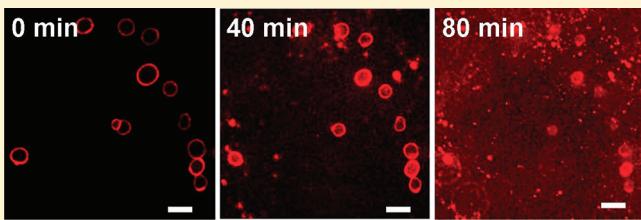


# Design of a Photoswitchable Hollow Microcapsular Drug Delivery System by Using a Supramolecular Drug-Loading Approach

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**ABSTRACT:** In this study, photoswitchable microcapsules were fabricated based on host–guest interactions between  $\alpha$ -cyclodextrin ( $\alpha$ -CD) and azobenzene (Azo). Carboxymethyl dextran-*graft*- $\alpha$ -CD (CMD-*g*- $\alpha$ -CD) and poly(acrylic acid) *N*-aminododecane *p*-azobenzeneaminosuccinic acid (PAA-C<sub>12</sub>-Azo) were assembled layer by layer on CaCO<sub>3</sub> particles.  $\alpha$ -CD-rhodamine B ( $\alpha$ -CD-RhB), used as a model drug, was loaded on PAA-C<sub>12</sub>-Azo layers by host–guest interaction. After removal of CaCO<sub>3</sub> particles by ethylenediaminetetraacetic acid (EDTA), hollow microcapsules loaded with  $\alpha$ -CD-RhB were obtained. Since the interactions between  $\alpha$ -CD and Azo were photosensitive, the capsules could be dissociated with the irradiation of UV light, followed by the release of the model drug,  $\alpha$ -CD-RhB. Compared with traditional drug-loading approaches such as chemical bonding and physical adsorption, our supramolecular drug-loading system has a facile loading process, ideal bonding strength, and photoswitchable behavior. These photosensitive microcapsules exhibit great potential in biomedical applications.



## INTRODUCTION

As one of the most effective methods in cancer therapy, chemotherapy is always a hot topic in research. However, conventional antineoplastic drugs usually exhibit low aqueous solubility, high toxicity, and easy decomposition in physical environments. To overcome such deficiencies, drug delivery systems such as polymer micelles,<sup>1,2</sup> vesicles,<sup>3,4</sup> hydrogels,<sup>5,6</sup> microgels,<sup>7,8</sup> etc. have been developed in past decades. To enhance the antitumor efficiency of antineoplastic drug use and to reduce the side effects, stimulus-responsive systems such as pH sensitive, light sensitive, and temperature sensitive drug delivery systems have been proposed to trigger drug release at tumor tissues.<sup>9–14</sup>

Layer-by-layer (LbL) microcapsules, emerged as a novel type of drug carrier, can be fabricated with well-controlled size, regular shape, controllable thickness, and variable wall compositions.<sup>15–18</sup> Moreover, it is documented that loading the antineoplastic drugs on the layers of LbL capsules has the advantage of bypassing multidrug resistance in cancer cells.<sup>19</sup> The traditional way of loading drugs on layers always uses physical adsorption or chemical bonding. However, by physical adsorption, the drug loading amount and drug release rate are hard to control due to its weak interactions. The uncontrollable drug release will cause the spreading of loaded antineoplastic drugs on capsule layers to the environment unselectively, leading to undesirable damage to the normal tissues. Using chemical bonding to load drugs on capsule layers also has drawbacks. First, the synthesis of loading drugs on capsules is specific and irreversible. Besides, the loading of more than two kinds of drugs into capsule layers is always difficult and complicated. Therefore, using another interaction instead of physical adsorption and covalent interaction to load antineoplastic drugs on capsule layers is critically important.

Supramolecular interaction, a noncovalent interaction, can be used to fix host and guest molecules together efficiently, specifically, and reversibly, and has been widely used in various applications.<sup>20–28</sup> In 2009, loading small-molecule drugs on the layers of LbL platforms using supramolecular interaction was reported by Hammond et al.<sup>29</sup> Among these host–guest interactions, some of them can respond to external stimuli, such as the interaction between azobenzene (Azo) and  $\alpha$ -cyclodextrin ( $\alpha$ -CD). The two isomers of Azo, the trans and cis forms, can be reversibly switched to each other upon photoirradiation.<sup>30–33</sup> Driven by hydrophobic and van der Waals interactions, *trans*-Azo can be well-recognized by  $\alpha$ -cyclodextrin ( $\alpha$ -CD). However, when *trans*-Azo is transformed to *cis*-Azo,  $\alpha$ -CD cannot include the bulky *cis* form anymore due to the mismatch. Therefore, host–guest assembly and disassembly between azobenzene and  $\alpha$ -CD can be controlled by UV light.<sup>34–39</sup>

