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Light-responsive polymer micelles, nano- and microgels based on the reversible photodimerization of coumarin

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ABSTRACT

This paper highlights our recent work on light-responsive polymer micelles, nano- and microgels prepared with amphiphilic or double-hydrophilic block copolymers (BCPs) bearing coumarin moieties. On the one hand, with amphiphilic BCPs, by incorporating coumarin chromophores onto either core-forming or shell-forming block, photo-controlled stabilization and de-stabilization of micelles could be achieved by reversible photo-crosslinking of polymer chains based on the reversible photodimerization of coumarin groups and photo-cleavage of cyclobutane bridges. On the other hand, various designs of double-hydrophilic BCPs bearing coumarin made possible the reversible size change of nano- and micrometer-sized hydrogel particles. We discuss the light-responsive behaviours and the underlying mechanisms of these coumarin-containing BCP micellar aggregates.

1. Introduction

Coumarin and its derivatives have been widely used in a variety of functional polymeric materials including liquid crystals, electro-optical polymers and biomaterials. A comprehensive review was written by Trenor et al. [1] Among the photochemical and photophysical properties of coumarin, the reversible dimerization activated upon absorption of photons of different wavelengths has attracted most attention and been used to impart reversible photo-crosslinking and photo-cleavage for polymers. Recently, our group has extended the use of this photoreaction in making new functional polymers to a new area, namely, light-responsive polymer micelles (nanoparticles with a hydrophobic core and a hydrophilic corona) and nano/microgels (hydrogel particles in the nano to micrometer size range built from water-soluble polymers). This paper highlights the recent progress made by our group in exploring the reversible photodimerization of coumarin for designing light-responsive or photocontrollable polymer particles in solution.

2. Photocontrollable polymer micelles

Amphiphilic BCPs in aqueous solution tend to self assemble into polymer micelles, like low-molecular-weight surfactants, due to the segregation of hydrophobic blocks. Such nanoscaled core-shell BCP micelles have been extensively investigated as nano-carriers for controlled drug delivery applications. As a drug carrier, BCP micelles should fulfill three conditions that are drug encapsulating, transportation in physiological fluid and on-site release. First, polymer micelles should be able to uptake hydrophobic drugs, which alone exhibit poor solubility and low stability in a physiological environment, by virtue of drug solubilization by the hydrophobic micelle core [2]. In the second phase, drug-loaded polymer micelles circulating in biological fluids, should be stable and resist to dilution and interactions with the biological medium (e.g., hydrolysis and enzymatic degradation). It is easy to imagine that part of polymer micelles may dissociate upon dilution to below the critical micelle concentration (CMC) due to thermodynamic instability and a premature leakage of drug could cause harmful side effects during transportation. To prevent the dissociation and stabilize the micelles, a number of strategies for chemical or physical crosslinking of either core or shell of BCP micelles have been developed [3–6]. Finally, after reaching the target (e.g., cancer tissues and cells), polymer micelles should be structurally disrupted to “open the door” allowing for fast drug release. To facilitate the release, on the one hand, many BCP micelles have been designed to react to such stimuli as pH or temperature change, photo-irradiation, ultrasound and redox reactions to trigger their disruption [7–11]. On the other hand, for those chemically crosslinked micelles, approaches for de-crosslinking to promote the de-stabilization have also been studied [5,12–14].

Using coumarin-containing BCPs, we have first proposed a strategy to address the conflicting requirement of micelle stability

