Colloid Polym Sci
DOI 10.1007/s00396-017-4013-0

ORIGINAL CONTRIBUTION

NIR- and UV-dual responsive amphiphilic copolymer micelles with light-dissociable PAG-side groups

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Received: 19 September 2016 / Revised: 28 November 2016 / Accepted: 3 January 2017

Abstract Amphiphilic random copolymer micelle of P(NVP-*co*-NHPM) that responds to both UV and NIR light was designed and investigated. *N*-hydroxyphthalimide methacrylate—bearing a photoacid generator functional group was synthesized and used to construct the hydrophobic segment of P(NVP-*co*-NHPM); the N–O bond can be photocleaved when exposing the polymer aqueous solution to 310 nm UV light irradiation, inducing the micellar dissociation and delivery of loaded substances. Dynamic light scattering (DLS), atomic force microscope (AFM), and transmission electron microscopy (TEM) were used to characterize the micellar dissociation and controlled release processes. Moreover, the upconverting nanoparticles ($NaLuF_4$:Gd/Yb/Tm) that can effectively absorb NIR light and convert it into visible and UV light were coloaded into polymer micelles to activate the micellar dissociation and the delivery of loaded cargoes via 980 nm NIR light.

Keywords Amphiphilic copolymer · Upconverting nanoparticle · Micelle · Photoacid generator

Electronic supplementary material The online version of this article (doi:10.1007/s00396-017-4013-0) contains supplementary material, which is available to authorized users.

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Introduction

Developing novel nano-aggregates or micelles based on the self-assembly of amphiphilic polymers remains a hot topic in the field of drug delivery, because of their distinct advantages like tunable sizes with narrow size distribution, encapsulation of hydrophobic drug molecules with a high loading capacity, passive targeting of tumor tissues via enhanced permeability and retention (EPR) effect, stimuli-responsiveness, and so on [1–6]. It is highly desirable that the drug delivery process is controllable at a specific site by triggering a change in properties of the micelles via an external stimulus, and so far stimuli like hydrolysis, redox, pH, temperature, and light have been extensively surveyed [7–15]. Compared to other stimuli, light is advantageous in providing the feasibility of remote and spatiotemporal control, which means that the light stimulation can be applied a long distance from the irradiation source to the object. Furthermore, the light stimulation process can be readily switched on/off at will in a confined area without the requirement of particular reagents or limiting byproducts, and several parameters such as the intensity and wavelength can be introduced to enable better and more precise control compared to other stimuli [16–21]. Generally speaking, strategies to design light-responsive micelles or nanoaggregates can be assorted into two categories. The first one refers to a phase transition of photoactive moieties on amphiphilic copolymers under light irradiation, which can induce changes in optical, mechanical, or chemical properties, leading to the disruption of the micelles and the release of loaded substances [22–24]. The second one deals with incorporating photocleavable chromosphores or dyes into amphiphilic polymers to form light-dissociable micelles [25–27]. Although different types of photocleavable groups have proved their effectiveness in

Published online: 19 January 2017

enabling amphiphilic polymers with light-induced dissociation behaviors, like pyrenylmethyl esters, *o*-nitrobenzyl esters, coumarinyl esters, and p-methoxy-phenacyl esters, development of photolabile amphiphilic polymer micelles with novel structures and mechanisms is still important to broaden their potential in related fields [17, 21, 28].

In this study, we proposed a novel strategy to fabricate light-responsive polymer micelles. The main idea is to utilize a hydrophilic monomer and a hydrophobic monomer bearing a photoacid side group to compose an amphiphilic polymer. Photoacid generators (PAGs) have been extensively used in fabricating smart photoresponsive polymer films or membranes, while applying it in designing polymer micelles is still few [29]. Here we choose *N*-hydroxyphthalimide methacrylate (NHPM) as a model PAG monomer to form amphiphilic polymer micelles. Since the N–O bond of the PAG monomer can be photocleaved under UV light irradiation, the hydrophobic-hydrophilic balance of the micellar system as well as the micellar structure will be destroyed, resulting in the release of incorporated cargoes [30–33]. Furthermore, in order to investigate the possibility of using NIR as a stimulation source to trigger the dissociation of polymer micelles and thus the drug delivery, we encapsulated upconverting nanoparticles (UCNPs) into the micellar cores. When NIR light is applied, UCNPs can convert NIR light into visible and UV light [34]. This is of significant meanings in practical applications that NIR light is a lower energy radiation with a reduced absorption and scattering by biological media and hence deeper penetration compared to UV irradiation in human tissues. Furthermore, the UV light generated by UCNPs could be absorbed by the surrounding photosensitive moieties in polymer micelles and thus it will be less harmful to living tissues around micelles compared to the UV light which directly excited and absorbed during its trip before reaching the micelles [16]. The concept proposed here will no doubt broaden the potential of light-responsive micelles in the applications like controlled drug delivery.