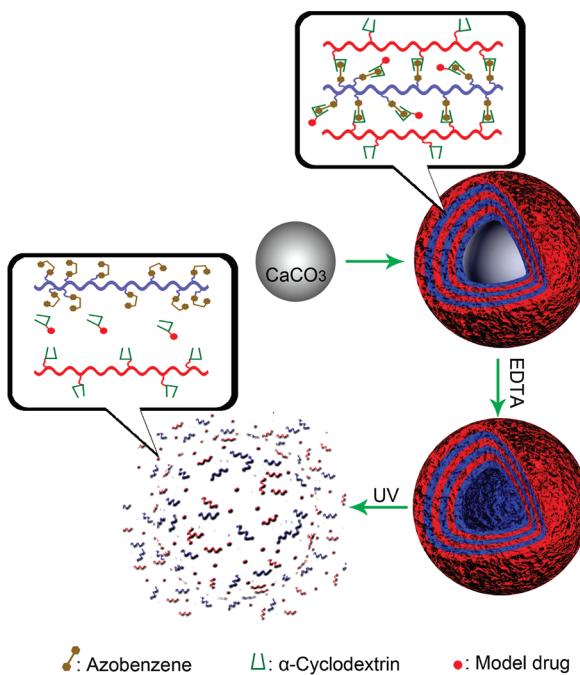
Here we designed a photoswitchable LbL capsule that uses supramolecular interaction as the driving force of LbL assembling and layer drug loading. The capsules were assembled by host polymeric layers containing  $\alpha$ -CD and guest polymeric layers containing Azo. It is known that the driving force for the LbL assembly of microcapsules mainly uses electrostatic attraction.<sup>40</sup> However, this limits the building blocks to a narrow range of oppositely charged and water-soluble polymers. Using supramolecular interaction instead of electrostatic interaction as the driving force of LbL can overcome such limitations and enhance the stability of microcapsules in various pH conditions.<sup>41</sup> Importantly,

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**Scheme 1.** Fabrication and Degradation Processes of (PAA-C<sub>12</sub>-Azo)/(CMD-g- $\alpha$ -CD& $\alpha$ -CD modified drug) Hollow Microcapsules



it is convenient to fabricate intelligent microcapsules based on the supramolecular interactions that can respond to external stimuli. Herein, an antineoplastic drug modified with  $\alpha$ -CD was loaded on the guest layers conveniently by supramolecular interaction. The obtained capsules were dissociated upon irradiation by a UV lamp ( $\lambda = 365$  nm) due to the transformation of *trans*-Azo to *cis*-Azo. Thereafter, the  $\alpha$ -CD modified antineoplastic drug was released from the Azo layers. The fabrication process and dissociating process of this LbL capsule are illustrated in Scheme 1.

## ■ EXPERIMENTAL METHODS

**Materials.** Poly(acrylic acid) (PAA) was purchased from Sigma-Aldrich; the average molecular weight of poly(acrylic acid) was reported to be  $1.0 \times 10^6$  by the supplier. Dextran with an average molecular weight of 15 000–25 000 was purchased from Fluka. 3-Amino-3-deoxy- $\alpha$ -cyclodextrin was purchased from Tokyo Chemical Industries (TCI). N-Hydroxysuccinimide (NHS), *N,N'*-dicyclohexylcarbodiimide (DCC), ethylcarbodiimide (EDC), and *p*-aminoazobenzene were obtained from Sigma-Aldrich and used as received. Dodecamethylenediamine, rhodamine B (RhB), and succinic anhydride were obtained from Shanghai Aladin Co., Ltd. (China) and used directly. *N,N'*-Dimethylformamide (DMF) was obtained from Shanghai Chemical Reagent Co. and used after distillation. Chloroacetic acid was the analytical reagent and was obtained from Shanghai Chemical Reagent Co. and used directly.

**Synthesis of Poly(acrylic acid) *N*-Aminododecane *p*-Azo-benzeneaminosuccinic Acid (PAA-C<sub>12</sub>-Azo).** PAA-C<sub>12</sub>-Azo was synthesized according to the literature.<sup>35</sup> Briefly, 1.972 g (10 mmol) of *p*-aminoazobenzene and 1.204 g (12 mmol) of succinic anhydride were dissolved in 25 mL of anhydride acetone. Then 0.79 g (10 mmol) of pyridine was added to the acetone solution with stirring for 6 h at 60 °C. The resulting

product was precipitated from the reaction solution. The product was obtained by centrifuge, and then washed with a large excess of acetone three times and dried for 2 days under vacuum drying. A 300 mg (1.0 mmol) sample of *p*-aminoazobenzene-SA and 174 mg (1.5 mmol) of N-hydroxysuccinimide were dissolved in 10 mL of anhydride tetrahydrofuran (THF). Then 313 mg (1.5 mmol) of DCC was added to the THF solution, followed by stirring for 3 h at room temperature. After removal of dicyclohexylurea (DCU) by centrifuge, the reaction mixture was poured into a 5 mL methanol solution of dodecamethylenediamine (200 mg, 1.0 mmol). After stirring for 1 day, the resulting products were precipitated from the reaction mixture. The product was obtained by centrifuge and washed with a large excess of methanol three times. DCC (40 mg, 0.19 mmol) was added to the solution of poly(acrylic acid) (400 mg, 5.5 mmol monomer units) in DMF (10 mL). After the formation of DCU was observed, NH<sub>2</sub>C<sub>12</sub>Azo (100 mg, 0.25 mmol) was added to the mixture. After additional stirring for 3 days, the formed DCU was removed by centrifuge. The reaction mixture was poured into a large excess of diethyl ether to recover the product. The copolymer obtained was purified by reprecipitation from methanol into diethyl ether twice.

