3. Results and discussion

3.1. Structure of supramolecular micelles

Two kinds of supramolecular systems were designed in the work: (1) MC/β-CD micelles by self-assembly of MC and β-CD with urea as a hydrogen bonds destroying reagent (Cai et al., 2007; Dou, Jiang, Peng, Chen, & Hong, 2003); (2) MC/MAh-β-CD micelles by self-assembly of MC and MAh-β-CD in aqueous solution. The yields of MC/β-CD and MC/MAh-β-CD supramolecular micelles are 33.8% and 41.8%, respectively.

The lipophilic interaction between MC and the hydrophobic cavities in β-CD is necessary to construct the supramolecular systems from β-CD and MC. However, MC is usually considered as a kind of hydrophilic polymer (Fig. 4A). To evaluate the lipotropy of MC, its dynamic contact angle (DCA) (Supplementary Data) was determined and compared with some other hydrophilic and hydrophobic polymers. By our results, MC shows a certain extent of lipotropy and may have lipophilic–lipophilic interaction with other hydrophobic molecules (Quesnel & Hildgen, 2005). The DCA results indicated that MC is appreciably hydrophobic and may be utilized as the hydrophobic guest molecule to enter the hydrophobic cavity of host molecule β-CD to form amphiphilic systems with CD as hydrophilic segment and MC as hydrophobic segment.

In the supramolecular micellar system, the proton environments of both host and guest molecules change remarkably because of the weak interaction between MC and β-CD, which can be monitored by ^{1}H NMR spectra. The protons of –OH on C2 and C3 of β-CD were more sensitive than other protons to the interactions of host and guest molecules, resulting in the change of the chemical shifts of these protons. As shown in Fig. 1A-a, compared with the spectrum of pure β-CD (Fig. 1A-b), a new peak appears at 5.4 ppm for the system of MC/β-CD and the peaks at 4.4 and 4.8 ppm shift to high field. For the system of MC/MAh-β-CD (Fig. 1B-a), the peak at 8.2 ppm in the spectrum of pure MAh-β-CD (Fig. 1B-b) disappeared but the peak at 6.2 ppm appeared. The shift of ^{1}H NMR signal of the protons of –OH on C2 and C3 can be attributed to the influences of the second force interactions.

The FT-IR spectra of freeze-dried micelles show significant differences around 1700 and 650–700 cm^{-1} compared to that of pure

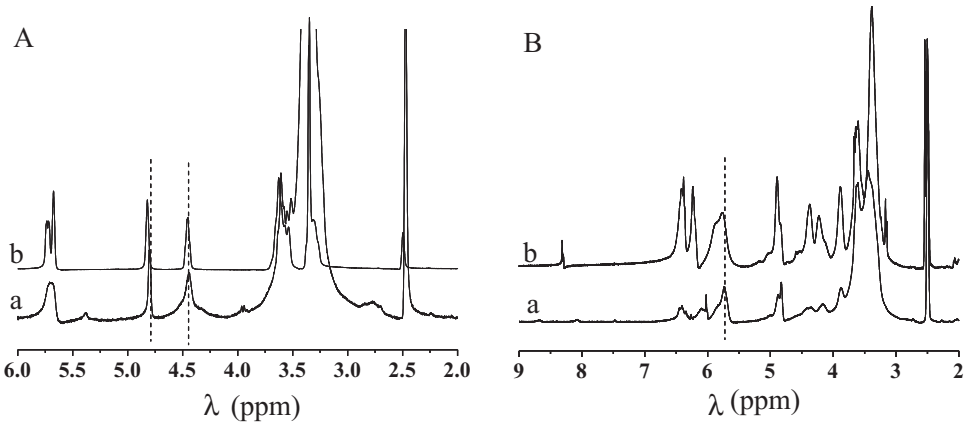

Fig. 1. ^{1}H NMR spectra of (A) (a) freeze-dried MC/β-CD micelle; (b) β-CD and (B) (a) freeze-dried MC/MAh-β-CD micelle; (b) MAh-β-CD.

block polymers and their mixtures with each other. As shown in Fig. 2C, the conspicuous peak of 1700 cm^{-1} by carbonyl group indicates the presence of MAh-β-CD in the supramolecular micelle system. The peaks of 802 cm^{-1} and 669 cm^{-1} for C–O–C bond are diminished in the micelles but the peak of 1050 cm^{-1} is enhanced and shifts to high wave number, which approve that the micelles are constructed really by the lipophilic interaction between β-CD and MC or MAh-β-CD and MC.

