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Light and reductive dual stimuli-responsive PEI nanoparticles: "AND" logic response and controllable release

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"AND" logic responsive polyetherimide (PEI)-based polymers **PENS** were constituted by attaching the photoresponsive *o*-nitrobenzyl phototrigger and reductive responsive disulfide linker to the polymer PEI. This dual-responsive system maintained micelle-like assembly upon single photo or reductive stimuli. The disassembly only occurred when photo and reductive signals were input at the same time. This smart system was therefore applied as a carrier for the controlled release of the anti-cancer drug doxorubicin (DOX), which exhibited effective release only when UV irradiation and GSH reduction were applied simultaneously.

Introduction

Stimuli-responsive nanoparticles that undergo structure and property changes in response to internal or external stimuli (including temperature,[1,2] pH,[3,4] redox,[5,6] and light,[7,8] *etc.*) have a wide spectrum of practical applications in fields such as catalysis,[9] smart interfaces,[10] tissue engineering,[11] biosensors,[12] diagnostics[13] and drug delivery.[14] Especially, stimuli-responsive nanoparticles serving as excellent drug carriers have attracted tremendous interest because of their suitable size to prolong the circulation time, enhanced stability to avoid degradation in blood, improved biocompatibility to decrease toxicity itself, and well-modulated drug release in response to external stimuli.[15,16] So far, many strategies including micelles, liposomes, microgels, dendrimers and even inorganic particles have been utilized to prepare stimuli responsive nanoparticles to achieve controllable drug release.[17–21]

Compared to the single stimuli-responsive systems, multi-stimuli responsive nanoparticles that are sensitive to two or more stimuli allow precise tuning of the guest release kinetics to fit the therapeutic window of the drug.[22–26] For example, the group of Hennink[27] has recently developed dual-stimuli sensitive peptide–hybrid ABC block copolymers which self-assemble into micelles above the cloud point of the thermosensitive poly(*N*-isopropylacrylamide) (pNIPAm) block. And the peptide linkage between the polymer blocks could be cut by a metalloprotease, leading to "shedding" of the corona of the micelles, which made these systems potentially suitable for enzyme-triggered drug delivery. While temperature lower than the cloud point also induced the disassembly of the micelles due to the transformation of the pNIPAm block from hydrophobic to hydrophilic. Thayumanavan and co-workers reported a series of triply stimuli responsive block copolymers which were responsive to the change of temperature, pH and redox potential, respectively, and could be used as carriers to achieve controlled release of loaded guest molecules.[28] Recently, we also prepared dual-stimuli responsive inorganic mesoporous silica nanoparticles (SPA-MSNs) by attaching a reductively cleavable photoreactive disulfide–phenylazide linker (SPA) on the surface.[29] Upon light irradiation, the generated phenylnitrene helped to chemisorb biocompatible dextran polymers or proteins to encapsulate the embedded guest molecules and the controllable release was achieved with treatment by reducing agents, which enabled the SPA-MSNs to be an excellent nanocarrier for controllable release.

Although the above multi-stimuli responsive nanoparticles were sensitive to multiple chemical and physical inputs, the release of their encapsulated cargo still occurred upon the application of a single stimulus. Due to the complexity of the targeting and release profile, it is necessary to design a more smart trigger mechanism from which the drug can be only released when multiple stimuli are present simultaneously, namely "AND" logic responsive systems based on the logic gate concept, leading to greater programmed specificity regarding where and when release is triggered.[30] However, "AND" logic multi-stimuli responsive nanoparticles are synthetically challenging and only limited successful examples have been reported so far.[31,32]

In this work, we report a new polymer micelle as a drug carrier for controllable release based on the "AND" logic response concept with two orthogonal molecular triggers. As shown in Scheme 1, polyetherimide (PEI) polymer was modified with a nitrobenzyl phototrigger derivative (**NBN**) to obtain