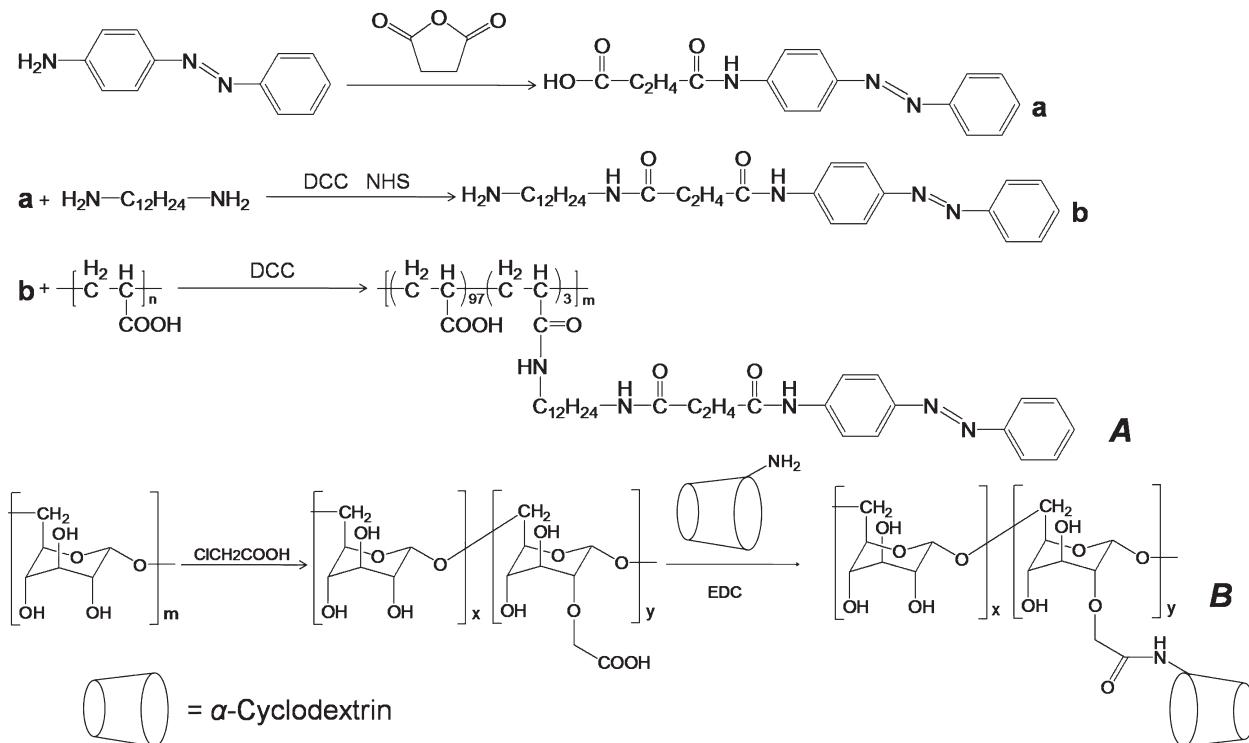
**Synthesis of Carboxymethyl Dextran-*graft*- $\alpha$ -CD (CMD-g- $\alpha$ -CD).** The synthesis of carboxymethyl dextran (CMD) was according to the literature.<sup>42</sup> Briefly, 1 g of dextran (containing 6.2 mmol of monomer units) was added into a mixture of 2-propanol (22 mL) and 14.3 M aqueous NaOH solution (4 mL), and the mixture was stirred at room temperature for 1 h. Then 1.89 g (20 mmol) of chloroacetic acid was added dropwise and the suspension was stirred for 90 min at 60 °C. The product was cooled to room temperature, the 2-propanol was removed, and methanol was added. The methanol was then removed and the residue was dissolved in 20 mL of distilled water; the pH of the aqueous solution was adjusted to acidic (pH 2–3) with 1 M HCl to convert COONa to COOH. Subsequently, the solution was purified by dialysis in a dialysis tube (molecular weight cutoff (MWCO) 8000–12 000) and lyophilized for 1 day at room temperature. Then, 34 mg of CMD (containing 0.15 mmol of monomer units) and 200 mg of 3-NH<sub>2</sub>- $\alpha$ -CD (0.21 mmol) were dissolved in 5 mL of deionized water. After the solution's pH value was adjusted to 5, 80 mg of EDC (0.52 mmol) was added into this solution and stirred for 24 h at room temperature. Subsequently, the solution was purified by dialysis in dialysis tube (MWCO 3500) and lyophilized for 2 days at room temperature.

**Synthesis of  $\alpha$ -CD-RhB.** To synthesize  $\alpha$ -CD-RhB, 60 mg (0.062 mmol) of 3-NH<sub>2</sub>- $\alpha$ -CD and 148 mg (0.30 mmol) of RhB were dissolved in 5 mL of deionized water. After the solution's pH value was adjusted to 5, 80 mg (0.52 mmol) EDC was added into this solution and stirred for 24 h at room temperature. The reaction mixture was poured into a large excess of acetone to recover the product. The residue was washed with acetone four times and dried for 2 days under vacuum drying.

**Fourier Transform Infrared Spectroscopy (FTIR).** The samples were analyzed by an FTIR (Perkin-Elmer Spectrum One, USA) spectrophotometer. Before the measurements, the samples were pressed into potassium bromide (KBr) pellets.

**<sup>1</sup>H Nuclear Magnetic Resonance.** The <sup>1</sup>H NMR spectra of the polymers were recorded on a Mercury VX-300 spectrometer at 300 MHz (Varian, USA) using D<sub>2</sub>O as a solvent and TMS as an internal standard.

