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

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A novel photo and reduction dual-responsive PEI micelles was fabricated and applied for “AND” logic responsive drug release.
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“AND” logic responsive polyetherimide (PEI)-based polymers PENS were constituted by attaching the photosensitive 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. And the disassembly only occurred when photo and reductive signal inputted at the same time. This smart system was therefore applied as carrier for the controlled release of 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 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 even inorganic particles have been utilized to prepare stimuli responsive nanoparticles to achieve the drug controllable release. 17-21

Compared to the single stimuli-responsive systems, multi-stimuli responsive nanoparticles that are sensitive to two or more stimuli allow precisely tuning the guest release kinetics to fit the therapeutic window of drug. 22-26 For example, the group of Hennink 27 recently had developed dual-stimuli sensitive peptide-hybrid ABC block copolymers which self-assembled 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 pNIPAm block from hydrophobic to hydrophilic characters. Thayumanavan and co-workers reported a series of triply stimuli responsive block copolymers which were response 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 a 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.

Scheme 1. The schematic presentations of the generation of the dual-responsive polymer PENS and its responsive behaviour with or without the photo or/and reductive stimuli.
Although above multi-stimuli responsive nanoparticles were sensitive with 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 more smart trigger mechanism from which the drug can be only released when multi-stimuli are present simultaneously, namely “AND” logic responsive systems based on the logic gate concept, leading to greater programed specificity regarding where and when release are triggered. However, “AND” logic multi-stimuli responsive nanoparticles are synthetically challenging that induced only limited successful examples have been reported so far.\(^\text{31,32}\)

In this work, we report a new polymer micelle as 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 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 add the disulfide reduction trigger to the photo-triggering PEN systems. If the crosslinks were broken by disulfide reductive cleavage, the inherent amphiphilic nature of the system would make it still preserving the micelle-like morphology; if the hydrophobic NBN was photo-cleaved, the crosslinked structures would also prevent the collapse of the micelles. Only when photo and reduction conditions were present simultaneously, the hydrophobic NBN was photo-cleaved and disulfide crosslinker was broken, the amphiphilic micelle concomitantly dissociated 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 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 magnetic resonance spectra (\(^1\)H, \(^13\)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 by using a CHF-XM-500w 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) which 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\(_2\)Cl\(_2\) for 3 times and the obtained organic solution was dried over Na\(_2\)SO\(_4\), and concentrated in vacuum. Recrystallization in ethanol gave the product (1.63 g, 61%) as a yellow solid. \(^1\)H 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\(_8\)NO\(_3\) [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 concentrated under reduced pressure to remove methanol, the residue was extracted with 30 mL CH\(_2\)Cl\(_2\) for 3 times and the obtain organic phase was dried over Na\(_2\)SO\(_4\) and concentrated in vacuum. Recrystallization in ethyl acetate/petroleum ether gave the product (1.29 g, 86%) as a yellow solid. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 7.62\) (s, 1H), 7.31 (s,1H), 5.77 (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\(_{12}\)NO\(_3\) [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 3 (1.2 g, 5.3 mmol) in 15 mL acetonitrile was added triethylamine (1.5 ml, 10.8 mmol) and N,N’-Diuccinimidyl 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\(_2\)CO\(_3\) solution and brine. After dried over Na\(_2\)SO\(_4\) and concentrated in vacuum, the crude product was recrystallization in chloroform/ petroleum ether and the product was gave as a yellowish solid (1.56g, 80%). \(^1\)H 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 (dd, 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\(_{16}\)H\(_{16}\)N\(_2\)O\(_4\) [M+NH\(_4\)]\(^+\): 368.1200; found 368.1184.
To a solution of polyethylenimine (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 group 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 vacuum. Reprecipitation in diethyl ether for 3 times gave the product as a yellowish solid.

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

To 50 mL 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 for PEN**

The photo-responsive behaviour of PEN was performed by irradiating its solution (0.1 mg/mL in DCM) in a quartz cuvette with a CHF-XM-500w lamp with a filter of 365 nm with intensity of 15 mW/cm². And photosynthesis data was collected by directly measuring the UV-vis absorption spectra of the solution in cuvette between certain time intervals of irradiation.

**“AND” logic-responsive behaviour study of PENS**

“AND” logic-responsive behaviour study of PENS were determined by the analysis of DLS. The cross-linked micelle of PENS was immersed in different buffer solutions with a concentration of 0.1 mg/mL. The buffer solutions used here were prepared as follows: (1) 10 mM of phosphate buffer (pH = 7.4) as the condition of [-hv, -GSH]; (2) 10 mM of phosphate buffer (pH = 7.4) and GSH (10 mM) as the condition of [-hv, +GSH]; (3) 10 mM of phosphate buffer (pH = 7.4) and irradiation at 365 nm for 8 min as the condition of [+hv, -GSH]; and (4) 10 mM of phosphate buffer (pH= 7.4), GSH (10 mM) and irradiation at 365 nm for 8 min as the condition of [+hv, +GSH]. For each experiments, the solution was shaken at 37 °C on a shaking table at 200 rpm and the obtained solution was measured by DLS.