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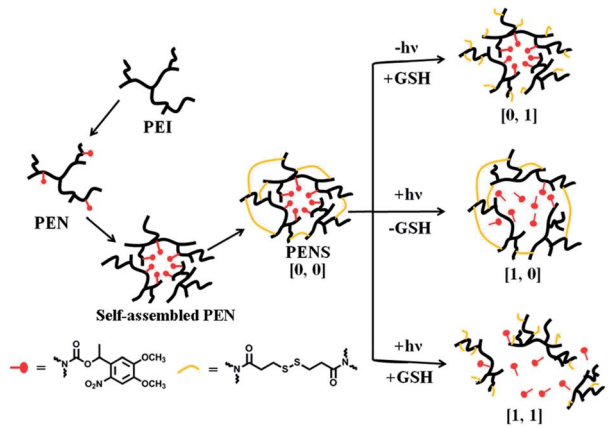


Scheme 1 Schematic presentations of the generation of the dual-responsive polymer **PENS** and its responsive behaviour with or without the photo and/or reductive stimuli.

photosensitive amphiphilic polymers **PEN** which were expected to form self-assembled micelles in water due to their amphiphilic nature. Then, dithiodipropionic acid was used as the crosslinker to stabilize the micelles (**PENS**) as well as adding the disulfide reduction trigger to the photo-responsive **PEN** systems. If the crosslinks were broken by disulfide reductive cleavage, the inherent amphiphilic nature of the system would make it still preserve the micelle-like morphology; if the hydrophobic **NBN** was photocleaved, the crosslinked structures would also prevent the collapse of the micelles. Only when photo and reduction conditions were present simultaneously, would the hydrophobic **NBN** be photocleaved and the disulfide crosslinker broken, with the amphiphilic micelle concomitantly dissociating back to hydrophilic PEI derivatives leading to the disassembly of the micelle. After complexing a hydrophobic drug doxorubicin (DOX), effective release could only be achieved using the simultaneous application of both light and a reducing agent. This smart system is expected to possess improved selectivity in targeting and to be appropriate for intracellular controlled release.

Experimental section

Materials

All reagents were purchased from commercially available sources such as Aldrich or TCI and used without further purification. Dichloromethane (DCM) was distilled from CaH_2 before use, and NEt_3 (TEA) was redistilled from CaH_2 and dried over KOH pellets.

Characterizations

Proton and carbon nuclear magnetic resonance (^1H, ^{13}C NMR) spectra were recorded on a Bruker Avance 500 (400 MHz) spectrometer. Mass spectra were recorded on a Micromass GCTTM and a Micromass LCTTM. Irradiations were carried out using a CHF-XM-500 W lamp with 365 nm filter. Absorption spectra were recorded on a Shimadzu UV-2550 UV-vis spectrometer. A NICOMP zetasizer measuring at a fixed scattering angle of 90° was used to determine particle size distribution by dynamic light scattering (DLS). Transmission Electron Micrographs (TEM) were measured on a JEOL JEM-1400 at 120 kV.

Synthesis of compounds

1-(4,5-Dimethoxy-2-nitrophenyl)ethanone (compound 2). To a solution of 10 mL conc. HNO_3 in an ice-bath, acetic anhydride was added and stirred for 30 min. To that solution, **1** (2.17 g, 12 mmol) dissolved in 2.5 mL acetic anhydride was slowly added. The reaction was stirred for another 5 h and then poured in 200 mL ice-water. The residue was extracted with 30 mL CH_2Cl_2 3 times and the obtained organic solution was dried over Na_2SO_4, and concentrated in a vacuum. Recrystallization in ethanol gave the product (1.63 g, 61%) as a yellow solid. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.62$ (s, 1H), 6.77 (s, 1H), 3.99 (s, 6H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 154.0, 149.6, 138.5, 132.9, 108.6, 106.8, 56.7, 56.6, 30.4; MS (ESI): *m*/*z*: calcd for $C_{10}H_{11}NO_5$ $[M + H]^+$: 226.1; found 226.1.