**Preparation of ~10  $\mu$ m CaCO<sub>3</sub> Particles.** CaCO<sub>3</sub> particles with narrow size distribution were prepared according to the

**Scheme 2.** Synthesis Route of PAA-C<sub>12</sub>-Azo (A) and CMD-g- $\alpha$ -CD (B)

literature.<sup>43,44</sup> Briefly, 5 mL of 0.33 M  $K_2CO_3$  solution was rapidly poured into 5 mL of 0.33 M solution of  $CaCl_2$  containing 10 mg of poly(allylamine hydrochloride) (PAH) at room temperature. After intense agitation for 30 s, the reaction mixture was left still for about 2 min. Then the precipitate was filtered off, thoroughly washed with distilled (DI) water and acetone, and dried in air. The whole process was protected from light wherever possible.

**Fabrication of  $(PAA-C_{12}-Azo)_5/(CMD-\alpha-CD\&\alpha-CD-RhB)_5$  or  $(PAA-C_{12}-Azo)_5/(CMD-\alpha-CD\&free RhB)_5$  Microcapsules.** PAH captured  $CaCO_3$  particles were used as colloid template for the fabrication of microcapsules. In order to absorb the polyanion PAA-C<sub>12</sub>-Azo and CMD-g- $\alpha$ -CD on the surface,  $CaCO_3$  particles were first coated with a layer of PAA-C<sub>12</sub>-Azo to compensate the surface potential of the negative particles. Briefly, a total of 150 mg of  $CaCO_3$  particles was symmetrically dispersed in 1 mL of PAA-C<sub>12</sub>-Azo solution (1 mg/mL). The suspension was shaken constantly for 15 min to establish a PAA-C<sub>12</sub>-Azo layer. After adsorption, the particles were isolated by centrifugation (4000 rpm for 1 min), followed by washing with 1 mL of DI water three times. For adsorption of the next layer, 1 mL of CMD-g- $\alpha$ -CD& $\alpha$ -CD-RhB solution (containing 1 mg/mL CMD-g- $\alpha$ -CD and 10 nmol/mL  $\alpha$ -CD-RhB) or CMD-g- $\alpha$ -CD&free RhB solution (containing 1 mg/mL CMD-g- $\alpha$ -CD and 10 nmol/mL RhB) was added, followed by the same washing protocol. The LbL process was repeated to get the microcapsules with a designed number of layers. The whole process was protected from light wherever possible.

Hollow microcapsules were formed by dissolving the  $CaCO_3$  core using 0.4 M EDTA solution with pH 7.4. Three centrifugations (10 000 rpm for 3 min) and water washing steps were applied to remove the EDTA and isolate the microcapsules for analysis.

**Characterization of Hollow Microcapsules.** The hollow capsules were viewed with confocal laser scanning microscopy

(CLSM) (Nikon C1-si, BD Laser at 543 nm). For transmission electron microscopy (TEM), one drop of a concentrated capsule solution was placed on a clean TEM grid and allowed to dry in air. TEM analysis was carried out with a JEM-100CX II instrument operating at an acceleration voltage of 100 kV.

**Hollow Microcapsule Incubation.** The  $CaCO_3$  particles coated with five bilayers of  $(CMD-g-\alpha-CD\&\alpha-CD-RhB)/(PAA-C_{12}-Azo)_5$  or  $(CMD-g-\alpha-CD\&free RhB)/(PAA-C_{12}-Azo)_5$  films were dispersed in 1 mL of 0.4 M pH 7.4 EDTA solution to remove the core. The hollow microcapsules were imaged by CLSM and then incubated in EDTA solution at room temperature for 24 h in the dark. After that, the microcapsules were imaged by CLSM again.

**Photodissociation of  $(CMD-g-\alpha-CD\&\alpha-CD-RhB)_5/(PAA-C_{12}-Azo)_5$  Microcapsules.** The photodissociation process of  $(CMD-g-\alpha-CD\&\alpha-CD-RhB)_5/(PAA-C_{12}-Azo)_5$  microcapsules was viewed with CLSM. An appropriate amount of the capsules was dispersed in 0.4 M pH 7.4 EDTA solution under the irradiation of UV light (365 nm) and was observed with CLSM continuously.

**In Vitro Drug Release.** An 80 mg sample of  $CaCO_3$  particles coated with five bilayers of  $(CMD-g-\alpha-CD\&\alpha-CD-RhB)/(PAA-C_{12}-Azo)_5$  films was dispersed in 1 mL of 0.4 M pH 7.4 EDTA solution to remove the core. Then the hollow microcapsules were isolated with centrifugation (10 000 rpm for 3 min) and dispersed in 1 mL of DI water. The  $(CMD-g-\alpha-CD\&\alpha-CD-RhB)_5/(PAA-C_{12}-Azo)_5$  capsule solution was evenly divided into two parts and put into two dialysis tubes (MWCO 8000–12 000 Da) respectively and quickly. The dialysis tubes were directly immersed into 200 mL of 0.1 M pH 7.4 buffer solution, respectively. Aliquots of 2 mL were withdrawn from the solution periodically. The volume of solution was kept constant by adding 2 mL of buffer solution after each sampling. The amount of RhB

