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Near-Infrared Light-Triggered Dissociation of Block Copolymer Micelles Using Upconverting Nanoparticles

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Supporting Information

ABSTRACT: We demonstrate a novel strategy enabling the use of a continuous-wave diode near-infrared (NIR) laser to disrupt block copolymer (BCP) micelles and trigger the release of their "payloads". By encapsulating $NaYF_4$:TmYb upconverting nanoparticles (UCNPs) inside micelles of poly(ethylene oxide)-*block*-poly(4,5-dimethoxy-2-nitrobenzyl methacrylate) and exposing the micellar solution to 980 nm light, photons in the UV region are emitted by the UCNPs, which in turn are absorbed by *o*-nitrobenzyl groups on the micelle core-forming block, activating the photocleavage reaction and leading to the dissociation of BCP micelles and release of co-loaded hydrophobic species. Our strategy of using UCNPs as an internal UV or visible light source upon NIR light excitation represents a general and efficient method to circumvent the need for UV or visible light excitation that is a common drawback for light-responsive polymeric systems developed for potential biomedical applications.

The growing interest in using light to trigger the disruption of block copolymer (BCP) micelles or vesicles is due to the possibility of remote activation and increased spatial and temporal release of loaded species from these nanovectors.[1] By incorporating appropriate photoresponsive moieties into a BCP structure, photochemical reactions such as trans−cis isomerization, molecular dimerization, and bond cleavage can lead to micellar disruption as a result of the photoinduced structural and/or property changes. These changes include photoinduced shifting of the hydrophilic−hydrophobic balance,[2] reversible photo-cross-linking,[3] photocleavage of block junctions,[4] and photoinduced main-chain disintegration.[5] Although several approaches to regulate the structure of BCP micelles using light have been proved effective, a major common concern remains which hampers their potential use in practical applications. All explored photoreactions require high-energy ultraviolet (UV) or visible light, while biomedical applications prefer longer-wavelength near-infrared (NIR) light that has deeper penetration into tissue and is less detrimental to healthy cells. One way to surmount this obstacle is to utilize two-photon absorption of NIR light, as reported by a few groups using BCP micelles and other polymeric materials.[6] However, the photoreactions activated by two-photon absorption of NIR light are generally slow and inefficient due to the typically low two-photon-absorbing cross sections of the chromophores. Moreover, the simultaneous absorption of two photons necessitates high laser power density and thus requires the use of a femtosecond pulse laser. Recently, an appealing alternative for using NIR light based on lanthanide-doped upconverting nanoparticles (UCNPs) has emerged. UCNPs absorb NIR light and convert it to higher-energy photons in the UV, visible, and NIR regions.[7] In contrast to two-photon absorption, the excitation of UCNPs by NIR light occurs via sequential, multiple absorptions with real energy levels, which requires much lower power density so that a continuous-wave (cw) diode NIR laser can be sufficient as the excitation source. By providing the UV or visible light needed for useful photoreactions, UCNPs have already been used as a NIR-triggered delivery vehicle by coating the "to-be-delivered" species on the nanoparticle surface,[8] and for NIR-induced reversible ring-closing and ring-opening of a dithienylethene photoswitch.[9]

In this Communication, we demonstrate a novel strategy for NIR light-triggered dissociation of BCP micelles by making use of UCNPs. As illustrated in Figure 1a, the strategy consists of loading the UCNPs into the micelle core, together with hydrophobic "payloads". Upon absorption of NIR light (980 nm), the nanoparticles emit photons in the UV and visible regions that, in turn, are absorbed by the photoresponsive moieties making up the micelle core-forming hydrophobic block. Figure 1b shows the UCNPs and BCP used to validate this concept. $NaYF_4$:TmYb core−shell nanoparticles[7−9] were loaded into micelles made from a photosensitive diblock copolymer composed of hydrophilic poly(ethylene oxide) (PEO) and a hydrophobic polymethacrylate bearing photolabile *o*-nitrobenzyl groups (PNBMA). Upon excitation with a cw 980 nm laser, the $NaYF_4$:TmYb UCNPs emit photons in several spectral regions, including ∼350 nm. In the BCP design, the addition of the two methoxy groups on the nitrobenzyl moiety shifts the absorption maximum from ∼300 to 350 nm so that the photoresponsive groups can be cleaved upon absorption of the UV light emitted by UCNPs. Photocleavage of the nitrobenzyl groups converts the polymethacrylate block into hydrophilic poly(methacrylic acid), which shifts the hydrophilic−hydrophobic balance toward the destabilization of micelles.[10] As shown below, our studies prove the efficacy of this approach, which represents one that is general and readily applicable to all photosensitive BCP micelles, vesicles, and other nano- or microvectors and is a viable solution to resolve the wavelength problem.