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and easy on-site release. The idea was to make an amphiphilic BCP whose hydrophobic block bears some coumarin pendant groups. After formation of micelles, the photodimerization of coumarin groups through a cycloaddition reaction under $\lambda > 310$ nm irradiation gives rise to micelle crosslinking that stabilizes the micelles; subsequently, upon absorption of photons at $\lambda < 260$ nm, the cleavage of cyclobutane bridges can occur leading to micelle de-cross-linking and this would de-stabilize polymer micelles. The first example using reversible photodimerization of coumarin to stabilize and de-stabilize BCP micelles was reported by our group in 2007 [14]. The chemical structure of the designed and synthesized BCP, with a random copolymer of 4-methyl-(7-(methacryloyl)oxy-ethyloxy) coumarin and methyl methacrylate (P(CMA-*co*-MMA)) as the hydrophobic block and a hydrophilic block of poly(ethylene oxide) (PEO), is shown in Fig. 1(a). With an aqueous micellar solution of PEO_{112}-*b*-P(CMA_8-*co*-MMA_{20}) as example, the reversible photoinduced dimerization and cleavage reactions could be monitored by UV–vis spectroscopy as shown in Fig. 1(b) (monomeric coumarin has a maximum absorption at ~320 nm while coumarin dimer doesn't). The dimerization degree of coumarin groups could be reversibly switched between a certain range (from ~70% to 40%) in a number of cycles of alternating UV irradiations at $\lambda > 310$ nm and $\lambda_{max} = 254$ nm. The incomplete photoreactions, especially the cleavage of cyclobutanes, were possibly caused by the high concentration of chromophores as well as the occurrence of photoreaction in the opposite direction under the uesd irradiation wavelengths resulting a photostationary state. Polymer micelles after crosslinking reaction did exhibit better stability. After drying the aqueous solution of crosslinked micelles, those micelles were still stable and existed in micellar state even after being redispersed in dimethyl sulfoxide (DMSO), which is a good solvent for the two blocks. As can be seen from the TEM images in Fig. 1(c), crosslinked polymer micelles were swollen in DMSO, showing larger sizes than those in water. Moreover, the release rate of polymer micelles loaded with a model hydrophobic compound, Nile Red (NR), into a THF/water (2/3, v/v) solution was found to be dependent on the photodimerization and photo-cleavage of coumarin groups. The micelles with a crosslinked core could slow down the release rate while subsequent micelle core de-cross-linking could recover the release rate partially. Those results

