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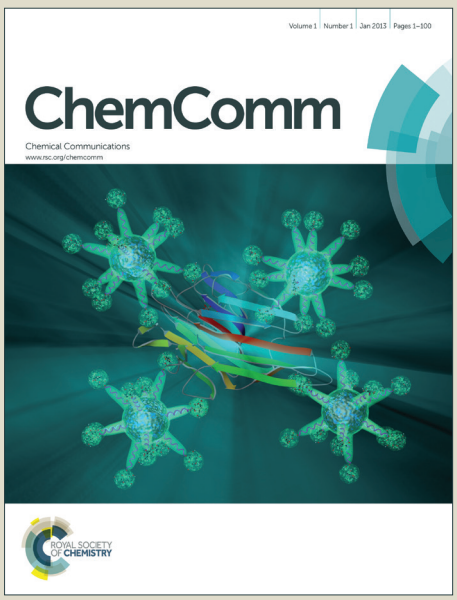

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Reversible morphology transitions of supramolecular polymer self-assemblies for switch-controlled drug release

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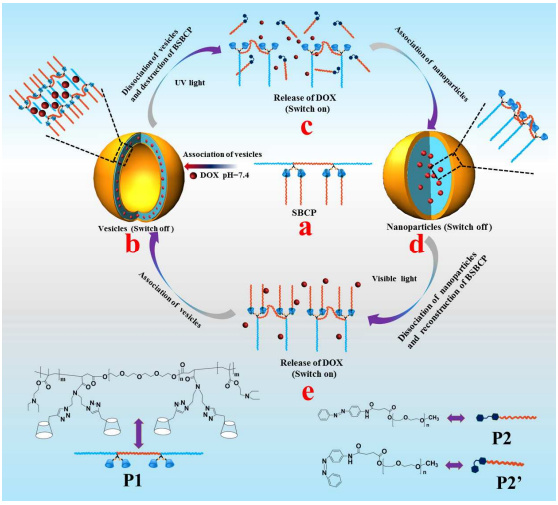
A novel method for switch-controlled drug release was developed through the reversible morphology transitions of supramolecular branched copolymer self-assemblies. The reversible transitions from vesicles to nanoparticles were successfully achieved by alternating UV and visible light irradiation to obtain morphology-controlled drug release in a switch mode.

Supramolecular self-assemblies, such as vesicles, micelles, nanoparticles, microcapsules, hydrogels and tubes, have attracted considerable research attention because of their various applications in chemistry, biotechnology, and materials science.[1] The advantages of supramolecular self-assemblies include its encapsulation property, controllable permeability and surface functionality.[2] An important aspect of supramolecular self-assemblies is that their function could be achieved by controlling the morphology of the assemblies, which would endow them with diverse properties. Intensive experimental[3] and theoretical[4] studies showed that the morphology of supramolecular self-assemblies could be tuned by adjusting molecular parameters (block species and polymerization degree of different blocks),[5] solution parameters (solvent species and selective solvent content),[6] and stimulus parameters (pH, photo, temperature, and ultrasound).[7] In our recent work, we found that the supramolecular self-assembly morphology of amphiphilic β-cyclodextrin (β-CD) dimmers could transfer from spherical nanoparticles to branched aggregates under ultrasound[8] or from branched aggregates to spherical nanoparticles after addition of completive guest molecules.[9] Although several morphology-tunable supramolecular self-assemblies have been reported,[10] utilizing the morphology transitions of the self-assemblies to control drug release has been rarely investigated.[11]

In this study, we present a switch-controlled drug release system through light-triggered reversible morphology transitions of supramolecular self-assemblies from vesicles to nanoparticles on the basis of the destruction and reconstruction of supramolecular branched copolymer (2(mPEG)-*g*-(PDEA-*b*-PEG-*b*-PDEA)-*g*-2(mPEG), SBCP; Scheme 1a). SBCP was synthesized through the orthogonal self-assembly of poly((diethylamino)ethyl-methacrylate)-*b*-polyethyleneglycol-*b*-poly((diethylamino)ethyl-methacrylate) containing two *β*-CD units at every terminal ((*β*-CD)$_2$-*g*-(PDEA-*b*-PEG-*b*-PDEA)-*g*-(*β*-CD)$_2$, P1) and methoxypolyethyleneglycols with single *trans*-Azo end-capping (mPEG-*t*Azo, P2). SBCP self-assembled into vesicles when the pH of the polymer solution was increased from 6.0 to 7.4. Doxycycline (DOX) molecules as a model drug were synchronously encapsulated into the vesicles (Scheme 1a–b). After alternating UV/visible light irradiation, the host–guest interactions between the *β*-CD and Azo groups in SBCP self-assemblies underwent reversible dissociation–association and led to the reversible morphology transitions from vesicles to nanoparticles (Scheme 1b–d and 1d–b) accompanied by controlled release of DOX in on–off switch mode.