In the X-ray diffraction patterns of pure MC and freeze-dried micelles, the diffraction pattern of $2\theta = 10.5^\circ$ of the unincluded methyl cellulose present in both of the two spectra, which indicate the existence of the unincluded MC segment with in the supramolecular micelle. On the other side, the diffraction pattern of $2\theta = 19.8^\circ$, which is shown in Supplementary Data, is a fingerprint for the channel structure of cyclodextrin inclusion complex (Dong, Xu, et al., 2008). The result confirms the coexistence of free MC segments and the inclusion complex, which can be used as hydrophobic and hydrophilic segment of the supramolecular micelle.

Based on the above results, the formation of supramolecular micelles can be illustrated in Fig. 3. With the naked MC segment (A) as the core and hydrophilic MC/CD inclusion complex (B) as the corona, SMPMs can be produced by self-assembly of the amphiphilic MC/β-CD and MC/MAh-β-CD systems.

3.2. Morphologies of supramolecular micelles

The morphologies of MC and micelles measured by transmission electron microscope (TEM) are shown in Fig. 4.

Fig. 4A shows that the shape of MC swelling in aqueous solution is irregular. In Fig. 4B and C, the freeze-dried supramolecular micelles are dispersed individually in a regular spherical shape with

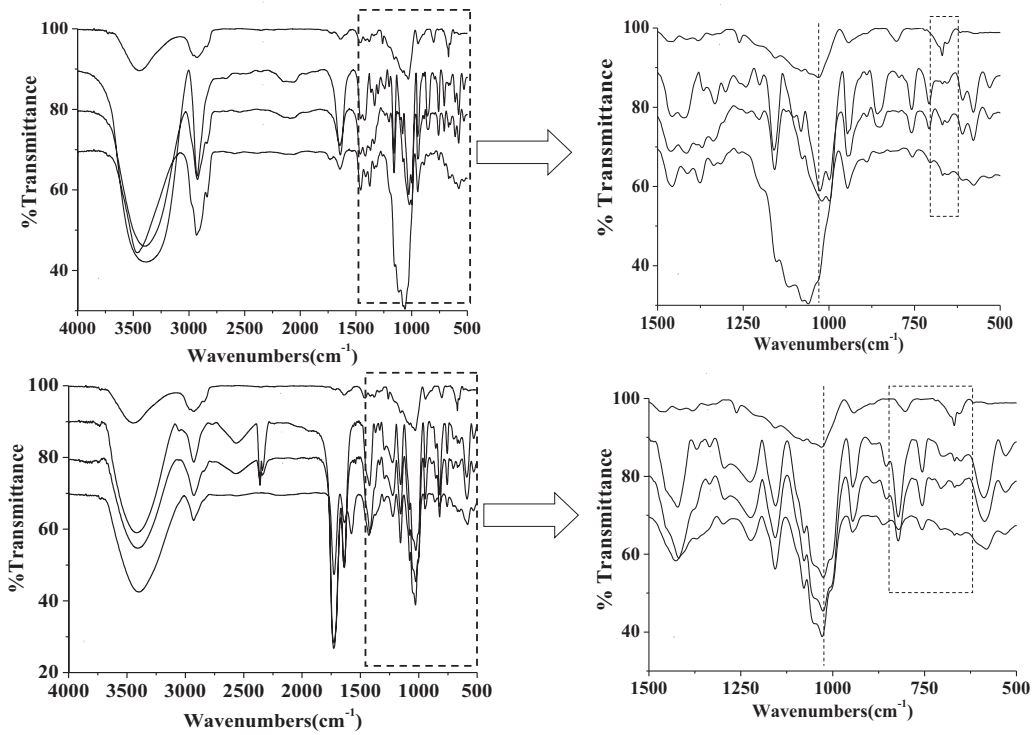

Fig. 2. The FT-IR spectra of (A): (a) MC; (b) β-CD; (c) MC + β-CD mixture; (d) freeze-dried MC/β-CD micelles. (B) (a) MC; (b) β-CD; (c) MC + β-CD mixture; (d) freeze-dried MC/β-CD micelles. (C) (a) MC; (b) MAh-β-CD; (c) MC + MAh-β-CD mixture; (d) freeze-dried MC/MAh-β-CD micelles. (D) (a) MC; (b) MAh-β-CD; (c) MC + MAh-β-CD mixture; (d) freeze-dried MC/MAh-β-CD micelles.