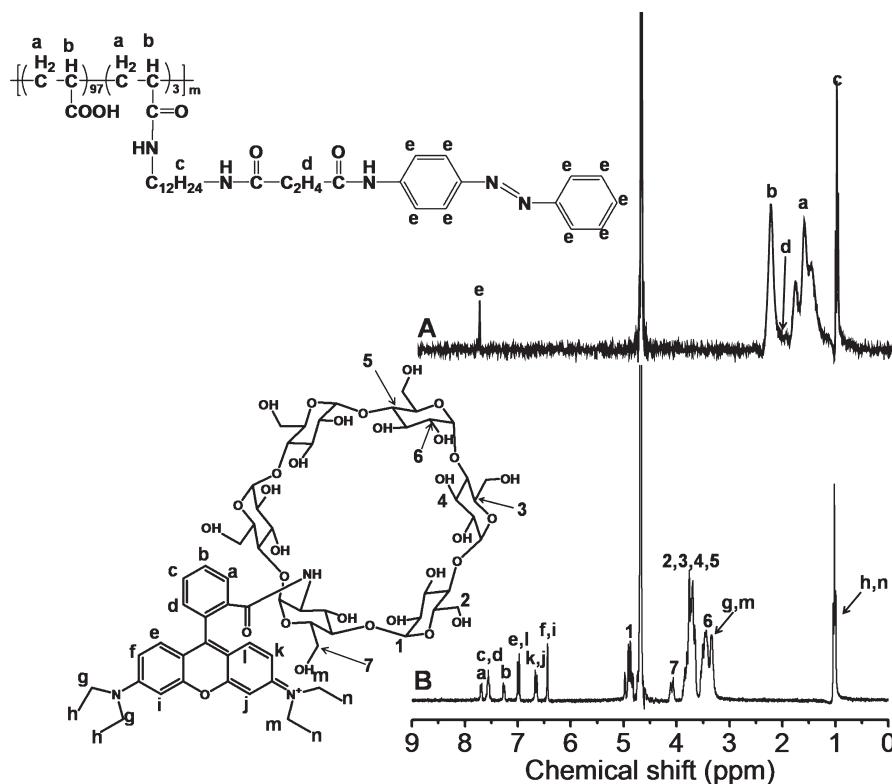


Figure 1. <sup>1</sup>H NMR spectra of PAA-C<sub>12</sub>-Azo (A) and  $\alpha$ -CD-RhB (B).

released from the capsules was measured based on an RF-530/PC spectrofluorophotometer (Shimadzu) with absorbance at 554 nm, and the cumulative drug release was calculated as follows: cumulative amount released (%) =  $(M_t/M_\infty)(100)$ , where  $M_t$  is the amount of drug released from the capsules at time  $t$  and  $M_\infty$  is the amount of drug loaded in the capsules.

## RESULTS AND DISCUSSION

**Synthesis of PAA-C<sub>12</sub>-Azo, CMD-g- $\alpha$ -CD, and  $\alpha$ -CD-RhB.** PAA-C<sub>12</sub>-Azo was synthesized based on Scheme 2A. The characteristic signals of PAA chain and Azo appear simultaneously in the <sup>1</sup>H NMR spectrum of PAA-C<sub>12</sub>-Azo (Figure 1A), suggesting the successful synthesis of PAA-C<sub>12</sub>-Azo. The molecular weight of PAA-C<sub>12</sub>-Azo was determined by GPC measurement ( $M_n \sim 120$  kDa, PDI 1.32), and the substitution degree of Azo (the number of Azo molecules to one acrylic acid unit of PAA) was calculated as 3% from the <sup>1</sup>H NMR spectrum.

CMD-g- $\alpha$ -CD was synthesized from CMD and 3-NH<sub>2</sub>- $\alpha$ -CD as shown in Scheme 2B. Dextran was first transformed into the CMD, and the degree of substitution of CMD (the number of carboxyl groups to the anhydroglucose unit of CMD) was calculated as 0.95 from the <sup>1</sup>H NMR spectrum. Then CMD was reacted with 3-NH<sub>2</sub>- $\alpha$ -CD between carboxy groups in CMD and the amino group in 3-NH<sub>2</sub>- $\alpha$ -CD using EDC as a coupling reagent. The structures of CMD and CMD-g- $\alpha$ -CD were confirmed by FTIR as shown in Figure 2, respectively. It was found that the compositions of CMD and CMD-g- $\alpha$ -CD were in accordance with the expected structures. In Figure 2A, the characteristic peak at 1730 cm<sup>-1</sup> of CMD is ascribed to a carboxyl group. However, as shown in Figure 2B, the peak at 1730 cm<sup>-1</sup> was diminished and the peak at 1650 cm<sup>-1</sup> which belongs to the

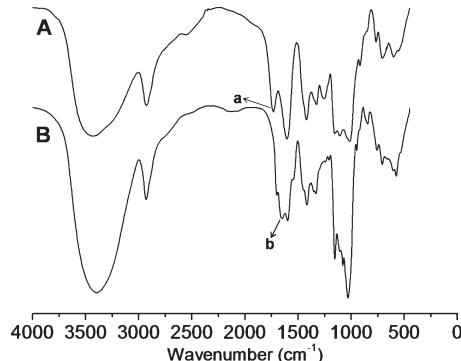
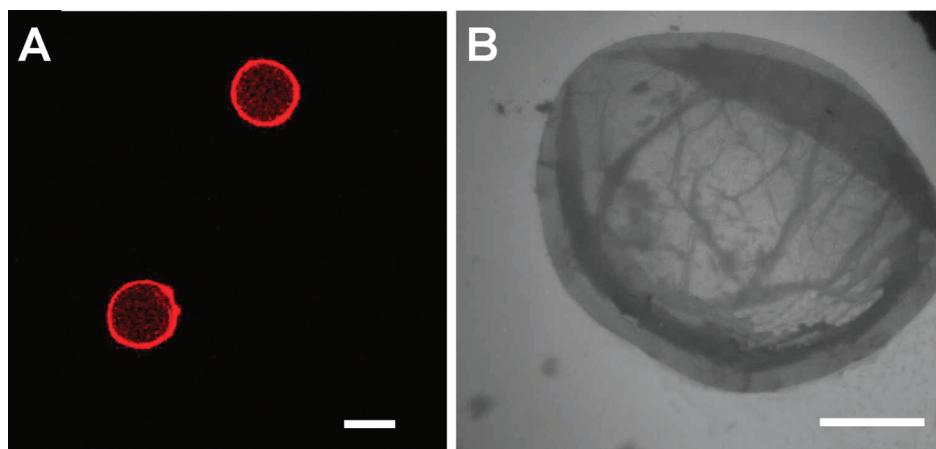


Figure 2. FTIR spectra of CMD (A) and CMD-g- $\alpha$ -CD (B).