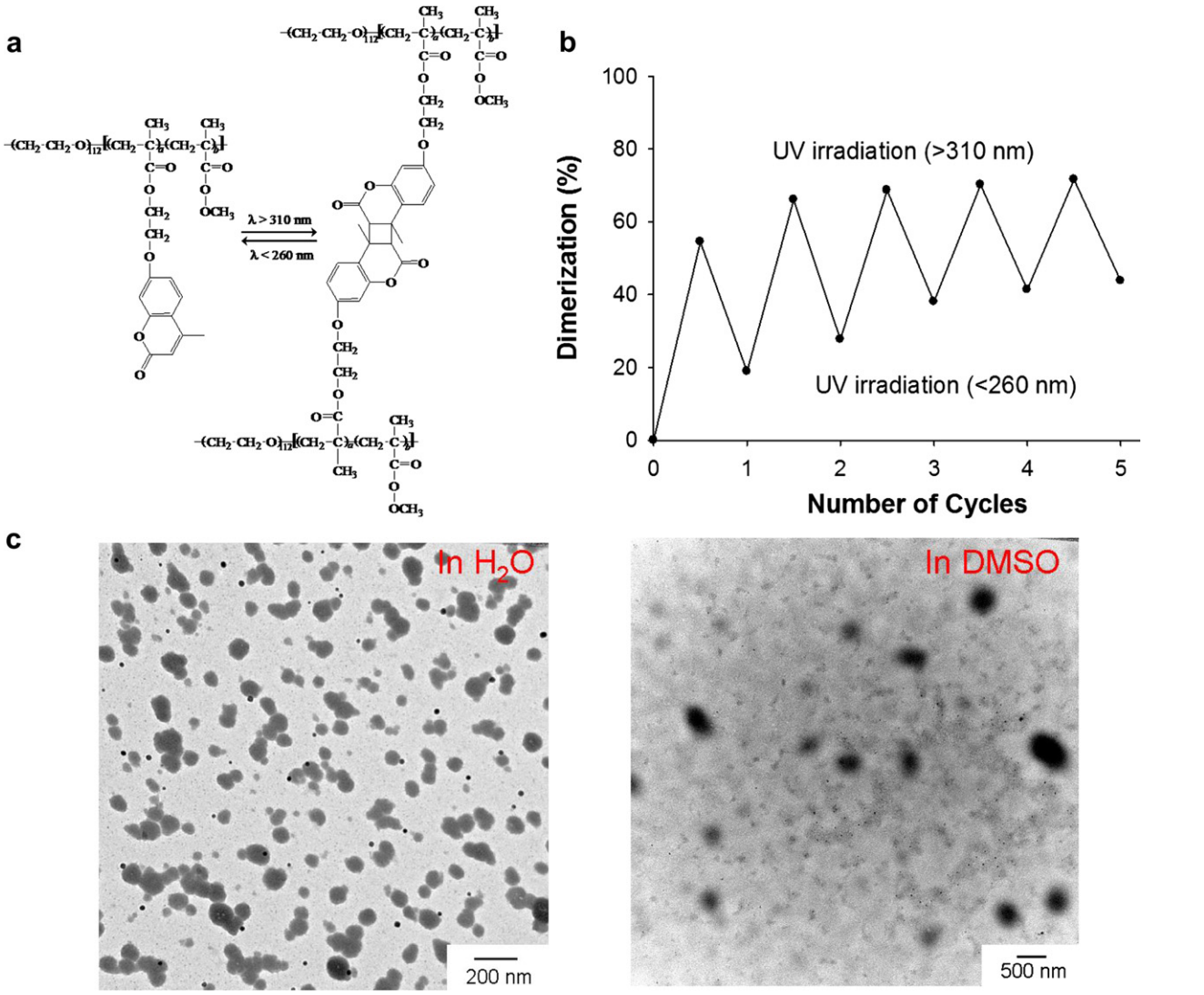

Fig. 1. (a) Chemical structure of amphiphilic block copolymer PEO-*b*-P(CMA-*co*-MMA) and reversible photodimerization ($\lambda > 310$ nm) and photo-cleavage reaction ($\lambda < 260$ nm); (b) UV–vis spectra showing the photocontrollable dimerization degree of coumarin groups in aqueous solution of BCP micelles subjected to alternating UV irradiations at $\lambda > 310$ nm and $\lambda < 260$ nm; (c) TEM images of crosslinked BCP micelles in H_2O (left) and in DMSO (right). Reprinted with permission from Ref. [14].

demonstrated for the first time that the reversible photo-crosslinking and de-crosslinking based on the photoreactions of pendant coumarin groups could be used to first afford the stability of BCP micelles and then to trigger the de-stabilization. The concept of "stabilization-on-demand" is appealing and could find more applications.

Besides the core-crosslinking approach, we have also prepared shell-crosslinked reverse BCP micelles using photodimerization of coumarin. The chemical structure of the designed BCP is shown in Fig. 2(a), which is composed of poly(dimethylaminoethyl methacrylate) (PDMAEMA) as the hydrophilic block and a random copolymer of coumarin methacrylate and methyl methacrylate (P(CMA-*co*-MMA)) as the hydrophobic block [15]. Using a sample of $PDMAEMA_{54}$-*b*-P(CMA_{19}-*co*-$PMMA_{55}$), reverse micelles could be prepared in a mixed organic solvent of THF/CH_2Cl_2 (1/1, v/v) by adding hydrochloric acid (HCl). PDMAEMA block with quarternized tertiary amine groups could form the hydrophilic core because of the poor solubility in the organic solvent, while hydrophobic P(CMA-*co*-MMA) chains formed the shell of micelle. The reverse micelles were then exposed to UV light of $\lambda > 310$ nm to dimerize the coumarin units. The successful shell-crosslinking was confirmed by size exclusion chromatograph (SEC) measurements as shown in Fig. 2(b). For non-crosslinked reverse micelles, the presence of some triethylamine (TEA) in the eluting solution (THF) could convert the PDMAEMA block back to the non-quarternized form by trapping HCl and, consequently, led to the total dissolution of the micelles, displaying a peak at almost the same elution time as molecularly dissolved BCP. By contrast, shell-crosslinked micelles were stable even in the presence of TEA and their elution peak was found at lower elution times, indicating the well-preserved micelle aggregates. Since crosslinking of coumarin was reversible, photo-de-crosslinking was achieved by exposing the micellar solution to UV light of $\lambda < 260$ nm. Photo-de-crosslinked micelles were disintegrated as revealed by their shifted elution peaks corresponding to dissolved chains and disrupted micellar aggregates, while only a very small fraction of micelles remained unaffected.