The core−shell $NaYF_4$:TmYb nanoparticles (core = $NaYF_4$: 0.5 mol % Tm^{3+}:30 mol % Yb^{3+}; shell = $NaFY_4$) were synthesized using a literature method.[11] These UCNPs possess uniform hexagonal rod shapes and have an average diameters of ∼30 nm

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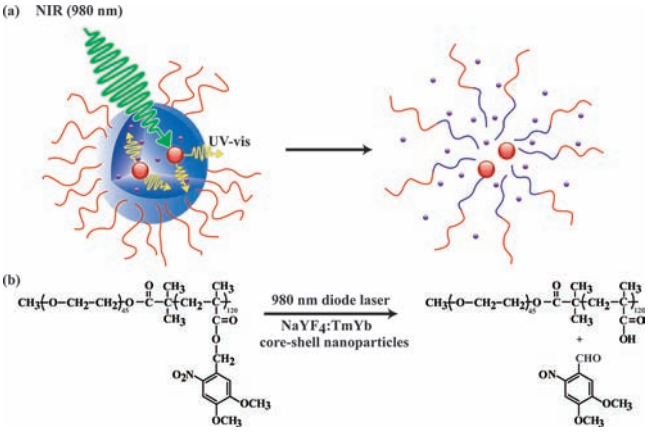

Figure 1. (a) Schematic illustration of using NIR light excitation of UCNPs to trigger dissociation of BCP micelles. (b) NIR light-triggered photoreaction with the used BCP of PEO-*b*-PNBMA and UCNPs of $NaYF_4$:TmYb.

(Figure S2). The BCP, PEO_{45}-*b*-$PNBMA_{120}$, was prepared by using atom-transfer radical polymerization (for synthesis and characterization details, see Supporting Information). We succeeded in loading the UCNPs into the micelle core by first dissolving the BCP and UCNPs in THF and then adding this solution dropwise to water to induce the formation of micelles and the concomitant encapsulation of the nanoparticles. After removal of THF and centrifugation, the resulting UCNP-loaded micelles were collected and could readily be redispersed in water. Figure 2a shows a photograph of an aqueous solution of UCNP-loaded micelles (diluted to ~0.2 mg/mL with respect to the BCP) upon exposure to a 980 nm diode laser. The photoluminescence of visible light is readily observed in the region where the path of the laser beam travels through the solution. Scattering of emitted blue light is caused by the micelle aggregates. Also shown are the emission spectra of the neat UCNPs and the UCNP-loaded micellar solution upon the 980 nm excitation, together with the absorption spectrum of the micellar solution before NIR light exposure. The UV light emitted from the UCNPs around 350 nm overlaps well with the absorption band of *o*-nitrobenzyl groups on the micelle core-forming PNBMA block. As compared to neat UCNPs, the emission intensity of UV light of the UCNP-loaded micellar solution is much weaker, indicating that the UV photons delivered by the UCNPs are absorbed by *o*-nitrobenzyl moieties in the micelle core. The TEM images in Figure 2b,c were recorded using the micellar solution before and after NIR light exposure, respectively. Before exposure, UCNPs were clearly loaded inside almost all BCP micellar aggregates with an average diameter of ~83 nm, the inset showing two micelles containing each 4−5 nanoparticles. With respect to all the micelles in Figure 2b, while the number of encapsulated nanoparticles varies from micelle to micelle, most of them contain two UCNPs with an average of 2.5 nanoparticles per micelle (Figure S9). For the same micellar solution after 980 nm excitation (5 W, 4 h), the complete disintegration of micelles is visible. As a result, the nanoparticles are released from the micelles and coexist with the polymer in the form of irregularly shaped spots. These results indicate that a cw 980 nm laser can trigger the dissociation of UCNP-loaded BCP micelles.