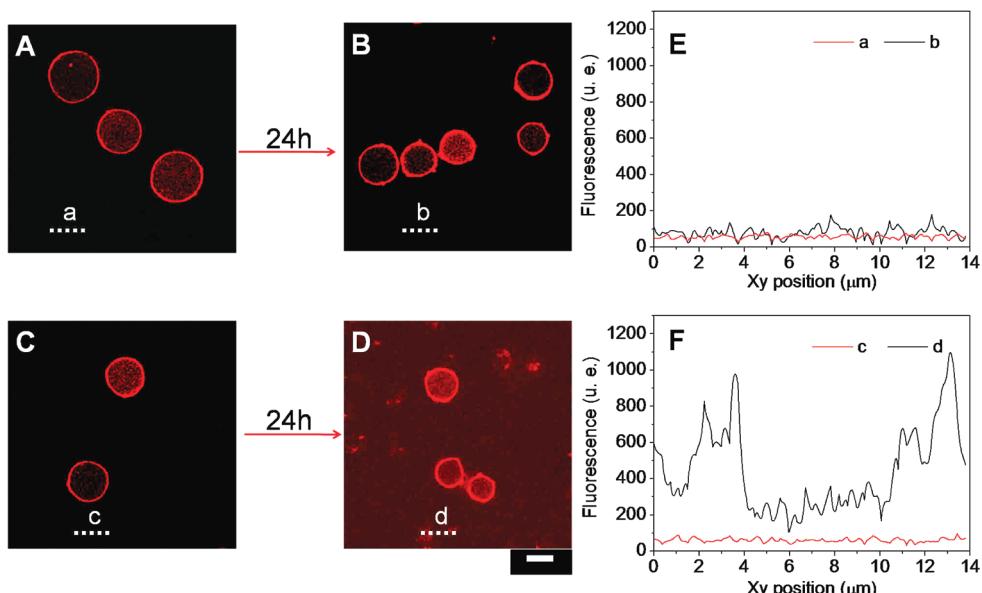
amide group of CMD-g- $\alpha$ -CD appeared. The results demonstrated that most of the carboxyl groups of CMD were converted to the amide groups of CMD- $\alpha$ -CD, indicating the successful synthesis of CMD-g- $\alpha$ -CD.

Molecular weights of CMD and CMD-g- $\alpha$ -CD were measured by size exclusion chromatography multiangle laser light scattering (SEC-MALLS). The number-average molecular weights of CMD and CMD-g- $\alpha$ -CD are 23 800 ( $M_w/M_n = 1.677$ ) and 82 600 ( $M_w/M_n = 1.703$ ), respectively. The substitution degree of  $\alpha$ -CD in CMD-g- $\alpha$ -CD (the number of  $\alpha$ -CD molecules to one anhydroglucose unit of CMD) is calculated as 60% from the molecular weights.

$\alpha$ -CD-RhB was synthesized from RhB and 3-NH<sub>2</sub>- $\alpha$ -CD. The RhB was reacted with 3-NH<sub>2</sub>- $\alpha$ -CD between carboxy groups in RhB and the amino group in 3-NH<sub>2</sub>- $\alpha$ -CD using EDC as a coupling reagent. The characteristic signals of RhB and  $\alpha$ -CD



**Figure 3.** CLSM (A) and TEM (B) images of  $(\text{PAA-C}_{12}\text{-Azo})_5/(\text{CMD-}g\text{-}\alpha\text{-CD}\&\alpha\text{-CD-RhB})_5$  capsules. The scale bars of A and B are 10 and 5  $\mu\text{m}$ , respectively.



**Figure 4.** CLSM images of  $(\text{PAA-C}_{12}\text{-Azo})_5/(\text{CMD-}g\text{-}\alpha\text{-CD}\&\alpha\text{-CD-RhB})_5$  (A, B) and  $(\text{PAA-C}_{12}\text{-Azo})_5/(\text{CMD-}g\text{-}\alpha\text{-CD}\&\text{RhB})_5$  (C, D) microcapsules incubated in 0.4 M EDTA solution at pH 7.4 for 24 h in dark. Scale bar 10  $\mu\text{m}$ . The curves in parts E and F correspond to the fluorescent intensities of the dotted lines (a, b) and (c, d), respectively.