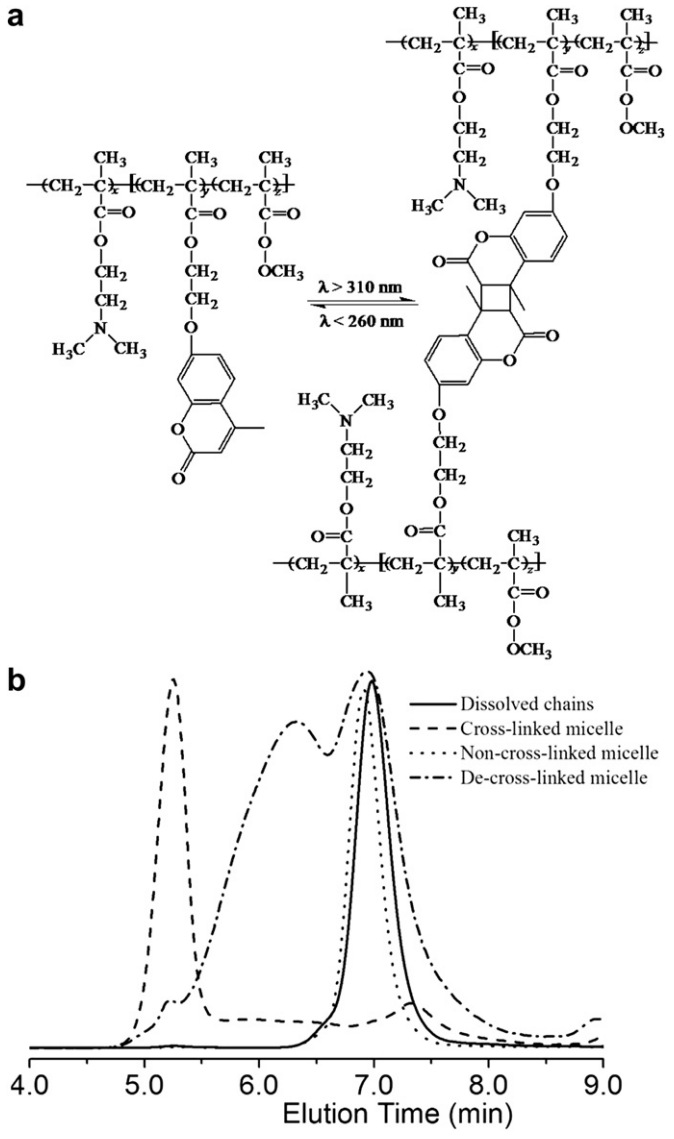

Fig. 2. (a) Chemical structure and photoreaction of the coumarin-containing BCP used to prepare shell-cross-linked reverse micelles; (b) size exclusion chromatography (SEC) traces of molecularly dissolved BCP chains, non-crosslinked micelles in the presence of triethylamine (TEA), photo-crosslinked micelles (UV irradiation at $\lambda > 310$ nm) in the presence of TEA and photo-de-crosslinked micelles (UV irradiation at $\lambda < 260$ nm). Reprinted with permission from Ref. [15].