1-(4,5-Dimethoxy-2-nitrophenyl)ethanol (compound 3). To a solution of **2** (1.5 g, 6.7 mmol) in 50 mL methanol was added $NaBH_4$ (0.26 g, 6.8 mmol). The reaction was stirred at room temperature for 1 h and acidified with 1 N HCl to pH = 6. After concentration under reduced pressure to remove the methanol, the residue was extracted with 30 mL CH_2Cl_2 3 times and the obtained organic phase was dried over Na_2SO_4 and concentrated in a vacuum. Recrystallization in ethyl acetate–petroleum ether gave the product (1.29 g, 86%) as a yellow solid. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.57$ (s, 1H), 7.31 (s, 1H), 5.57 (q, $J = 6.3$ Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 1.56 (d, $J = 6.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 153.7, 147.7, 136.9, 108.5, 107.7, 65.8, 56.4, 56.3, 24.3; MS (ESI): *m*/*z*: calcd for $C_{10}H_{13}NO_5$ $[M + NH_4]^+$: 245.1; found 245.1.

1-(4,5-Dimethoxy-2-nitrophenyl)ethyl (2,5-dioxopyrrolidin-1-yl) carbonate (NBN). To a solution of **3** (1.2 g, 5.3 mmol) in 15 mL acetonitrile was added triethylamine (1.5 mL, 10.8 mmol) and *N*,*N*′-disuccinimidyl carbonate (1.62 g, 6.3 mmol). The reaction was stirred at room temperature overnight and concentrated under reduced pressure to remove the solvent. The residue was dissolved in 50 mL ethyl acetate and washed with citric acid solution (20% wt), saturated Na_2CO_3 solution and brine. After drying over Na_2SO_4 and concentrated in a vacuum, the crude product was recrystallized in chloroform–petroleum ether and the product was obtained as a yellowish solid (1.56 g, 80%). ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.62$ (s, 1H), 7.08 (s, 1H), 6.51 (q, $J = 6.3$ Hz, 1H), 4.07 (s, 3H), 3.96 (s, 3H), 2.80 (s, 4H), 1.77 (d, $J = 6.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 168.5, 154.3, 150.6, 148.4, 139.3, 131.2, 107.9, 107.1, 56.6, 56.4, 25.4, 21.9; MS (ESI): *m*/*z*: calcd for $C_{15}H_{16}N_2O_9$ $[M + NH_4]^+$: 368.1200; found 386.1184.

Synthesis of photo-responsive nitrobenzyl modified polyetherimide amphiphilic polymers (PEN)

To a solution of polyethyleneimine (50 mg, 0.002 mmol) and triethylamine (0.1 mL, 0.7 mmol) in dry DCM (20 mL), **NBN** (71 mg, 0.19 mmol, P/N = 6; 61 mg, 0.166 mmol, P/N = 7; 53 mg, 0.14 mmol, P/N = 8, P/N = the molar ratio of amine groups in

PEI to **NBN**) which was dissolved in 5 mL DCM was added slowly. The reaction was stirred at room temperature overnight and concentrated in a vacuum. Reprecipitation in diethyl ether 3 times gave the product as a yellowish solid.

Synthesis of nitrobenzyl and dithiodipropionic acid modified polyetherimide dual-responsive polymer (PENS)

In 50 mL of pH 9.0 buffer solution, 50 mg **PEN** was dispersed to constitute the micelle solution. To that solution, 3,3′-dithiodipropionic acid (47 mg, 0.22 mmol), NHS (67 mg, 0.58 mmol) and EDC·HCl (134 mg, 0.67 mmol) were added. The reaction was stirred at room temperature for 24 h and dialyzed (molecular weight cut off 3500) in deionized water for another 48 h. Lyophilisation of the dialysate gave the product as a yellowish solid.

Photo-responsive behaviour study of PEN

The photo-responsive behaviour of **PEN** was studied by irradiating its solution (0.1 mg mL^{-1} in DCM) in a quartz cuvette with a CHF-XM-500 W lamp with a filter of 365 nm with intensity of 15 mW cm^{-2}. Photolysis data was collected by directly measuring the UV-vis absorption spectra of the solution in the cuvette between certain time intervals of irradiation.