Experimental section

Materials

Methacryloyl chloride, *N*-hydroxyphthalimide, and *N*-vinyl-2-pyrrolidone (NVP) were purchased from Aladdin and used without further purification. Nile red (NR) was purchased from Sigma-Aldrich. 2, 2-Azobisisobutyronitrile (AIBN) was purified by recrystallization from 95% ethanol. Ultrapure water used in this study was prepared using a FDY-1002-UV-P purification system. Upconverting nanoparticles (UCNPs) of $NaLuF_4$:Gd/Yb/Tm were prepared according to the literature [35, 36].

Characterization

The ^{1}H NMR (400 MHz) spectrum was investigated with a Bruker spectrometer with $CDCl_3$ as solvent. DLS measurements were performed with a Zetasizer (Malvern Nano-ZS90 instrument) to determine the average diameter and size distribution of the prepared micelles at 25 °C. Absorption spectra and optical transmittance were recorded on an Evolution 220 spectrophotometer (Thermo Fisher Instrument Co. Ltd.) at 25 °C. The UV light of 310 nm was generated from Zolix EQ-1500 tunable monochromatic light source, the intensity of the light was tested using CEL-NP 2000 optical power meter. Fluorescent spectra were recorded on a PTI QM40 fluorometer at 25 °C. AFM observations were conducted using a Benyuan CSPM5500A scanning probe system, the samples were prepared by coating the micellar solution (0.1 mg mL^{-1}) onto silicon sheet and dried at room temperature overnight. TEM observations were carried out with a JEM2100 microscope; the micellar solution (0.03 mg mL^{-1}) was deposited onto a copper grid coated with carbon film (400 mesh) and dried overnight at 25 °C.

Synthesis of *N*-hydroxyphthalimide methacrylate (NHPM)

The photoacid monomer was synthesized according to a literature method [37]. Briefly, 67.3 g (413.0 mmol) of *N*-hydroxyphthalimide and 86.3 g (826.0 mmol) of methacryloyl chloride were both dissolved in 210 mL THF at 0 °C, afterwards 50 mL triethylamine was added dropwisely into the THF solution while maintaining the temperature at 0 °C. The reaction mixture was then stirred for an additional 20 h, and the resulting product was precipitated in water and washed twice with water. The yellowish solid was recrystallized in ethanol (yielding 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95–7.76(m, 4H), 6.48(s, 1H), 5.92(s, 1H), 2.10(s, 3H).

Synthesis of PAG-based amphiphilic random copolymer of P(NVP-*co*-NHPM)

The copolymer was synthesized by firstly dissolving the two monomers of NVP (3.12 g, 28.12 mmol) and NHPM (2.78 g, 12.03 mmol) and the initiator of AIBN (31.7 mg, 1.93×10^{-1} mmol) in 21 mL DMF in a sealed ampoule, afterwards the system was vacuumed, and the free radical polymerization process was carried out at 70 °C for 24 h. The resulting product was precipitated twice in diethyl ether and dried under vacuum at 30 °C for 24 h to obtain the final

product. The yield of the resulting polymer was 35% and Mn (GPC) and Mw/Mn (GPC) were determined as 1.07×10^4 and 1.34, respectively.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13–7.77 (Ar-H), 3.68–3.16 (N-C-H), 3.11–1.22 (C-H).

Preparation of polymer micelles in aqueous solution

P(NVP-*co*-NHPM) micellar solution was prepared using the following procedure: P(NVP-*co*-NHPM) (10 mg) was dissolved in DMF (2 mL), after that ultrapure water was then added at a rate of 0.2 vol% per minute under mild stirring until the water content reached 68.0 vol% in the system. The solution was further stirred for another 12 h and then fourfold water was added to quench the aggregates. DMF was completely removed by dialysis (MW cutoff 3500 Da) against distilled water for 3 days, water was frequently refreshed (every 2 h in the daytime) during this process.