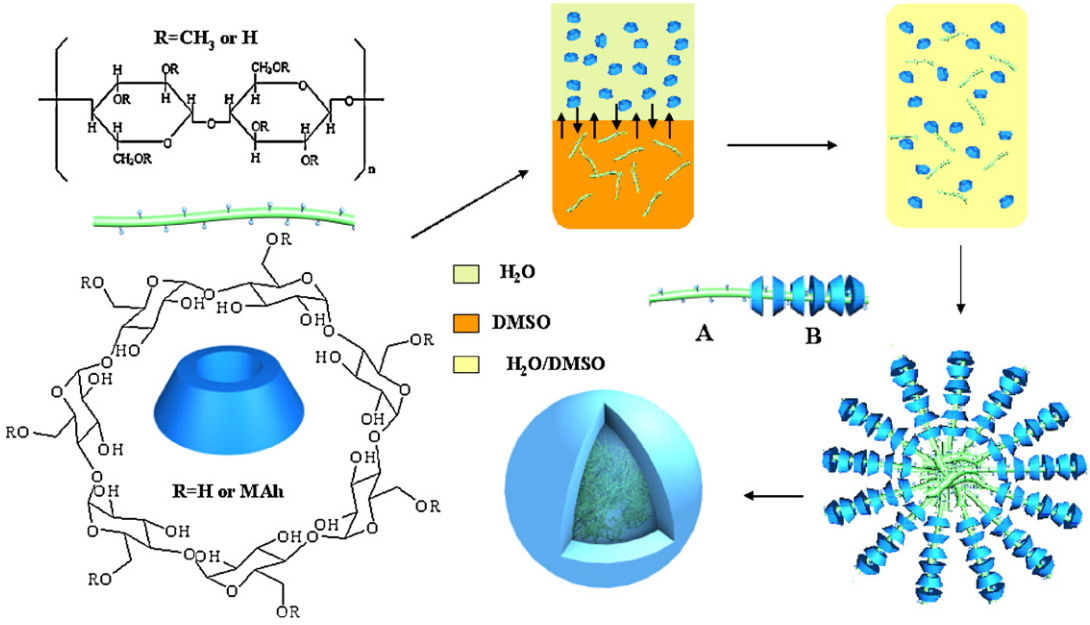

Fig. 3. Schematic illustration for the formation of supramolecular micelles from methylcellulose and β-cyclodextrin.

diameter of 25 ± 5 nm. The critical micelle concentration (CMC) was detected by fluorescence measurement using pyrene as a probe (Supplementary Data). For the micelle systems reported here, the intensities at 423 nm are analyzed as a function of the polymer concentrations. The CMC values were determined from the intersection of the tangent to the curve at the inflection with the horizontal tangent through the points at low concentration. The CMCs of two kinds of drug loaded micelles were also determined, which were nearly the same as that of the micelles without drug. The CMC of micelles constructed by MC/MAh-β-CD were lower than that of MC/β-CD, which suggests that it is easier for MAh-β-CD to form supramolecular micelles with MC in this appropriate condition.

From the fluorescence emission spectra of the supramolecular micelles (Fig. 5), the total fluorescence intensity of pyrene significantly increases along with the concentration of supramolecular micelles. Red shifts of the (0, 0) band from 375 nm to 380 nm (Fig. 5A and B) were observed for MC/β-CD micelle and MC/MAh-β-CD micelle, respectively. The results indicated the transfer of pyrene from aqueous to hydrophobic region and the presence of the hydrophobic core of the supramolecular micelles (Bains, Patel, & Narayanaswami, 2011; Dong, Li, et al., 2008; Vorobyova, Yekta, & Winnik, 1998).