"AND" logic-responsive behaviour study of PENS

The "AND" logic-responsive behaviour of **PENS** was determined by the analysis of DLS. The cross-linked micelle of **PENS** were immersed in different buffer solutions with a concentration of 0.1 mg mL^{-1}. The buffer solutions used here were prepared as follows: (1) 10 mM of phosphate buffer (pH = 7.4) for the conditions of [$-h\nu$, −GSH]; (2) 10 mM of phosphate buffer (pH = 7.4) and GSH (10 mM) for the conditions of [$-h\nu$, +GSH]; (3) 10 mM of phosphate buffer (pH = 7.4) and irradiation at 365 nm for 8 min for the conditions of [$+h\nu$, −GSH]; and (4) 10 mM of phosphate buffer (pH = 7.4), GSH (10 mM) and irradiation at 365 nm for 8 min for the conditions of [$+h\nu$, +GSH]. For each experiment, the solution was shaken at 37 °C on a shaking table at 200 rpm for 24 h and the obtained solution was measured by DLS.

The loading and release of anti-tumour drug doxorubicin (DOX)

The loading of DOX was undertaken by adding a DMF solution (1 mL) of 10 mg **PENS** and 4 mg DOX to 9 mL deionized water, the unloaded drug was removed by dialyzing (molecular weight cut-off: 3500) in deionized water for 48 h. Then, the remainder was lyophilized to give the final anti-tumour drug loaded **PENS**.

The DOX release profiles in different conditions were determined by the dialysis technique. The DOX loaded **PENS** (1 mg) was dispersed in 10 mL pH 7.4 buffer to form the drug loaded micelle solution. 4 × 2 mL of the above solution was placed within four dialysis tubes (molecular weight cut-off: 3500), respectively, followed by dialysis against different buffer solutions as described above for the "AND" logic-responsive behaviour study of **PENS**. For each experiment, the solution was shaken at 37 °C on a shaking table at 200 rpm, and at different time intervals, 300 μL of the medium was taken out for analysis by UV-vis spectroscopy with an ultra-micro cell and then returned to the medium.

$$\text{The drug loading efficiency} = (\text{the quality of loading drug/the quality of polymer}) \times 100\%$$

$$\text{The drug release efficiency} = (\text{the quality of release drug/the quality of loading drug}) \times 100\%$$

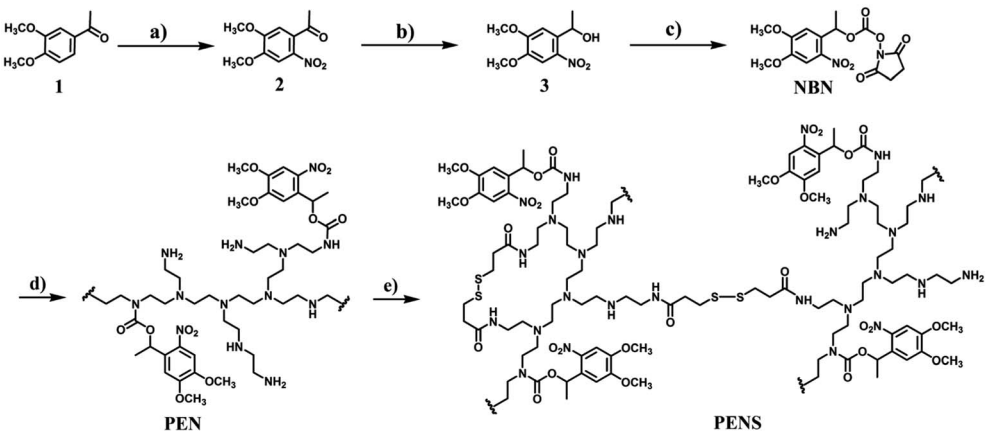
Results and discussion

As shown in Scheme 2, the *o*-nitrobenzyl containing **NBN** compound was synthesized from 3,4-dimethoxyacetophenone in three steps by (1) nitration by conc. HNO_3 under the catalysis of acetic anhydride; (2) the reduction reaction by $NaBH_4$; (3) an activating reaction using *N*,*N*′-disuccinimidyl carbonate. All the compounds were well prepared and characterized.

The polymer **PEN** was prepared by the nucleophilic substitution reaction between the photosensitive **NBN** compound and polymer PEI and purified by reprecipitation in diethyl ether 3 times. Here, three different feed ratios of PEI to **NBN** with P/N ratios (the molar ratio of the amine groups of PEI to **NBN**) at 6, 7 and 8 were used. Taking the feed ratio P/N = 6 as an example, the real P/N was determined to be 6.67 by the ^1H NMR spectrum recorded in $CDCl_3$ (Fig. 1), which was calculated from the integral ratio of peaks a and b (7.4 and 7.0 ppm, assigned to the aromatic ring protons of **NBN**) to that of multi-peaks f (around 3.0 ppm, assigned to the alkyl chain protons of PEI).