NR-loaded micellar solution was prepared by dissolving Nile red together with P(NVP-*co*-NHPM) (10 mg) in 2 mL DMF before adding ultrapure water into the system. The UCNPs and Nile red coloaded micelles were prepared using the same procedure. All micellar solutions used for measurement were kept at a polymer concentration of 0.03 mg mL^{-1}.

Photoreaction of copolymer micellar solutions upon UV or NIR irradiation

The UV light induced photoreaction experiment was conducted by filling 1.5 mL micellar solution into a sealed square quartz cuvette, and a UV spotlight with a wavelength of 310 nm generated from a Zolix EQ-1500 tunable monochromatic light source was used to induce photoreaction of the micellar system. The distance between the quartz wall and the spotlight was maintained at 1 cm. The photoreaction procedure was monitored using absorption and emission spectra, optical transmittance, and DLS analysis.

For the photoinduced release experiment, the NR-loaded micelles (0.03 mg mL^{-1}, 1.5 mL) were irradiated and monitored with the same procedure. The aqueous solution of UCNP-NR coloaded micelles (0.03 mg mL^{-1}, 1.5 mL) were exposed to NIR light from a 980 nm diode laser with different intensities, the distance between the quartz wall and the spotlight was about 0.2 cm. The release process of incorporated cargoes was determined using the fluorescence emission spectra. The normalized intensity was calculated by comparing the intensity of characteristic peak at 647 nm of Nile red polymer micelles after light irradiation to that before irradiation.

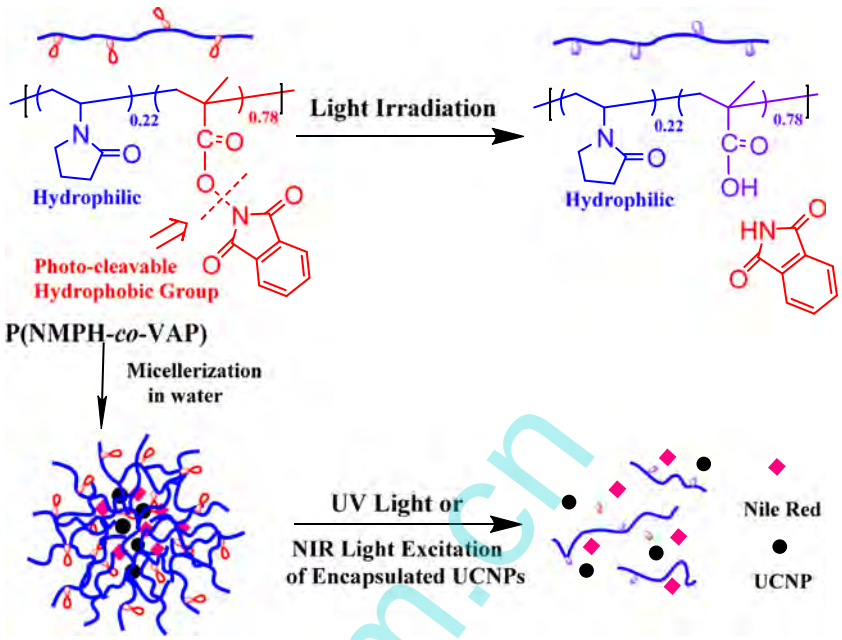
Results and discussions

Micellar formation and photoinduced disruption upon UV irradiation

The structure of the designed amphiphilic polymer and its photocleavage behaviors were depicted in Scheme 1. The hydrophobic part of the prepared polymer bears PAG side groups, whose N–O bonds can be photocleaved under UV light irradiation, resulting in the detached hydrophobic moieties and the hydrophilic residual part of poly(methacrylic acid) (PMAA). This hydrophilic-hydrophobic balance shift will destroy the formed micellar structure and subsequently release the loaded cargoes.