The drug loaded supramolecular micelles were prepared using prednisone acetate as a model drug. The morphologies of the drug loaded supramolecular micelles were examined by TEM. It is interesting that some drug loaded MC/β-CD micelles are polygonal but not spherical (Fig. 6A). Another noticeable phenomenon is that the hydrophobic cores inside the drug loaded micelles of MC/MAh-β-CD were enriched by prednisone acetate (Fig. 6B and C), which may be interpreted by the cooperative interaction of maleic acid group and drug.

3.3. *In vitro* drug release

In vitro drug release behaviors of the supramolecular micelles were evaluated at 37 °C (Fig. 7). Prednisone acetate released gradually from the micelles and the release steadily lasted for about 450 h and 700 h for drug loaded MC/β-CD and MC/MAh-β-CD micelles, respectively. The prolonged drug release time of the MC/MAh-β-CD system can be explained by the drug-enrichment cores (Fig. 6B and C) that were produced with a high concentration drug solution. The results also prove the strong interaction between MC and the hydrophobic drug. The amazing extended drug release time indicates the outstanding potential applications of the supramolecular polymer micelles in drug controlled delivery to improve the efficacy and convenience of therapy, especially the long-range therapy of some chronic diseases (Lee et al., 2011; Uhrich, 1999).

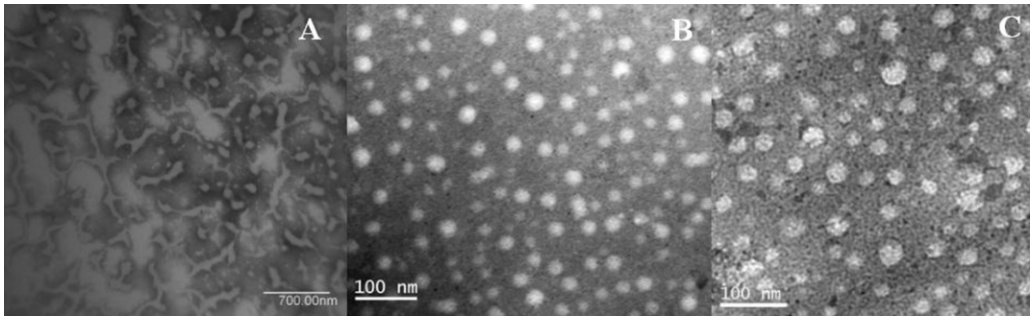

Fig. 4. TEM images of (A) MC; (B) freeze-dried MC/β-CD micelle; (C) freeze-dried MC/MAh-β-CD micelle.

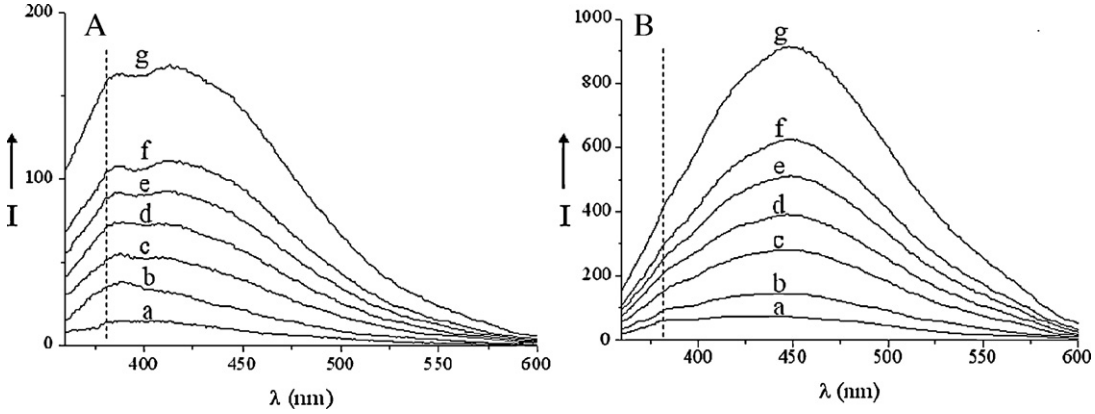

Fig. 5. Emission spectra of pyrene with different concentrations of freeze-dried supramolecular micelles: (A) MC/β-CD; (B) MC/MAh-β-CD (*a* = 0.033 mg/mL, *b* = 0.066 mg/mL, *c* = 0.133 mg/mL, *d* = 0.198 mg/mL, *e* = 0.266 mg/mL, *f* = 0.33 mg/mL, and *g* = 0.5 mg/mL).