The successful conjugation between **NBN** and PEI also could be confirmed by FT-IR and UV-vis spectra. As shown in Fig. 2a, the FT-IR spectrum of **PEN** (feed ratio P/N = 7) not only preserved the characteristic peaks of PEI, but also showed the characteristic stretching vibration peak at 1705 cm^{-1} of carbonyl groups, the linking bond between **NBN** and PEI. Moreover, the presence of other peaks at 1674, 1518 and 1273 cm^{-1}, belonging to benzene and nitro groups of **NBN**, further suggested the successful conjugation between **NBN** and PEI. In the UV-vis absorption spectra as shown in Fig. 2b, the appearance of the maximum absorption at 350 nm of **PEN**, originating from the **NBN** chromophore, also confirmed the successful constitution of photosensitive polymer **PEN**.

The photocleaving of the *o*-nitrobenzyl phototrigger in **PEN** was checked by the evolution of UV absorption upon light irradiation. Based on the photolysis mechanism for *o*-nitrobenzyl phototriggers,[33–35] **PEN** was photolyzed to yield the parent PEI, one molecule of carbon dioxide and corresponding nitroso ketone derivatives as photo byproducts (as shown in Fig. 3a). The photolysis process of the **PEN** with feed ratio P/N = 7 was initiated by irradiating the DCM solution of **PEN** (0.1 mg mL^{-1}) with 365 nm UV light (15 mW cm^{-2}) and explored by UV spectroscopy. As shown in Fig. 3b, with the increase of irradiation time, the UV absorption of **PEN** at 291 nm decreased rapidly and a new peak at 380 nm appeared and increased due



Scheme 2 Synthesis procedure for **NBN**, **PEN** and **PENS**: (a) HNO_3–$(CH_3CO)_2O$, rt, 5 h, 61% yield; (b) $NaBH_4$–CH_3OH, rt, 1 h, 86% yield; (c) *N*,*N*′-disuccinimidyl carbonate–TEA–CH_3CN, rt, overnight, 80% yield; (d) PEI–TEA–DCM, rt, overnight; (e) 3,3′-dithiodipropionic acid–EDC·HCl–NHS, rt, 24 h.

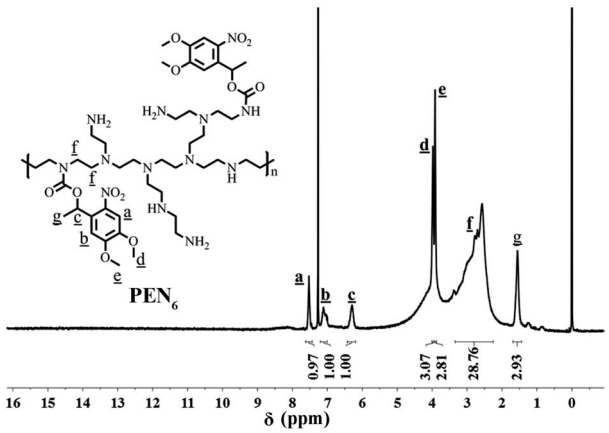


Fig. 1 ^{1}H NMR spectrum of the photo-responsive polymer **PEN** with feed ratio P/N = 6.