3. Photoresponsive nano- and microgels

Nano- and microgels are naometer- and micrometer-sized hydrogel particles formed by crosslinked water-soluble polymers, respectively. For drug delivery applications, they have a number of interesting features as compared to large-size hydrogels: [16–18] 1) excellent biocompatibility due to the high-volume of absorbed water, 2) possible development of intravenous injection, especially with nanogel, 3) easy up-taking by cells, 4) better colloidal stability and 5) faster response to stimuli. The general method for preparing nano- and microgel particles is to use the traditional emulsion polymerization or dispersion polymerization. However, these polymerizations may produce gel particles containing a large number of surfactants and residual monomers that need to be removed by further purification. In recent years, the so-called double-hydrophilic block copolymers (DHBCPs), whose two blocks can be soluble in water, have been wildly studied because of their unique self-assembly behaviours in aqueous solution under various stimuli [19,20]. By combining self-assembly of DHBCPs and their core- or shell-crosslinking strategy, stimuli-responsive nano- or microgel particles can be prepared with possibly well-controlled size, crosslinking density and morphology.

Recently, our group prepared and characterized photo-responsive nanogel particles designed from DHBCPs containing coumarin pendant groups [21]. The polymer design principle is as follows. While water-soluble, one block in the DHBCP is a polymer having a lower critical solution temperature (LCST) and it bears coumarin units. When an aqueous solution of the DHBCP is heated to T > LCST, micelles with coumarin in the core can be formed. The micellar solution can then be exposed to $\lambda > 310$ nm UV light for micelle core-crosslinking through coumarin dimerization. Subsequently, when the micellar solution is cooled to T < LCST, nanogel particles are obtained because the crosslinking prevents the dissolution of water-soluble polymer chains from occurring. Because of reversibility of the photoreaction of coumarin, the crosslinking density of nanogel particles in solution can be optically tuned by controlling the photo-de-crosslinking through photo-cleavage of cyclobutanes. Since the amount of water absorbed by hydrogels is related to the crosslinking density of the polymer, the photocontrol over the coumarin dimerization degree means that it would be possible to optically control the swelling degree of nanogel particles, i.e., their size in solution.

The chemical structure of the DHBCP designed to investigate this approach is shown in Fig. 3(a). One block is the "permanently"

hydrophilic PEO, while the other one is a thermo-responsive block of a random copolymer of 2-(2-methoxyethoxy)ethyl methacrylate and coumarin methacrylate (P(MEOMA-*co*-CMA)) that displays an LCST at ~25 °C. With PEO_{112}-*b*-P($MEOMA_{83}$-*co*-CMA_6) as example, the block copolymer solution was firstly equilibrated at 40 °C (above LCST) to produce the micelles and then irradiated by $\lambda > 310$ nm UV light to fully photo-crosslink the micelle cores. After the solution was cooled down to 10 °C (below LCST), nanogel particles having a uniform size of ~39 nm and with a coumarin dimerization degree of ~85% were obtained. After photo-de-crosslinking by irradiation of the nanogel solution with $\lambda < 260$ nm UV light, the decrease in crosslinking density, as revealed by a drop