The micellar structure is formed by gradually adding water into the DMF solution of the copolymer. Since the hydrophobic monomer of *N*-hydroxyphthalimide methacrylate comprises the main part of the prepared copolymer (78 mol%), the micellar structure is quickly formed once the added water content exceeds a certain value. The critical water content (CWC) is determined by investigating the turbidity change of the aqueous solution. As shown in Fig. 1a, the transmittance of the solution with the initial polymer concentration of 5 mg mL^{-1} started to decrease at the water content of 7.8 wt% and quickly drops to 0.3% once the water content reached 35.0 wt%, indicating the formation of polymer micelles in aqueous solution. The calculated CWC of P(NVP-*co*-NHPM) was determined as 13.5 wt%. DLS was also used to survey the structure of polymer micelles as a function of water content. It is known that the derived count rate (DCR) is a parameter that indicates the size and concentration of scattering particles. As shown in Fig. 1a, the value of DCR increased sharply from 34 to 2588 when the water content increased from 11.0 to 16.0 wt%, meaning the transformation of copolymer chains from flexible coils into micellar globules. The average size of polymer micelles as a function of water content was also envisaged. As shown in Fig. 1b, P(NVP-*co*-NHPM) formed into micelles at water content above 16.0 wt%, and the micellar structure became more stable with higher water content in the solution as the average size of the micelles decreased to some extent. The critical micellar concentration (CMC) was determined to be 8.37×10^{-2} mg mL^{-1}, according to the I_{373}/I_{384} ratios of P(NVP-*co*-NHPM) in pyrene previous saturated aqueous solution with fluorescence probe technique (Fig. S1 in the Supporting Information).

The photoresponsive behaviors of the obtained micelles were investigated using 310 nm UV light irradiation. The N–O photocleavage will induce the hydrophobic segment of *N*-hydroxyphthalimide methacrylate to release the hydrophobic moiety phthalimide into the aqueous environment and cause the change of hydrophobic-hydrophilic balance, leading to the disruption of polymer micelles. As shown in Fig. 2a, with the increasing irradiation time of 310 nm UV light (0.41 mW



Scheme 1 Schematic illustration of UV- and NIR-dual responsive behaviors of amphiphilic random copolymer of P(NVP-*co*-NHPM) micellar system

cm^{-2}), the absorption peak of *N*-acyloxyphthalimide at 310 nm decreased gradually, ascribing to the continuous photolysis of photochromophores. Similar result was also obtained when exposing micelles upon other light intensity, which was shown in Fig. S2 in Supporting Information. The inset of Fig. 2a showed the exponential decays of the normalized absorption intensity at 310 nm (I_{310}) of micellar aqueous solution upon 310 nm irradiation with different intensities, the decreased intensity during the irradiation process indicated that N–O bonds were gradually cleaved from the hydrophobic segment of P(NVP-*co*-NHPM) over time. It was also shown that this photocleavage process could be enhanced by tuning the light intensity, the final value of I_{310} after light irradiation of 0.15, 0.27, and 0.41 mW cm^{-2} were 40.2, 31.2, and 22.7%, respectively.

The light-induced micellar dissociation would also result in the turbidity change of the solution. As shown in Fig. 2b, the transmittance increased from 83.0 to 95.0% after light irradiation of 0.15 mW cm^{-2}. This turbidity change can be even greater if increasing the light intensity to 0.27 and 0.41 mW cm^{-2}, which is 83.0 to 98.0% and 83.0 to 99.0%, respectively.

The size change of polymer micelles before and after light irradiation was also investigated. Figure 3 showed that the average diameter of polymer micelles decreased from 353 nm to 307, 283, and 252 nm as a function of irradiation time of the light intensity of 0.15, 0.27, and 0.41 mW cm^{-2}, respectively. Fig. S3 in Supporting Information showed the size distributions of polymer micelles upon 310 nm light irradiation with different intensities. Moreover, as shown in Fig. S4 in Supporting Information, the longer time of irradiation can result in a more completed micellar disruption.

Figure 4 showed the AFM images of polymer micelles before and after UV irradiation. As shown in Fig. 4a, before light irradiation, the dried micelles appeared to be typical spherical particles with different sizes ranged from 40 to 470 nm and an average size of 207 nm. It should also be noted that the size distribution was quite related to the concentration of the micellar solution, since the samples were prepared using a diluted micelle solution (0.1 mg mL^{-1}). Some of polymer micelles may resembled into smaller particles during the dilution and bigger particles in the drying process, resulting in a