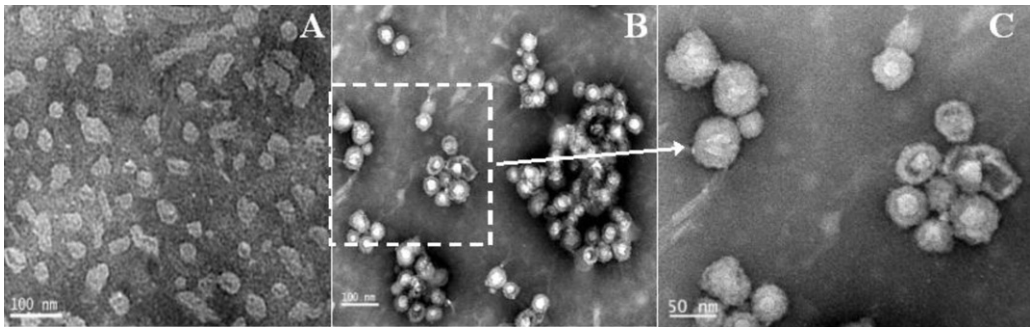

Fig. 6. TEM image of (A) freeze-dried drug loaded MC/β-CD micelle on 100 nm scale; (B) freeze-dried drug loaded MC/MAh-β-CD micelle on 100 nm scale; (C) freeze-dried drug loaded MC/MAh-β-CD micelle on 50 nm scale.

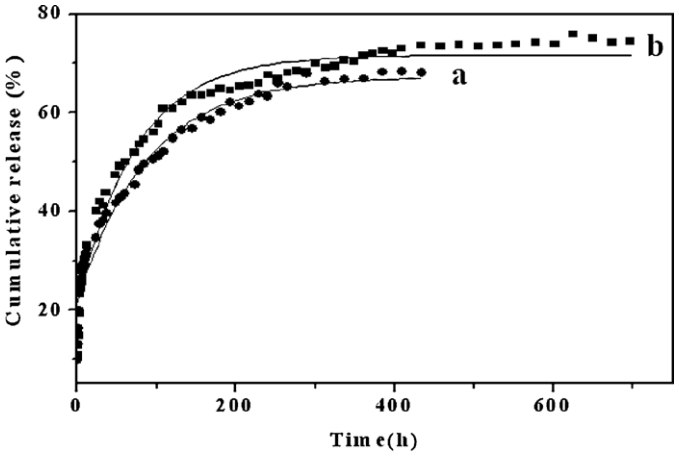

Fig. 7. Drug release behavior of drug loaded supramolecular micelles: (a) MC/β-CD; (b) MC/MAh-β-CD.

4. Conclusions

Methylcellulose (MC) was detected appreciably hydrophobic and utilized as the hydrophobic guest molecule to enter the hydrophobic cavity of host molecule β-cyclodextrin (β-CD) to form amphiphilic supramolecular polymers MC/β-CD and MC/MAh-β-CD with β-CD as hydrophilic segment and MC as hydrophobic segment. The supramolecular polymer micelles were obtained from the self-assembly of the amphiphilic MC/β-CD and MC/MAh-β-CD systems with the free segment of MC as the core and β-CD inclusion complex as the corona. In practice, bio-resource-based supramolecular micelles on nanoscale were constructed in aqueous solution by one-pot self-assembly of MC with β-CD or with MAh-β-CD. The release of prednisone acetate from the micelles was steady and lasted for about 450 h by MC/β-CD and 700 hrs by MC/MAh-β-CD, respectively.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carbpol.2012.05.079.

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