We performed further experiments to ensure that the NIR-triggered micellar dissociation is a direct consequence of the photocleavage of *o*-nitrobenzyl side groups from the PNBMA block and determine if NIR light can induce release of hydrophobic species co-loaded with the UCNPs within the micelles. The former experiments were carried out using a model hydrophobic compound, Nile Red (NR).[6,10] The same basic methods as used for the UCNP-loaded micelles were employed, except that NR was dissolved in THF with BCP and UCNPs before being added to water for the formation of micelles and the encapsulation of the nanoparticles with dye molecules. For control experiments, micelles with only loaded NR were also prepared. Figure 3a illustrates the setup used to detect NIR light-induced photocleavage of *o*-nitrobenzyl groups or release of NR from UCNP-loaded BCP micelles. A quartz cuvette filled with water is sealed with a dialysis cap that has a membrane at the bottom of it (molecular weight cutoff = 3500). The membrane is immersed in the water. A solution of UCNP-loaded micelles is placed in the cap. By sampling the water underneath the dialysis membrane using either absorption or fluorescence emission spectra, the presence of released molecules can be assessed. In the first of such experiments (Figure 3b), absorption spectra were recorded using a UCNP-loaded micellar solution (without NR) in the dialysis cap before and after exposure to NIR light. Without any NIR light exposure, no changes in the spectra of the water could be detected, even after 24 h. In contrast, for the same micellar solution after being exposed to NIR light, absorption bands corresponding to the photocleaved nitrosobenzaldehyde in the 350−450 nm region were detected. The increasing absorbance over time indicates a continuous diffusion of cleaved molecules through the membrane. This result confirms the occurrence of photocleavage of *o*-nitrobenzyl groups in the micelle core upon 980 nm NIR light excitation, which is responsible for the dissociation of micelles. In the second experiment (Figure 3c), micelles loaded with both UCNPs and NR were utilized. Since NR is very hydrophobic and its fluorescence is quenched in water, pluronic F-127 was added to the water in the cuvette to increase the solubility of NR and provide an observable readout indicating the release of NR from NIR light-disrupted micelles. Comparing the plots of normalized fluorescence emission intensity of NR at 640 nm makes it clear that the release of the hydrophobic dye is much faster after NIR light exposure of the micellar solution, as a result of the dissociation of micelles.

It should be mentioned that the experiments shown in Figure 3 were designed as proof-of-principle demonstrations to confirm the NIR light-induced photocleavage of *o*-nitrobenzyl moieties in UCNP-loaded BCP micelles and the resulting release of encapsulated hydrophobic payloads from disrupted micelles. The experimental conditions were not optimized or controlled to assess the rates of these NIR light-triggered processes (for example, the 4 h NIR laser exposure time was chosen arbitrarily; the relative volumes of the micellar solution and the aqueous solution in the cuvette as well as the size of dialysis membrane could all affect the apparent diffusion rates). A more straightforward way to monitor the rate of NIR-induced release of NR would be to measure its fluorescence emission change directly on the micellar solution.[6,10] Any disruption of micelles that bring encapsulated NR molecules into an aqueous medium results in a fluorescence quenching effect. We thus performed the measurements shown in Figure 4, which compare the fluorescence emission spectral changes of NR upon exposure of the micellar solutions to the 980 nm NIR laser. In these experiments, 2 mL of the micellar solution was used and no stirring was applied.

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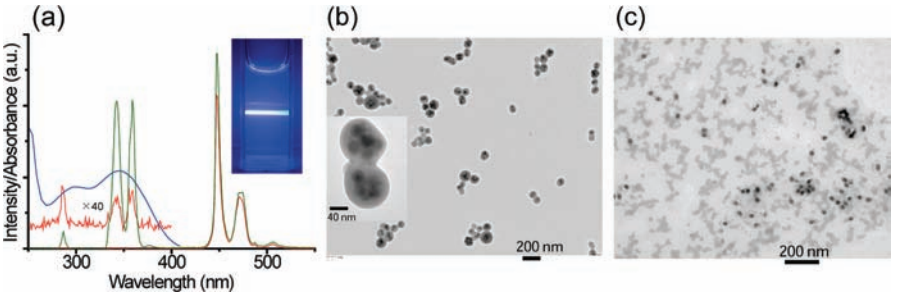

Figure 2. (a) Photograph of a UCNP-loaded micellar solution upon a 5 W, 980 nm diode laser exposure, its absorption spectrum (blue line), and emission spectra of the neat UCNPs (green line) and the micellar solution (red line), the emission of the micellar solution in the UV region being amplified. (b) TEM image of UCNP-loaded BCP micelles before NIR light irradiation, the inset showing two magnified micelles containing several nanoparticles. (c) TEM image of the same micellar solution after NIR irradiation (5 W, 4 h), showing the disintegration of BCP micelles.