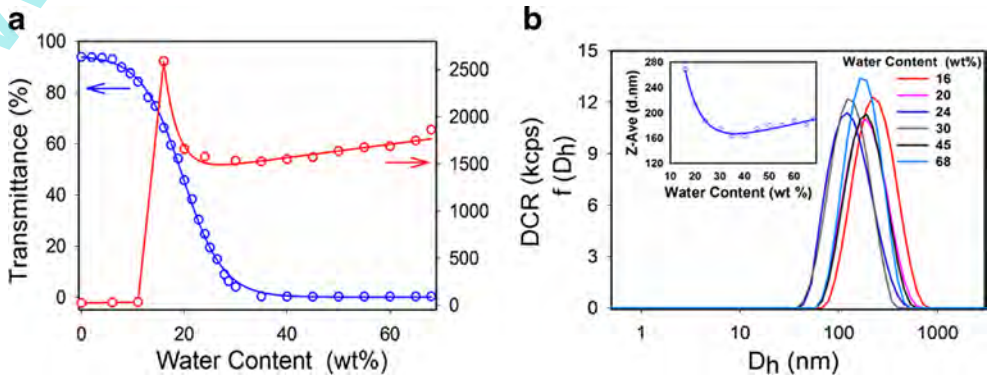


Fig. 1 **a** Plots of optical transmittance (*left*) and DCR (*right*) vs amount of water added to P(NVP-*co*-NHPM) in DMF solution (5 mg mL^{-1}). **b** DLS analysis of polymer solution (5 mg mL^{-1}) during micellization by adding water to the DMF solution

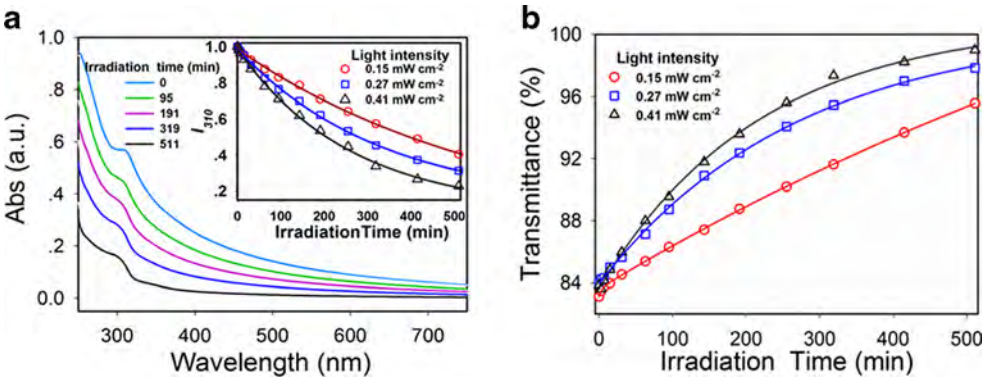


Fig. 2 **a** UV − vis spectra of polymer micelles upon 310 nm (0.41 mW cm^{-2}) light irradiation, with the inset showing plots of the normalized absorption intensity at 310 nm (I_{310}) vs irradiation time with different intensities. **b** Plots of optical transmittance at 621 nm of polymer micelles vs irradiation time

broad size distribution of the nanoparticles. As shown in Fig. 4b, after light irradiation (310 nm, 0.41 mW cm^{-2}), almost all of the spherical micelles disappeared or shrunk (Fig. S5 in the Supporting Information), this again proved that the UV light could induce dissociation of amphiphilic polymeric micelles.

The photoinduced release of NR-loaded micelles upon UV irradiation.

Nile red was chosen as a model hydrophobic guest and incorporated into the micellar cores to investigate the release behavior of the micellar system under UV light irradiation. The NR-loaded micelles were prepared by dissolving NR and amphiphilic copolymers in DMF before adding ultrapure water into the system. As shown in Fig. 5a, the NR-loaded micelles before irradiation showed a characteristic absorption peak at 647 nm in fluorescence emission spectra (λ_{ex} 550 nm), indicating the NR molecules were successfully loaded into the hydrophobic micellar cores. It should be noted that the intensity peak is blue-shifted by about 21 nm (from 647 to 626 nm) during UV irradiation (310 nm, 0.41 mW cm^{-2}). This phenomenon can be ascribed to the emission of NR that solubilize in water, which is quite low but strong. Controlled release behavior of the loaded NR from polymer micelles as a function of irradiation time was also investigated using the same lamp. It can be seen that the intensity at 647 nm decreased along with the increasing irradiation time, which suggested the NR molecules were gradually released from the micelles during the process. The inset of Fig. 5a showed the results of the time dependence of the changes in normalized fluorescence emission intensity at 647 nm (I_{647}), which dropped 80% after 20 min exposure and declined nearly to 0 after 1 h irradiation, indicating all of the loaded substances can be delivered within 1 h from the micelles. The average diameter of the NR-loaded micellar aggregates were also found to decrease from 310 to 197 nm under the same irradiation condition (511 min, 0.41 mW cm^{-2}) under DLS tests (the details can be seen in Fig. S6 in Supporting Information).