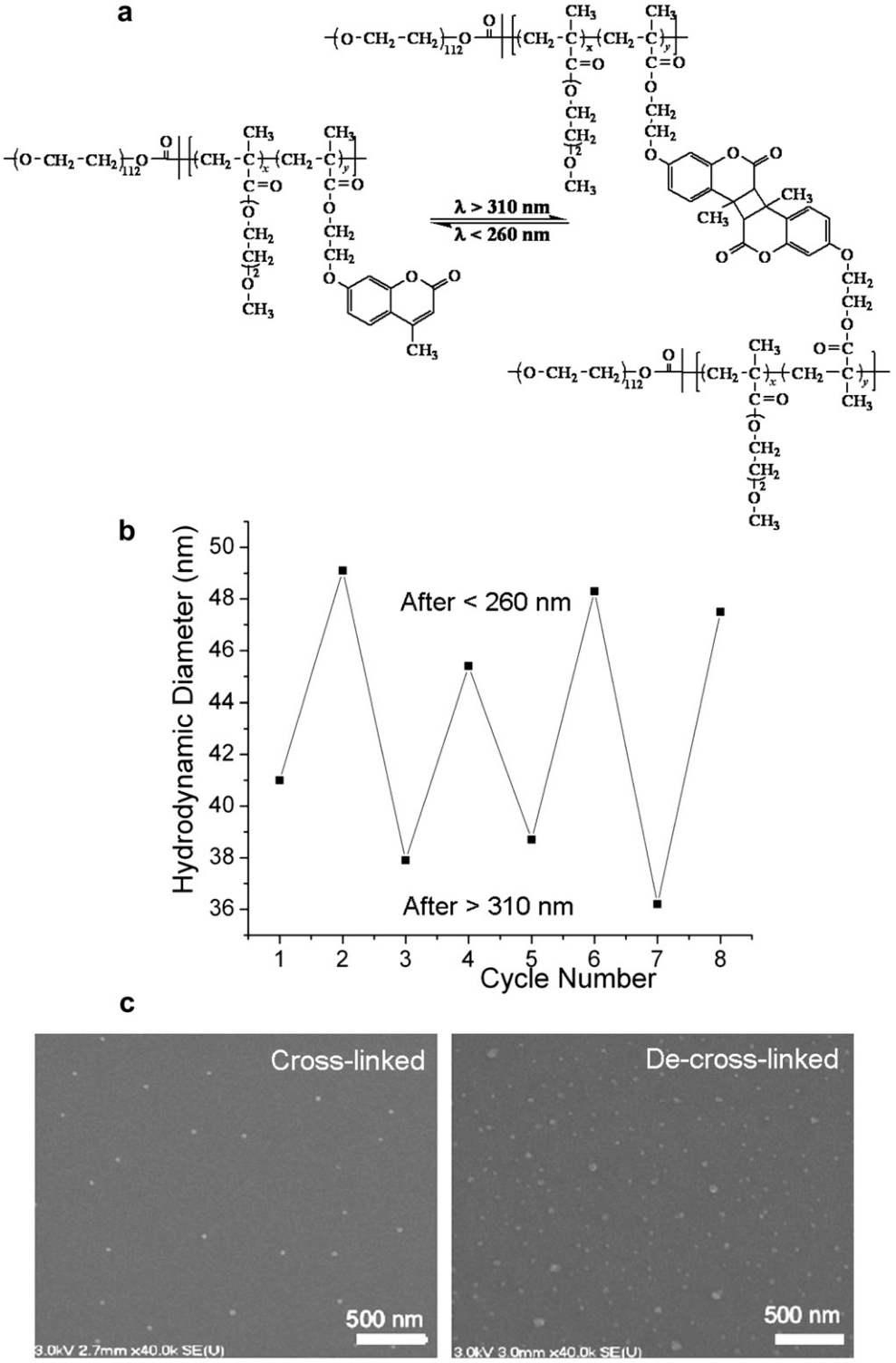

Fig. 3. (a) Chemical structure and reversible photoreaction of the water-soluble block copolymer PEO-*b*-P(MEOMA-*co*-CMA); (b) reversible change in hydrodynamic diameter of PEO_{112}-*b*-P($MEOMA_{83}$-*co*-CMA_6) nanogel particles at 10 °C upon alternating photo-de-crosslinking at $\lambda < 260$ nm and photo-crosslinking at $\lambda > 310$ nm (with the solution heated to 40 °C before cooling back to 10 °C); (c) SEM images of crosslinked and de-crosslinked PEO_{112}-*b*-P($MEOMA_{83}$-*co*-CMA_6) nanogel particles. Reprinted with permission from Ref. [21].

of the coumarin dimerization degree from ~85 to 25%, resulted in more swollen nanogel particles having an average size of ~48 nm. Furthermore, as can be seen from the dynamic light scattering (DLS) results in Fig. 3(b), this photoinduced volume change of nanogels could be repeated for many times by re-cross-linking the particles at 40 °C, followed by cooling the solution to 10 °C. This large photoinduced volume change of nanogels could also be observed in dry state. SEM images of the crosslinked and de-crosslinked nanogels are shown in Fig. 3(c). Moreover, the photoinduced size change of nanogel particles appears to be fast, with the volume increase over de-crosslinking completed within ~100 s. The potential application of such photo-controlled volume change of nanogels on drug delivery was also investigated [21]. The results revealed that nanogels with a highly crosslinked core had a slower release rate and the de-crosslinking could accelerate the drug diffusing speed, suggesting the possibility of photocontrollable delivery using coumarin-containing nanogels.