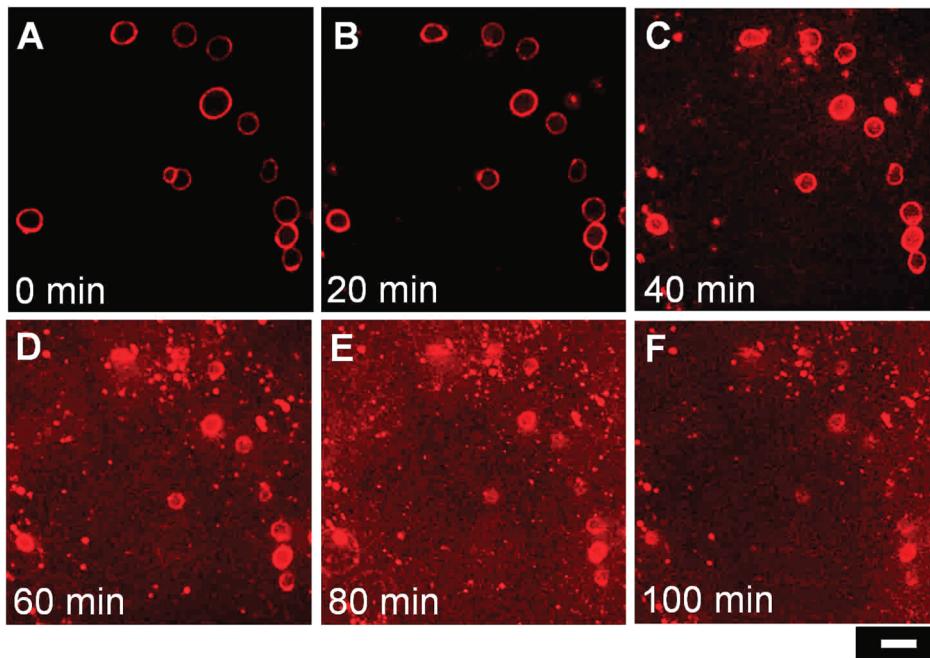
appear simultaneously in the  $^1\text{H}$  NMR spectrum of  $\alpha\text{-CD-RhB}$  (Figure 1B), suggesting the successful synthesis of  $\alpha\text{-CD-RhB}$ .

**Fabrication of  $(\text{CMD-}g\text{-}\alpha\text{-CD}\&\alpha\text{-CD-RhB})_5/(\text{PAA-C}_{12}\text{-Azo})_5$  Microcapsules.** Five  $(\text{CMD-}g\text{-}\alpha\text{-CD}\&\alpha\text{-CD-RhB})_5/(\text{PAA-C}_{12}\text{-Azo})$  bilayers were assembled on  $\text{CaCO}_3$  particles. As  $\text{CaCO}_3$  particles were captured with PAH, the surface potential of  $\text{CaCO}_3$  particles has positive charge.  $\text{CaCO}_3$  particles were first coated with a layer of negatively charged  $\text{PAA-C}_{12}\text{-Azo}$ . Then  $\text{CMD-}g\text{-}\alpha\text{-CD}\&\alpha\text{-CD-RhB}$  and  $\text{PAA-C}_{12}\text{-Azo}$  were assembled on the  $\text{CaCO}_3$  particles with host–guest interaction between  $\alpha\text{-CD}$  and Azo. It should be noted that the self-assembly interactions between the layer of  $\text{PAA-C}_{12}\text{-Azo}$  and the layer of  $\text{CMD-}g\text{-}\alpha\text{-CD}$  were not electrostatic interactions but host–guest interactions since both  $\text{PAA-C}_{12}\text{-Azo}$  and  $\text{CMD-}g\text{-}\alpha\text{-CD}$  are negatively charged. It is well-known that the host–guest interaction is specific, highly efficient, and reversible. Using supramolecular interaction instead of electrostatic interaction as the driving force of LbL can enhance the

stability of microcapsules under various pH conditions. Moreover, it is convenient to fabricate intelligent microcapsules since some supramolecular interaction can respond to external stimuli.

$(\text{CMD-}g\text{-}\alpha\text{-CD}\&\alpha\text{-CD-RhB})_5/(\text{PAA-C}_{12}\text{-Azo})_5$  microcapsules were obtained by removal of the core in EDTA solution. Hollow microcapsules were observed by CLSM in water. As shown in Figure 3A, regular spherical microcapsules with a diameter of around 10  $\mu\text{m}$  were dispersed separately in water. Red fluorescent shells excited from RhB by a 543 nm wavelength laser were in existence simultaneously. The red fluorescent shell indicated that the  $\alpha\text{-CD-RhB}$  was loaded on the layers.  $\text{CMD-}g\text{-}\alpha\text{-CD/PAA-C}_{12}\text{-Azo}$  microcapsules were also observed by TEM. As shown in Figure 3B, the hollow microcapsule could be observed clearly from the TEM image.

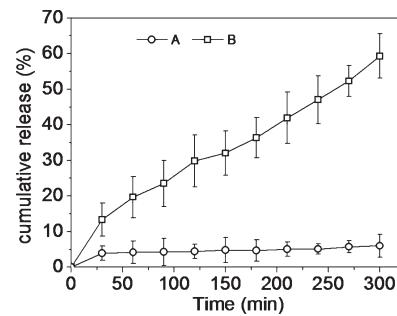
**Hollow Microcapsule Incubation.** To discuss the differences between the supramolecular drug-loading approach and the physical-adsorbing drug-loading approach, the  $(\text{CMD-}g\text{-}\alpha\text{-CD}\&\text{free}$



**Figure 5.** Snapshots of the photodissociation of  $(\text{PAA-C}_{12}\text{-Azo})_5/(\text{CMD-}g\text{-}\alpha\text{-CD+}\alpha\text{-CD-RhB})_5$  microcapsules (A–F). The time interval between the snapshots is 20 min. Scale bar 15  $\mu\text{m}$ .