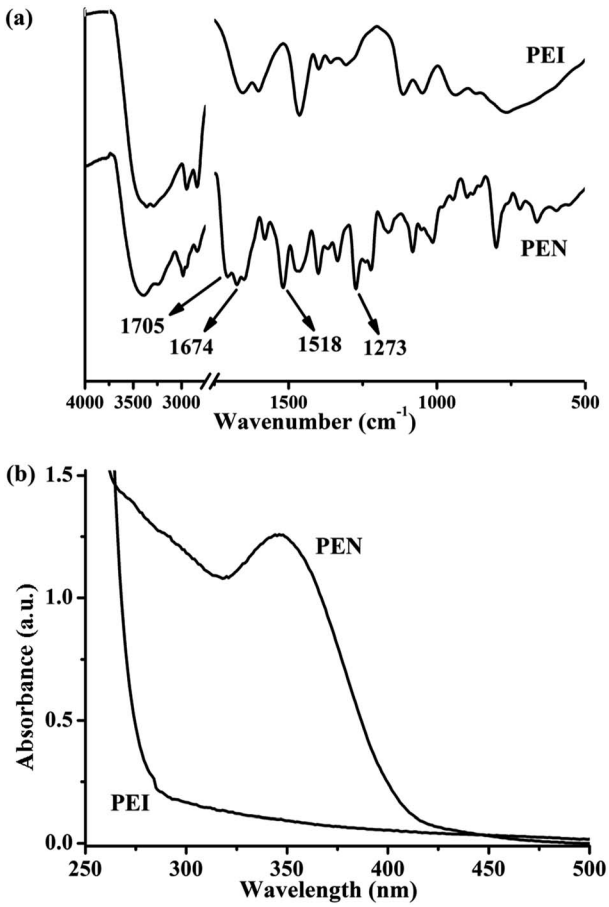


Fig. 2 (a) FT-IR and (b) UV-vis spectra of polymer PEI and **PEN** (feed ratio P/N = 7).

to the formation of the nitroso ketone photo product,[36,37] which suggested the photolysis of the nitrobenzyl phototrigger proceeded effectively and gradually. After 8 min irradiation, there were no more changes in the spectra, suggesting the achievement of maximum photocleavage. Thus, to ensure the complete photoreaction of the phototrigger, all the illumination experiments for the photo-responsive study of the micelles were set at 8 min.

Based on the amphiphilic character, the **NBN** containing polymer **PEN** would self-assemble into polymeric micelles in water which had a hydrophobic core and hydrophilic shell. To further stabilize and introduce a reductive response into the micelles, 3,3′-dithiodipropionic acid was used to couple with the outer amine groups of **PEN** in the presence of EDC and NHS (as shown in Scheme 2). The final formation of crosslinked micelles of **PENS** with excellent water dispersion was proved by the S wt% from XPS analysis. According to the different feed ratios of P/N, three **PENS** polymers were constituted and assigned as $\mathbf{PENS_6}$, $\mathbf{PENS_7}$ and $\mathbf{PENS_8}$, respectively. The details of the content characterization are listed in Table 1.

To investigate the reductive and light responses of the crosslinked **PENS** micelles, the micelles were exposed to GSH and irradiation with UV 365 nm light respectively and simultaneously, because the disulfide bond of the crosslinkers can be cleaved through the thiol–disulfide exchange reaction upon

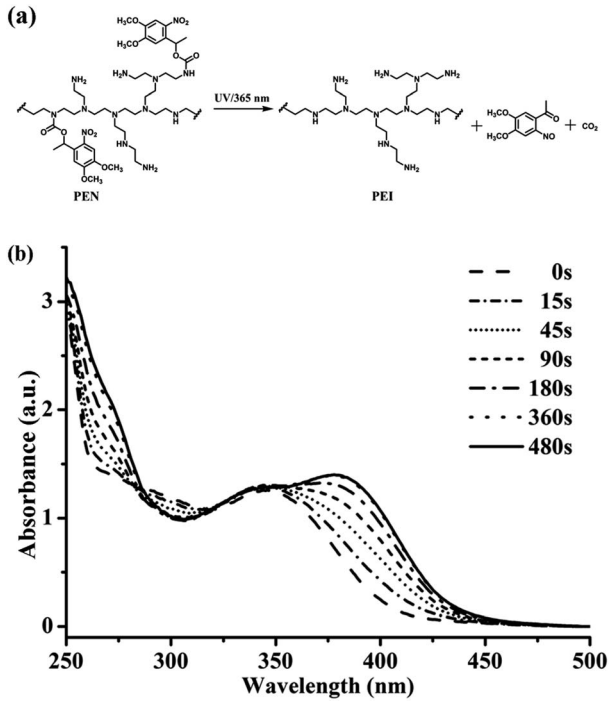


Fig. 3 Illustration of the photolysis of polymer **PEN** with feed ratio P/N = 7: (a) the proposed photolysis mechanism; (b) evolution of the UV-vis absorption spectra as a function of irradiation time. Light source is a CHF-XM-500 W lamp at wavelength of 365 nm with intensity of 15 mW cm^{-2}.