In another study, the LCST-mediated self-assembly of a coumarin-containing DHBCP gave rise to the formation of larger crosslinked particles, in the form of vesicles, with a size of several micrometers [22], which we refer to as microgels. In this case, the copolymer is composed of a block of poly(*N*-isopropylacrylamide) (PNIPAM) and another block being a random copolymer of 2-(dimethylamino)ethyl methacrylate and coumarin methacrylate (P(DMAEMA-*co*-CMA)) containing ~5 mol% of coumarin units (chemical structure shown in Fig. 4(a)) [22]. With the sample of P(DMAEMA$_{49}$-*co*-CMA$_3$)-*b*-PNIPAM$_{74}$ dissolved in water, polymer vesicles with a P(DMAEMA-*co*-CMA) corona and PNIPAM membrane were formed by heating the solution to 40 °C (T > LCST of PNIPAM). To preserve the vesicle structure, P(DMAEMA-*co*-CMA) corona was crosslinked by irradiation with $\lambda > 310$ nm UV light. When the solution was cooled back to room temperature (T < LCST of PNIPAM), structurally-stabilized microgel particles could be collected by using centrifugation to remove free chains. By switching the solution temperature between below and above the LCST of PNIPAM, microgel particles displayed a large and reversible size change. As shown in Fig. 4(b), the DLS results indicate a size increase of the particles from ~1.32 μm to 3.45 μm upon cooling the solution from 40 °C to 20 °C, and shrinkage of the particles upon heating the solution back to 40 °C. The large-size transition of microgel particles was also confirmed by TEM and optical microscopic images. The dry samples prepared by casting the solution at the two temperatures showed particles with an average diameter of ~1.5 μm at 40 °C and ~3 μm at 20 °C, which corresponds to a volume increase of 700%. This large volume transition of microgels can be attributed to the slight crosslinking of coumarin and the hydration and dehydration of PNIPAM chains in the vesicles. The slight crosslinking provided a size memory effect that, upon heating to 40 °C, allows the vesicles to undergo a contraction driven by the dehydration of PNIPAM. Microgels prepared in this condition maintained the photoresponsive properties as well. If needed, microgels can be dissociated by applying the photo-de-crosslinking.

4. Discussion and outlook

Our recent studies found that coumarin moieties can easily be incorporated into structures of amphiphilic BCPs or DHBCPs and used for reversible photo-crosslinking of their self-assembled micellar aggregates in solution. These works have expanded the use of coumarin photochemistry in designing stimuli-responsive polymer nano- and micro-particles, and opened new ways of developing photoresponsive nanomaterials with possibility of a spatial and temporal control of their properties or behaviours due to the use of light. The use of coumarin photodimerization to crosslink BCP micelles, nano- and microgels has at least two appealing features as compared to other chemical crosslinking methods: 1) the photoreaction can be fast, highly efficient and