$\text{RhB}_5/(\text{PAA-C}_{12}\text{-Azo})_5$  microcapsules were selected as the control. As shown in Figure 4, the CLSM images of fresh  $(\text{CMD-}g\text{-}\alpha\text{-CD+free RhB})_5/(\text{PAA-C}_{12}\text{-Azo})_5$  microcapsules and  $(\text{CMD-}g\text{-}\alpha\text{-CD+}\alpha\text{-CD-RhB})_5/(\text{PAA-C}_{12}\text{-Azo})_5$  microcapsules are similar. Both microcapsules can load model drug in layers successfully, proved by the regular, spherical, and red fluorescence, and no drug was released. However, after 24 h of incubating in water in the dark, differences could be found from the images taken by CLSM of these two microcapsules. The background of  $(\text{CMD-}g\text{-}\alpha\text{-CD+}\alpha\text{-CD-RhB})_5/(\text{PAA-C}_{12}\text{-Azo})_5$  microcapsules was still black (Figure 4B) and the fluorescent intensity had no obvious changes (Figure 4E), while the red fluorescence could be observed obviously in the background of  $(\text{CMD-}g\text{-}\alpha\text{-CD+free RhB})_5/(\text{PAA-C}_{12}\text{-Azo})_5$  microcapsules (Figure 4D) and the fluorescent intensity increased dramatically (Figure 4F). Results demonstrated that a large amount of model drug had been released from the  $(\text{CMD-}g\text{-}\alpha\text{-CD+free RhB})_5/(\text{PAA-C}_{12}\text{-Azo})_5$  microcapsules during the past 24 h while the model drug in  $(\text{CMD-}g\text{-}\alpha\text{-CD+}\alpha\text{-CD-RhB})_5/(\text{PAA-C}_{12}\text{-Azo})_5$  microcapsules did not. This difference was attributed to the fact that the interactions between free RhB and layers is relatively weak; therefore, RhB would be released from the capsules uncontrollably. Oppositely, the host–guest interaction between  $\alpha\text{-CD-RhB}$  and PAA- $\text{C}_{12}\text{-Azo}$  was strong enough to keep the model drug in the layers.

**Photodissociation of  $(\text{CMD-}g\text{-}\alpha\text{-CD+}\alpha\text{-CD-RhB})_5/(\text{PAA-C}_{12}\text{-Azo})_5$  Microcapsules.** In order to study the photodissociation of  $(\text{CMD-}g\text{-}\alpha\text{-CD+}\alpha\text{-CD-RhB})_5/(\text{PAA-C}_{12}\text{-Azo})_5$  microcapsules, CLSM was used to observe the capsules irradiated by UV light. After core removal and dipping into EDTA solution, the dissociation of capsules was observed with CLSM immediately. As shown in Figure 5A, after core removal the core–shell structure of the capsules was still in existence. Red fluorescence can be observed only from shells of capsules and the background remained black, indicating that  $\alpha\text{-CD-RhB}$  was held completely in the intact  $(\text{CMD-}g\text{-}\alpha\text{-CD+}\alpha\text{-CD-RhB})_5/(\text{PAA-C}_{12}\text{-Azo})_5$  shells. However, with the irradiation of



**Figure 6.** Drug release behaviors of  $(\text{PAA-C}_{12}\text{-Azo})_5/(\text{CMD-}g\text{-}\alpha\text{-CD+}\alpha\text{-CD-RhB})_5$  microcapsules in the dark (A) and under 365 nm UV light irradiation (B).

UV light, the red fluorescence of regular shells disappeared gradually with increasing red fluorescence in the background (Figure 5B–E). It is evident that 80 min later the core–shell structure of the capsules was destructed and the  $\alpha\text{-CD-RhB}$  loaded on the shells of capsules got spread, suggesting that the  $(\text{CMD-}g\text{-}\alpha\text{-CD+}\alpha\text{-CD-RhB})_5/(\text{PAA-C}_{12}\text{-Azo})_5$  microcapsules dissociated with the release of  $\alpha\text{-CD-RhB}$  under the irradiation of UV light.

**In Vitro Drug Release at Different Conditions.** UV light was used to control the drug release of  $(\text{CMD-}g\text{-}\alpha\text{-CD+}\alpha\text{-CD-RhB})_5/(\text{PAA-C}_{12}\text{-Azo})_5$  microcapsules since the Azo bond could be shifted between *trans* and *cis* forms by UV light. As shown in Figure 6, in dark environment, the drug release was very slow and less than 5% of drug was released in 300 min. However, the drug release was accelerated dramatically with UV irradiation due to the dissociation of microcapsules. As a result, more than 60% of drug was released from the microcapsules within 300 min. The results demonstrated that the drug release of  $(\text{CMD-}g\text{-}\alpha\text{-CD+}\alpha\text{-CD-RhB})_5/(\text{PAA-C}_{12}\text{-Azo})_5$  microcapsules was controllable by using UV irradiation.

## ■ CONCLUSIONS

A new kind of photoswitchable and hollow LbL microcapsules via host–guest interactions between  $\alpha$ -CD and Azo was fabricated.  $\alpha$ -CD-RhB was used as a model drug and loaded on the PAA-C<sub>12</sub>-Azo layers of hollow capsules. Since the interactions between  $\alpha$ -CD and Azo were photosensitive, the capsules could be dissociated and release drug under the irradiation of UV light, showing a controllable release behavior. Compared with traditional drug-loading approaches such as chemical bonding and physical adsorption, this supramolecular drug-loading approach exhibits convenient drug loading, ideal bonding strength, and photoswitchable drug release. These photoswitchable microcapsules will find wide application in biomedical fields.

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