Scheme 1. Switch-controlled release of DOX through light-triggered reversible morphology transitions of supramolecular self-assemblies from vesicles to nanoparticles on the basis of the

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destruction and reconstruction of supramolecular branched copolymers (SBCP). (a) Chemical structure of SBCP constructed by the host–guest interactions of P1 and P2; (a-b) Association of initial vesicles on SBCP with DOX loading (switch off); (b-c) Dissociation of vesicles and destruction of SBCP induced by UV light irradiation with the release of DOX (switch on); (c-d) Association of nanoparticles based on the self-assembly of P1 (switch off); (d-e) Dissociation of nanoparticles and reconstruction of SBCP induced by visible light irradiation with the release DOX (switch on); and (e-b) Association of vesicles again (switch off).

SBCP was synthesized by directly mixing aqueous solutions of P2 (0.04 M) and P1 (0.01 M) at pH 6.0. The detailed synthesis and characterization of P1 and P2 are shown in Supporting Information (Fig. S1–S5 and Table S1). The 2D NOESY spectra of the mixed solutions with a 1/4 molar ratio of P1 to P2 showed that the signals of the *t*AZO protons (i-H and j-H) of P2 were correlated with the signals ofthe inner protons of *β*-CD (3-H and 5-H) in P1 (Fig. S6A). This result indicated the occurrence of the complexation between the *β*-CD and *t*Azo moieties. Isothermal titration calorimetry (ITC) was performed to confirm the host–guest interactions. In a typical experiment, using single functionalized P1 and P2 as model molecules, the aqueous solution of P2 (12.0 mM) was trickled into the solution of P1 (0.6 mM), and an exothermic binding isotherm was obtained. The association constant (K_t) of *β*-CD and *t*Azo was 1.45 ×10^3 M^{-1}, which indicated that these moieties can strongly bind to each other through the host–guest interactions (Fig. S6B). UV absorption at 348 nm of the *t*Azo groups in mixed solutions increased with increasing P1 content because of the host–guest inclusion between *t*Azo and *β*-CD[12] (Fig. S7) and reached the maximal value when the molar ratio of P1/P2 increased to 1/4. These results indicated that SBCP was successfully constructed through the host–guest inclusion between the *β*-CD and *t*Azo moieties. The dissociation process of SBCP was also investigated. The ITC results in Fig. S6B showed that the K_t of *β*-CD and *t*AZO was 1.45 × 10^3 M^{-1} in the adducted SBCP; this K_t value was less than half of that of the simple *t*Azo/*β*-CD complex (5.36 × 10^3 M^{-1}).[13] It has been reported that the lower K_t indicated that the inclusion complex is easy to be dissociated under some stimuli.[14] Therefore, the reduced interaction force induced rapid UV light-induced dissociation. The same conclusion has been reported by Yuan et al.[12] Azo can transform between *t*AZO and *c*AZO after alternating UV/visible light irradiation.[15] In the 2D ^{1}H NMR NOESY spectra of the SBCP solution (Fig. S8A and S8B), the correlation peaks between *c*Azo protons and the inner protons of *β*-CD disappeared at 365 nm UVlight irradiation, whereas the correlation peaks appeared again after visible light irradiation. This finding indicated the reversible construction process of SBCP.