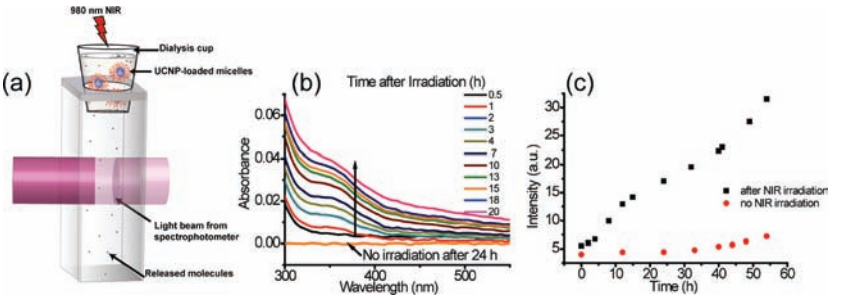

Figure 3. (a) Setup used to detect species diffusing from a BCP micellar solution through a dialysis membrane into aqueous solution underneath. The diffusing molecules are either photocleaved nitrosobenzaldehyde or released Nile Red (NR) from disrupted BCP micelles as a result of 980 nm excitation. (b) Absorption spectral change over time for nitrosobenzaldehyde molecules cleaved by NIR light exposure of UCNP-loaded micelles (5 W, 4 h). (c) Increase in the normalized fluorescence intensity of NR measured at 640 nm (λ_{ex} = 550 nm) over time for two aqueous solutions of micelles loaded with both UCNPs and NR, one of which was subjected to NIR light exposure, while the other was not.

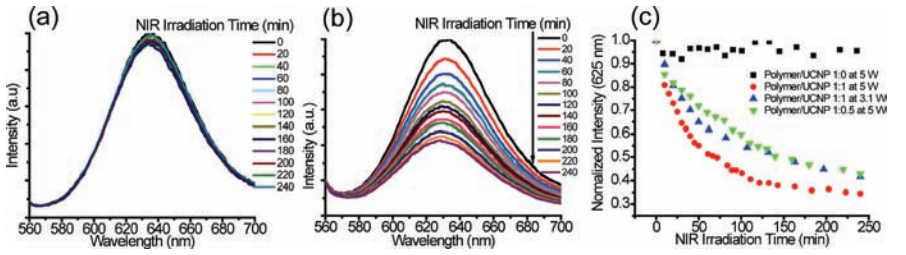

Figure 4. Fluorescence emission measurements carried out on aqueous solutions of BCP micelles (1 mg/mL, 2 mL) loaded either with both UCNPs and NR or with only NR, upon NIR light exposure: (a) emission spectra of NR ($\lambda_{excitation}$ = 550 nm) for the micellar solution with only NR encapsulated; (b) emission spectra of NR for the micellar solution with both UCNPs and NR loaded; and (c) plots of normalized fluorescence intensity of NR vs NIR light exposure time under different conditions (polymer/UCNP is the weight ratio used in the preparation of UCNP-loaded BCP micelles). All solutions were not stirred.

For micelles containing only NR (Figure 4a), after 4 h exposure, no change in the fluorescence intensity is observed, indicating that the BCP micelles are stable and, consequently, NR molecules remain solubilized inside the hydrophobic core. The result is different for micelles loaded with both NR and UCNPs. In this case, exposure to the NIR laser results in a continuous decrease in the fluorescence intensity of NR over time, indicating micellar dissociation, which brings NR molecules into an aqueous medium and thus quenches its fluorescence. Using micelles loaded with both UCNPs and NR, the effects of the NIR laser power and concentration of UCNPs on NIR light-induced micellar dissociation and release were investigated. The results are presented in Figure 4c, which shows the changes in the normalized fluorescence intensity of NR as a function of NIR light exposure time. In all cases, the fluorescence intensity decreases quickly over the first 40−50 min, and then the decrease becomes less pronounced. As expected, the apparent release of NR is faster with a higher NIR laser power or with more UCNPs. In both cases, a more intense UV light emission from the NIR-excited UCNPs makes the photocleavage reaction faster, leading to faster dissociation of micelles and faster concomitant release of NR.

In conclusion, we have demonstrated, for the first time, a novel strategy enabling the use of a continuous-wave diode NIR laser to disrupt photosensitive BCP micellar delivery vehicles and trigger

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the release of their "payloads". By encapsulating $NaYF_4$:TmYb UCNPs inside micelles of PEO-*b*-PNBMA and using 980 nm light, photons in the UV region around 350 nm are generated, which in turn are absorbed by *o*-nitrobenzyl groups on the micelle core-forming block, activating the photocleavage reaction and leading to the dissociation of micelles. A hydrophobic compound, NR, co-loaded with UCNPs in the micelles could be released upon 980 nm excitation. This achievement is a significant step forward in finding an efficient and relatively universal method using a cw diode NIR laser to circumvent the need for UV or visible light that is a common drawback for light-responsive materials developed for potential biomedical applications. The strategy of using NIR light and UCNPs as an internal UV−visible light source is very general and can be applied not only to BCP micellar aggregates but also to many other photosensitive polymeric materials of which the potential for applications is limited due to the wavelength issue.

■ ASSOCIATED CONTENT

Supporting Information. Details on block copolymer synthesis and more characterization results using ^{1}H NMR, UV−vis, IR, fluorescence, and TEM. This material is available free of charge via the Internet at http://pubs.acs.org.

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