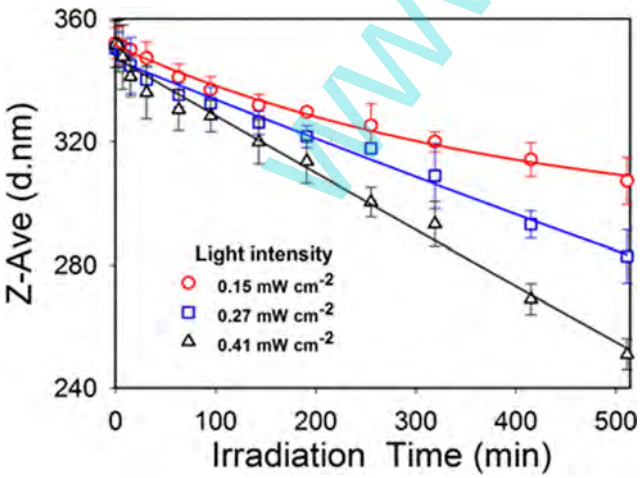


Fig. 3 Changes of average size of the micelles (0.03 mg mL^{-1}) under 310 nm light irradiation

The TEM images shown in Fig. 5b, c give us more insight into the photodissociation induced structure change of NR-loaded micelles. Before UV irradiation (310 nm, 0.41 mW cm^{-2}), the micelles appeared to be sphere shape with average diameter around 100 nm. The pink color of the micelle solution can be seen by naked eye due to the solubilization of NR molecules in polymer micelles. After light irradiation, all of the micelles were destroyed and no micelles with sphere shape can be seen in the TEM image, and the micelle solution also appeared to be transparent and colorless.

NIR-induced photoreaction of polymer micelles in aqueous solution.

One main limitation of using light to trigger drug release from micelles in vivo is the penetrability of the light. It is known that NIR light is more probable to be applied in clinical usage since it can penetrate much deeper compared to UV and visible light [38]. Here, we applied a novel strategy in which UCNPs were incorporated into the micellar system to trigger drug release, based on the fact that UCNPs are capable of converting NIR light into higher energy photons in the UV and visible regions, which subsequently triggered the photocleavage reactions and induced the release of the drugs.

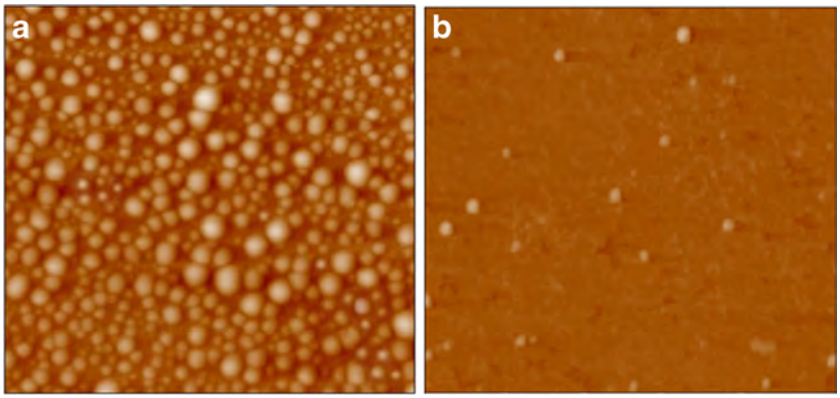


Fig. 4 AFM images (5 × 5 μm^2) of the micelles before (**a**) and (**b**) after 310 nm light irradiation (0.41 mW cm^{-2})