The initial vesicular morphology of the SBCP aqueous solution (pH=7.4, 1.5 mg/mL) was confirmed through transmission electron microscopy (TEM), dynamic light scattering/static light scattering (DLS/SLS), and ^{1}H NMR. TEM was conducted to visualize the formed self-assemblies. Fig. 1A reveals that these supramolecular self-assemblies exhibited a particulate vesicular morphology with an average diameter (D_{av}) of 121 nm, as evidenced by the distinct contrast between the dark periphery and lighter hollow part. The size was in accordance with the result of DLS, which showed an equivalent size of 128 nm (Fig. 2A). Furthermore, the R_g/R_h value determined by the combination of DLS and SLS can predict the particle morphology.[16] For example, a solid sphere exhibits an R_g/R_h of 0.774, whereas that of a thin-layer hollow sphere is 1.00. In the present study, the R_g/R_h value of SBCP self-assemblies was 1.01, indicating the presence of vesicle structures. This finding corresponded to the result of TEM. The wall thickness was about 24–42 nm as determined through the TEM results and in good agreement with the bilayer molecular length of 18.6 nm calculated for the mPEG-PDEA block,[12] thereby confirming the orthogonal assembly manner. In the ^{1}HNMR spectrum of SBCP at pH 7.4 (Fig. S9), signals around 7.6–7.9 ppmare associated with Azo. Moreover, PDEA signals around 2.3–1.0 ppm sharply decreased, whereas the signals of PEG and mPEG minimally changed. These results clearly showed that the PDEA segments were under the aggregated state, resulting inlost mobility, whereas all the PEG chains, as theshell of the aggregates, remained in the soluble state. The critical aggregation concentration (CAC) of the SBCP aqueous solution was 0.64 mg mL^{-1}, as monitored through the pyrene fluorescence probe method (Fig. S10A). On the basis of these results, we propose a sandwich model for the vesicle membrane as shown in Scheme 1b.

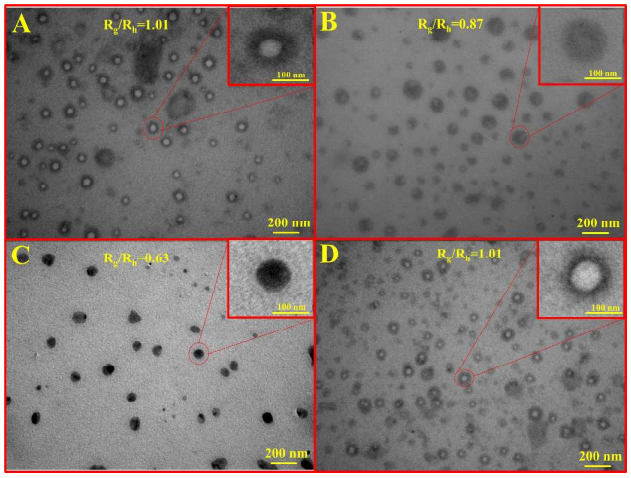

Fig. 1. Typical TEM images for light-triggered reversible morphology transitions of SBCP self-assemblies from vesicles to nanoparticles. (A) Vesicles without UV light; (B) Loose nanoparticles under 365 nm UV light for 5 min; (C) Solid nanoparticles under 365 nm UV light for 15 min; (D) Vesicles under visible light for 15 min.

The reversible morphology transitions of the initial SBCP self-assemblies from vesicles to nanoparticles were further studied. After exposing the solution to UV light irradiation at 365 nm for 5 min, P2 underwent photoisomerization to form mPEG-*c*AZO (P2'); subsequently, P2' was excluded from SBCP self-assemblies because the *β*-CD cavity cannot accommodate bulkier *c*Azo guest.[17] As a result, the bilayer structures of vesicles were gradually destroyed, inducing a partial disaggregation of vesicles and some loose nanoparticles appeared (Fig. 1B). These vesicles were completely dissociated and further reassembled into solid nanoparticles with a D_{av} of 97 nm and an R_g/R_h of 0.63 after exposure to UV light irradiation for 15 min (Fig. 1C). Interestingly, the vesicular morphology could be reconstructed by imposing visible light for 15 min (Fig. 1D). In particular, the shape, size, and R_g/R_h values of the vesicles were similar to the original values shown in Fig. 1A. In

contrast to the original SBCP self-assemblies, the DLS results showed that the D_z value decreased from 128 nm to 91 nm upon exposure to UV light and restored after exposure to visible light (Fig. 2A). Furthermore, the D_z value maintained a cycle change that corresponds to the alternating UV/visible light irradiation for several times, as shown in Fig. 2B. These results further implied a light-triggered reversible morphology transition of SBCP self-assemblies from vesicles to nanoparticles.