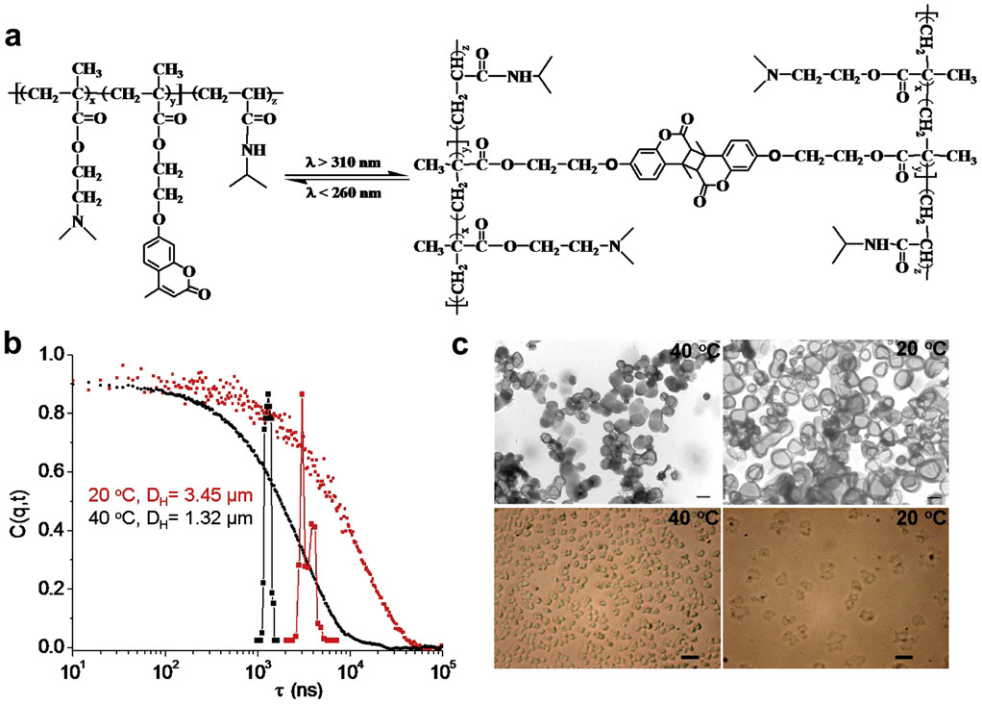

Fig. 4. (a) Chemical structure of the diblock copolymer P(DMAEMA-*co*-CMA)-*b*-PNIPAM containing photo-cross-linkable coumarin groups; (b) autocorrelation functions and relaxation time distribution (CONTIN) for the vesicle solution at 40 °C (black line) and 20 °C (red line); (c) TEM (top) and optical micrographs (bottom) of vesicles at 20 and 40 °C in the dry state (scale bars: 2 μm). Reprinted with permission from Ref. [22] (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

"green" (without added cross-linkers and reaction by-products); and 2) the photoreaction is reversible, which makes possible a "on-demand" tuning of the crosslinking density. To fully unveil the potential for applications of those photoresponsive polymer micelles, nano- and microgels based on the reversible photodimerization of coumarin, more studies remain to be done. Two research directions are discussed below.

First, it is of fundamental and applied interest to develop dual or multiple stimuli-responsive nanogels. As described above, the preparation through self-assembly of coumarin-containing DHBCPs offers a convenient way to make nanogels endowed with a rich stimuli-responsive behaviour due to the many choices of water-soluble polymers sensitive to pH and temperature changes. For example, with a diblock copolymer composed of PEO and coumarin-containing PDMAEMA, the size of nanogels could be controlled not only by the reversible photo-crosslinking of coumarin groups, but also by both pH and temperature change, since the hydration state of PDMAEMA, which is a weak polybase and has an LCST, depends also on the pH and temperature of the solution. It would be interesting to investigate how the release or diffusion of guest molecules loaded in nanogel particles could be affected by the multiple stimuli.

Secondly, controlled drug delivery applications of photoresponsive BCP micelles require a high biocompatibility of both blocks. For that reason, further investigation of the concept of all-optical stabilization and de-stabilization using coumarin-based biocompatible BCP micelles is worthy to be carried out. Recently, Akashi et al. reported the use of cinnamic acid to prepare a photoresponsive, biocompatible and degradable polyester by polycondensation; photoresponsive nanoparticles obtained from this polyester displayed significant volume change by the photocontrolled crosslinking and de-crosslinking reaction [23,24]. It is possible to synthesize biocompatible amphiphilic BCPs with a hydrophilic PEO block and a hydrophobic coumarin-containing polyester block. With this BCP design, on the one hand, micellar nanoparticles can easily be prepared using BCP self-assembly, while on the other hand, the photocontrollable release can be systematically investigated using the approach of "stabilization first and de-stabilization at a later time". Since the degradation rate of the polyester is dependent on the dimerization degree of cinnamic acid groups [23,24], the degradation of the BCP could also be photocontrolled by making use of the reversible dimerization of coumarin.

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