Here, we utilize UCNPs of NaLuF4:Gd/Yb/Tm to realize the concept, which emit photons with the highest intensity light at 475 nm when upon the 980 nm NIR excitation (Fig. S7 in the Supporting Information). The UCNPs were encapsulated together with NR molecules into the micelles and subsequently applying continuous-wave NIR light (980 nm, 7 W) to trigger it. The results of fluorescence spectra (λ_{ex} 550 nm) can be seen in Fig. 6a, the intensity of the characteristic peak of NR at 647 nm in the micellar solution (0.03 mg mL^{-1}, 1.5 mL) gradually decreased as a function of irradiation time, indicating that the incident NIR light was successfully converted into UV and visible light, which subsequently triggered the dissociation of the micelles and the delivery of incorporated cargos. This effect could be enhanced by increasing the power of irradiated light. As shown in Fig. 6a, the final value of I_{647} decreased to 0.8 and 0.6 under the intensity of 3 and 7 W, respectively. In order to provide more evidence, we used NIR laser to stimulate NR-loaded micelles without incorporation of UCNPs. The control experiment showed almost no change in the fluorescence spectra during the same NIR irradiation procedure (Fig. 6b), which suggested that the NIR triggered release was indeed activated by these encapsulated UCNPs. TEM images in Fig. 6c, d also indicated that the micelles were successfully disrupted by NIR laser in the presence of UCNPs encapsulated within the micellar core.

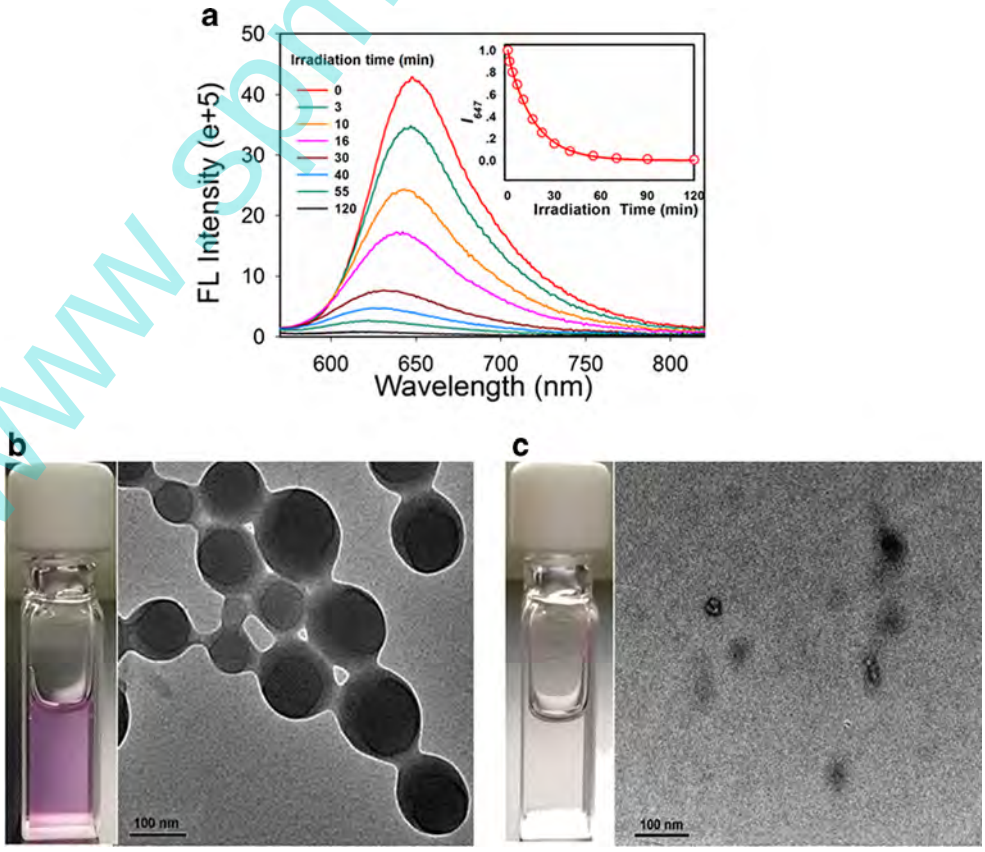


Fig. 5 **a** Fluorescence emission spectra of NR loaded micelles (λ_{ex} 550 nm) of polymer in aqueous solution upon light irradiation (310 nm, 0.41 mW cm^{-2}) with the inset showing the plots of normalized fluorescence intensity (I_{647}) of NR-loaded micelles as a function of irradiation time.TEM images of NR-loaded micelles before (**b**) and after (**c**) 310 nm light irradiation (0.41 mW cm^{-2})