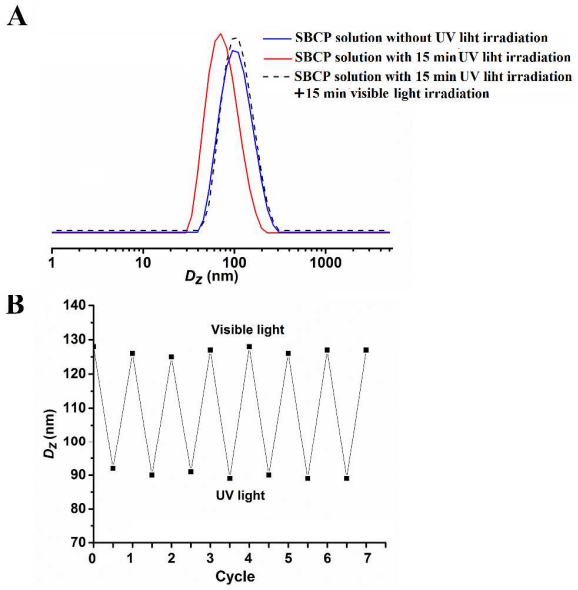

Fig. 2. DLS results of reversible self-assembly morphology transitions of the initial SBCP self-assemblies from vesicles to nanoparticles. (A) D_z distributions of SBCP self-assemblies by imposing UV and visible light irradiation; (B) cycle change of the D_z values of SBCP self-assembliesby alternately imposing UV and visible light irradiation.

The influence of UV light irradiation on the reversible morphology transitions of SBCP self-assemblies was further confirmed though UV/visible spectrophotometry and ^{1}H NMR. As shown in Fig. S11Aa, the P2 solution displayed a typical absorption of the *t*Azo groups at 348 nm. After adding 1/4 amount of P1, the absorption peak was strongly enhanced and the molar extinction coefficient of the *t*Azo species increased from 0.19 ×10^4 M^{-1} cm^{-1} to 0.48 × 10^4 M^{-1} cm^{-1} (Fig. S11Ab). This finding indicated the formation of SBCP.[12] After UV light irradiation, isomerization resulted in a remarkable decrease in absorption at 348 nm concomitant with a new characteristic peak at 433 nm, which is ascribed to the *c*Azo groups (Fig. S11Ac). This curve is similar to that of P2' (Fig. S11Ad) and indicated the destruction of SBCP. After visible light irradiation, the characteristic peak at 433 nm disappeared and cure e was similar to cure b, indicating the reconstruction of SBCP. In addition, the typical absorption of *t*Azo at 348 nm appeared repeatedly by imposing alternating UV/visible light irradiation tothe SBCP solution. This finding confirmed the reversible Azo group configuration transition from *trans* to *cis* (Fig. S12) with the cycle of destruction–reconstruction process of SBCP. ^{1}H NMR was performed to further confirm the structural changes in SBCP self-assemblies after UV/visible light irradiation. As shown in Fig. S11B, the signals of *β*-CD and Azo were enhanced, whereas those of PDEA could not be found after UV light irradiation (Fig. S11Bb) compared with those before irradiation (Fig. S11Ba). Hence, vesicles dissociated and hydrophilic *β*-CD and PEG in P1 formed the shell of nanoparticles after UV light irradiation. After visible light irradiation for 15 min, the signals of *β*-CD and Azo almost disappeared. This finding indicated the association of vesicles, which was in accordance with the results of TEM and DLS.

The reversible morphology transitions of SBCP self-assemblies can be utilized as a feasible medium for encapsulation and releaseof drug molecules. Therefore, DOX as a model drug was loaded into the vesicles for the release experiment. Measurements of DOX release provided a quantitative resultofthe morphology-controlled DOX release in a switch mode. Three release curves (a–c) in Fig. 3 represent the cumulative release amount of the controlsunder dark conditions without UV light irradiation (a), one cycle of UV/visible light irradiation (b), and three cycles of UV/visible light irradiation (c). In curve a, therelease rate of DOX was very slow and only a small amount of DOX (<20%) could be released after 10 h,suggesting that most DOX molecules were retained in the vesicles. Compared with curve a, curve b presented a switch-controlled DOX release after alternating UV/visible light irradiation. This phenomenon was also observed in curve c. Moreover, the cumulative release amount of curve c was higher than that of curve b as evidenced by the higher cycle release times.