Table 1 The P/N ratios of the different corresponding **PEN** and S wt% of different **PENS**

	P/N[a] (mol)	P/N[b] (mol)	S%[c] (wt)	S%[d] (mol)
$PENS_6$	6	6.67	5.11	7.37
$PENS_7$	7	7.14	7.03	10.26
$PENS_8$	8	8.06	7.82	11.35

[a] Feed ratio. [b] Determined by ^{1}H NMR spectroscopy. [c] Measured by XPS. [d] Calculated by XPS.

addition of GSH and the hydrophobic nitrobenzyl chromophore can be cleaved upon 365 nm irradiation. Firstly, the **PENS** micelles were added into buffer solution containing 10 mM of GSH. In these conditions, the stimuli was just the reductive signal [$-h\nu$, +GSH], the input signal of the logic gate system was set as 0 and 1 when GSH concentrations were 0 and 10 mM, respectively. Then, UV 365 nm light with intensity of 15 mW cm^{-2} was employed as the other input signal and also defined as 0 and 1 without and upon irradiation, respectively. Controlled by these two input signal, the stimuli-responsive behaviour of the micelles was characterized by dynamic light scattering (DLS). As shown in Table 2, in the [0, 0] ([$-h\nu$, −GSH]) state, the average hydrodynamic diameters were about 194 nm for **$PENS_6$**, 230 nm for **$PENS_7$** and 680 nm for **$PENS_8$**, respectively. Obviously, the different P/N ratios greatly affected the diameters of the **PENS** micelles, and the higher the grafted content of nitrobenzyl phototriggers on PEI, the smaller the

Table 2 The "AND" logic responsive change in diameters (nm) of **PENS** with different P/N ratios

	[$-h\nu$, −GSH] [0, 0]	[$-h\nu$, +GSH] [0, 1]	[+$h\nu$, −GSH] [1, 0]	[+$h\nu$, +GSH] [1, 1]
$PENS_6$	194	193	308	892
$PENS_7$	230	227	360	2980
$PENS_8$	680	780	903	1763

diameter of the micelles. This should be attributed to their amphiphilic nature, in which PEI is a hydrophilic polymer and the higher content of hydrophobic **NBN** would induce more compact aggregates, thus forming stable micelles with smaller diameters. In the presence of GSH, namely in the [0, 1] state, the disulfide bonds were broken but the polymers were still amphiphilic as with **PEN** which would help support their micelle morphologies (as illustrated in Scheme 1). As expected, the diameters of the micelles in the [0, 1] state were similar to the original diameters except for **$PENS_8$** (Table 2). When changed to the [1, 0] state, namely only upon light irradiation, the hydrophobic nitrobenzyl phototrigger was cleaved from the polymer but the crosslinked structure with disulfide bonds physically prevented the collapse of the micelles (Scheme 1). As summarized in Table 2, the diameters of the micelles increased about 110–130 nm compared with their original state, which was still the OFF state for the micelles. When light and GSH were input simultaneously, namely the [1, 1] state, both the hydrophobic nitrobenzyl phototrigger and disulfide were cleaved, which induced the disassembly of the polymers as illustrated in Scheme 1. The DLS analysis showed a significant increase in the diameters, especially for **$PENS_7$**, it increased 13 times that of the ones with no stimulus. Meanwhile, transmission electron microscopy (TEM) measurements of **$PENS_7$** in different conditions also exhibited similar results. As shown in Fig. 4, the morphology of the micelles was retained with the single photo or GSH stimulus, and only degraded when treated with both the two stimuli. This huge variation for micelles made **$PENS_7$** promising as a carrier for constructing an "AND" logic responsive drug release system.