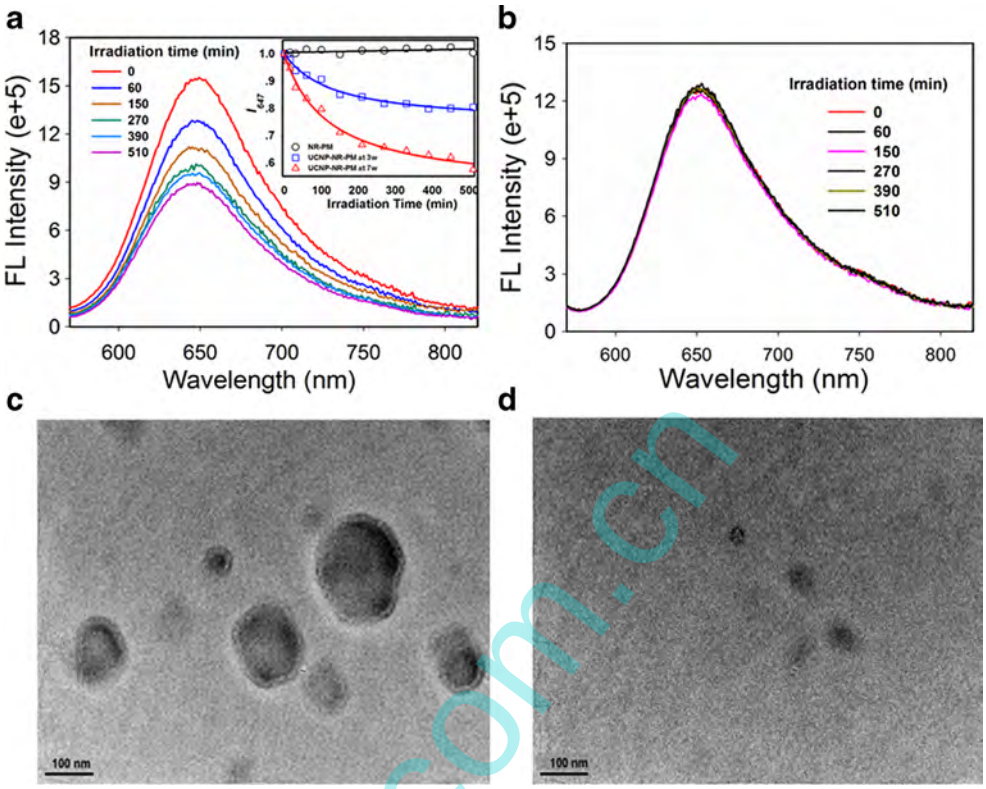


Fig. 6 Fluorescence emission of UCNP-NR coloaded micelles (**a**) (UCNP-NR-PM, 0.03 mg mL^{-1}, λ_{ex} 550 nm) upon NIR light (980 nm) exposure. The *inset* figure showing the plots of normalized fluorescence intensity of micelles at 647 nm vs NIR light exposure time under different intensities. Fluorescence emission of NR loaded micelles (NR-PM, 0.03 mg mL^{-1}, λ_{ex} 550 nm) upon NIR light (980 nm) exposure(**b**). TEM images of UCNP-NR coloaded micelles before (**c**) and after (**d**) NIR light irradiation

Conclusions

In conclusion, we prepared a light-responsive amphiphilic random copolymer of P(NVP-*co*-NHPM) with hydrophobic photoacid side groups, which could form polymer micelles in aqueous solution. The results showed that the micelles could be disrupted under UV irradiation due to the cleavage of the N–O bond of the photoacid side groups, leading to the release of hydrophobic NR molecules that previously loaded within the micellar cores. The photodissociation and drug release process could be well controlled by tuning the light intensity and the irradiation time. Moreover, by encapsulating NaLuF4:Gd/Yb/Tm upconverting nanoparticles into the micelles, NIR-responsiveness was enabled as the UCNPs can convert NIR light to visible or UV light, and this novel dual responsive micelle system can be potentially applied in different areas, like, nanoreactors, biosensors, and drug delivery.

Acknowledgements This work is supported by the Nature Science Foundation of China (NSFC 21374056), the Program for Changjiang Scholars and Innovative Research Team in University (IRT 14R33), the Fundamental Research Funds for the Central Universities (GK201603038, GK201601005), Shaanxi Innovative Research Team for Key Science and Technology (2013KCT-17), and the One Hundred Plan of Shaanxi Province.

Compliance with ethical standards

Conflict of interest We would like to declare that all of the authors in this work have no conflict of interest.

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