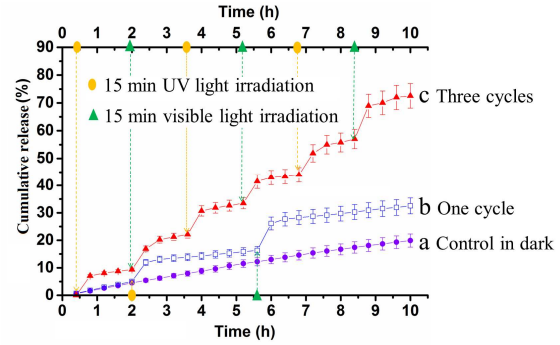

Fig. 3. Cumulative release curves of DOX under different UV/visible light irradiation times. (a) Control in dark without UV light irradiation, (b) One cycle of UV/visible light irradiation, and (c) three cycles of UV/visible light irradiation.

The staircase-like release curves b and c in Fig. 3 indicated that the release of DOX could be controlled in an "on–off" switch model. The related release mechanism was proposed as follows. Upon UV light irradiation, vesicles dissociated, SBCP was destroyed, and the switch state changed from "off" to "on" (Scheme 1b-c), thereby releasing DOX. Nanoparticles were then associated and encapsulated the remanent DOXs (Scheme 1c-d). In this case, the switch was under the "off" state and resulted in the inhibited release of DOX. Subsequently, nanoparticles dissociated and SBCP was reconstructed after visible light irradiation. Therefore, the release of DOX was enhanced because of the "on" state of the switch again (Scheme 1d-e). Vesicles were then associated because of the reassembly of SBCP (Scheme 1e–b) and encapsulated the remanent DOXs. The whole cycle of DOX release can be conducted for several times according to the curve c in Fig. 3. Therefore, the light-triggered reversible morphology transitions of SBCP self-

assemblies from vesicles to nanoparticles generated an effective switch-controlled drug release. Additionally, Du et al[18] also reported a ultrasound-driven vesicle-vesicle re-self-assembly drug release system, but it is different from the "on–off" switch-controlled release reported in this paper.

In summary, we present a switch-controlled drug release process through light-triggered reversible morphology transitions from vesicles to nanoparticles on the basis of SBCP self-assemblies. SBCP can first self-assemble into vesicles without UVlight irradiation and reassemble into solid nanoparticles with the dissociation of vesicles induced by UV light irradiation. Nanoparticles can be further dissociated with the association of similar vesicles under visiblelight irradiation. The reversible self-assembly morphology transition process, accompanied by the destruction and reconstruction of SBCP, can be utilized to conduct switch-controlled drug release. Drug release can be enhanced at the dissociation stage of vesicles and nanoparticles and inhibited when vesicles and nanoparticles were associated. This study will be helpful in designing supramolecular self-assemblies with reversible morphology transitionfor applications to controlled drug release.

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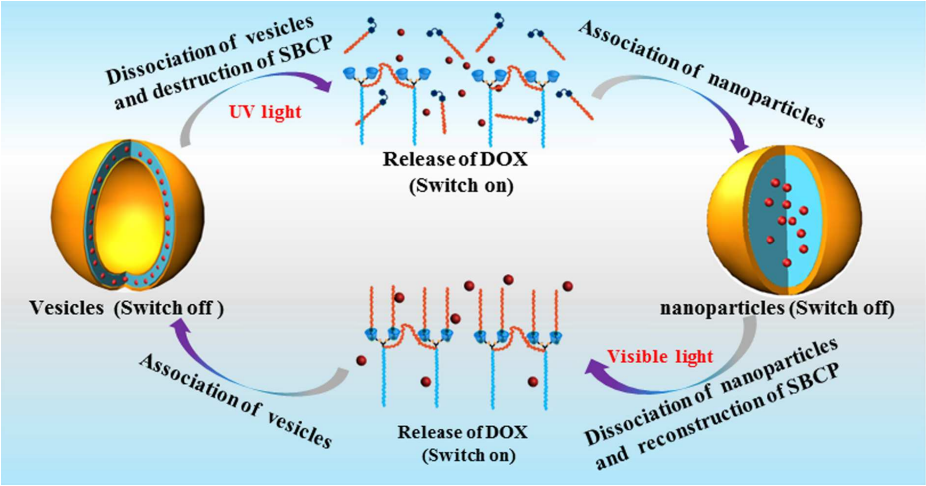

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