An anti-cancer drug DOX was selected as the drug model to explore the controlled drug release behaviour of our **$PENS_7$** micelles. The loading of DOX was prepared by mixing **$PENS_7$** and DOX in DMF directly, and then slowly adding to deionized water to form drug-loaded micelles. After dialysis and lyophilisation, drug loaded **$PENS_7$** micelles were obtained and the drug loading efficiency was determined to be 39% calculated from the UV absorption standard curve of DOX. Fig. 5 illustrated the drug release profiles of DOX loaded **$PENS_7$** micelles in different conditions. In the [0, 0] state, without light and GSH stimuli, the leaking of DOX was less than 20% within 50 h. With only GSH stimulus in the [0, 1] state, the release of DOX was similar to that in the [0, 0] state, suggesting no more drug was released in the presence of GSH. When changed to the [1, 0] state with light irradiation, the DOX release amount was about 35% within 50 h. It should be attributed to the slightly increased diameters of the micelles in this state that induced greater release of the

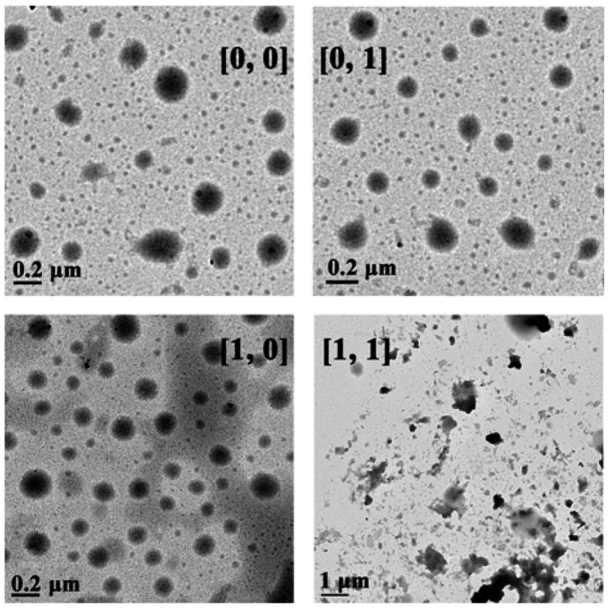


Fig. 4 TEM images of $PENS_7$ with different stimuli.

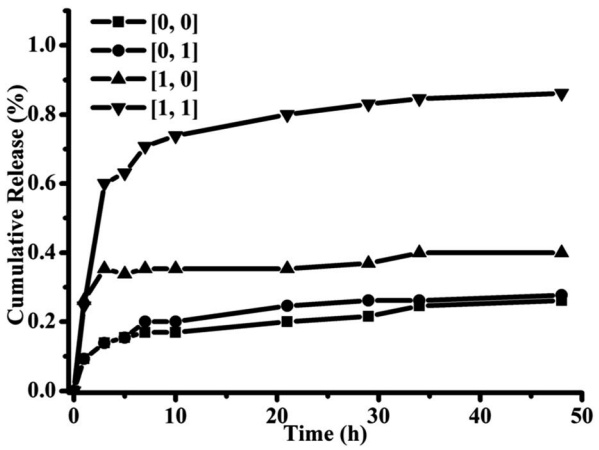


Fig. 5 DOX release from $PENS_7$ micelles with different stimuli *in vitro*.

drug. Only when the input signal turned to [1, 1] did the DOX release achieve the highest value and the release amount increased to 86% within 50 h. Although the drug release cannot be controlled in perfect ON and OFF states, this "AND" logic responsive release exhibited 4 times the release efficiency than the ones without any stimulus. We can speculate that this controlled release system would work effectively in tumour cells, where the reduction states reach their thresholds, and the manipulation of light provides precise control for the release.

Conclusions

In conclusion, we have prepared an amphiphilic polymer **PEN** with the hydrophobic nitrobenzyl phototrigger grafted on the hydrophilic polymer PEI, which could self-assemble into micelles in water and be further crosslinked by disulfide-containing linkers to constitute an "AND" logic responsive polymer **PENS**. With a single photo or reductive stimulus, the diameters of the **PENS** micelles changed a little; while the micelles disassembled when both photo and reductive stimuli were applied simultaneously. After physiologically encapsulating the hydrophobic drug DOX, the drug release of the **PENS** micelles also exhibited "AND" logic responsive properties; the optimal drug release efficiency was achieved only when the input signal was the [1, 1] state, which showed potential applications in targeted delivery.

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