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

The loading of DOX was prepared by adding a DMF solution (1 mL) of 10 mg PEN 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 remains 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 above solution was placed within four dialysis tubes (molecular weight cut off 3500), respectively, followed by dialysis against different buffer solution as described above for the “AND” logic-responsive behaviour study of PENS. For each experiments, 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 using UV-vis spectroscopy with an ultra-micro cell and then returned to the medium.

The drug loading efficiency = (the quality of loading drug/ the quality of polymer) × 100%

The drug release efficiency = (the quality of release drug/ the quality of loading drug) × 100%

**Results and discussion**

As shown in Scheme 2, the o-nitrobenzyl contained NBN compound was synthesized from 3,4-Dimethoxyacetophenone in three steps by 1) nitration by conc. HNO₂ in the catalysis of acetic anhydride; 2) reduction reaction by NaBH₄; 3) activating reaction by the N,N'-Disuccinimidyl carbonate. All the compounds were well prepared and characterized.

The polymer PEN was prepared by the nucleophilic substitution reaction between photosensitive NBN compound and polymer PEI and purified by the reprecipitation in diethyl ether for 3 times. Here, three different feed ratio of PEI to NBN with P/N ratio (the molar ratio of the amine group of PEI to NBN) at 6, 7 and 8 were proceeded. Taking the feed ratio P/N =
6 as example, the real P/N was determined to be 6.67 by \(^1\)HNMR spectra 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 peaks e and f (3.0 and 2.5 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 spectroscopies. 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 group 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 maximum absorption at 350 nm of PEN, originating from the NBN chromophore, also confirmed the successful constitution of photosensitive polymer PEN.

The photolysis of \(\alpha\)-nitrobenzyl phototrigger in PEN was checked by the evolution of UV absorption upon light irradiation. Based on the photolysis mechanism for \(\alpha\)-nitrobenzyl phototriggers, \(^{33-35}\) PEN was photolyzed to yield the parent PEI, one molecule of carbon dioxide and corresponding nitro ketone derivatives as photo byproducts (as shown in Fig. 3a). The photolysis process of the PEN with feed ratio P/N= 7 was proceeded by irradiating the DCM solution of PEN (0.1mg/mL) with 365 nm UV light (15 mW/cm\(^2\)) and explored by UV spectroscopy. As shown in Fig. 3b, with the increasing of irradiation time, the UV absorption of PEN at 291 nm decreased rapidly and a new peak at 380 nm was appeared and increased due to the formation of photo product of nitroso ketone. \(^{36,37}\) which suggested the photolysis of nitrobenzyl phototrigger was proceeded effectively and gradually. After 8 min irradiation, there was no more change explored in the spectra, suggesting the achievement of maximum photolysis. Thus, to ensure the complete photoreaction of the phototrigger, all the illumination experiments for the photoresponsive study of the micelles were set at 8 min.

Based on the amphiphilic character, the NBN contained polymers PEN would self-assemble into polymeric micelles in water which had a hydrophobic core and hydrophilic shell. To further stabilize and introduce reductive response to the

<p>| Table 1 The P/N ratio of the different corresponding PEN and S wt% of different PENs. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>P/N(^a) (mol)</th>
<th>P/N(^b) (mol)</th>
<th>S(^c) (wt)</th>
<th>S(^d) (mol)</th>
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<tr>
<td>PEN(_6)</td>
<td>6</td>
<td>6.67</td>
<td>5.11</td>
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<td>PEN(_7)</td>
<td>7</td>
<td>7.14</td>
<td>7.03</td>
</tr>
<tr>
<td>PEN(_8)</td>
<td>8</td>
<td>8.06</td>
<td>7.82</td>
</tr>
</tbody>
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\(^a\) feed ratio, \(^b\) determined by \(^1\)H NMR spectroscopy, \(^c\) measured by XPS, \(^d\) calculated by XPS.
micelles, 3,3'-dithiodipropionic acid was used to couple with the outer amine groups of PENS in the presence of EDC and NHS (as shown in Scheme 2). The final formation of crosslinked micelles PENS with excellent water dispersion were proved by the S wt% from XPS analysis. According to the different feed ratio of P/N, three PENS polymers were constituted and assigned as PENS$_6$, PENS$_7$, and PENS$_8$, respectively. The details of content characterizations were listed in Table 1.

To investigate the reductive and light response of the crosslinked PENS micelles, the micelles was dealt with GSH and irradiation of UV 365 nm light respectively and simultaneously, because the disulfide bond of the crosslinkers can be cleaved through the thiol-disulfide exchange reaction upon addition of GSH and 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 this condition, the stimuli resource was just reductive signal [-hν, +GSH], the input signal of 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 another 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] ([-hν, -GSH]) state, the average hydrodynamic diameters were about 193 nm for PENS$_6$, 230 nm for PENS$_7$, and 680 nm for PENS$_8$, respectively. Obviously, the different P/N ratio effected a lot on the diameters of the PENS micelles, and the higher the grafted content of nitrobenzyl phototrigger on PEI, the smaller the diameter of micelles. This should be attributed to their amphiphilic nature, in which PEI is a hydrophilic polymer and higher content of hydrophobic NBN would induce more compact aggregate, thus form stable micelles with smaller diameter. In the presence of GSH, namely in [0, 1] state, the disulfide bonds were broken but the polymers were still amphiphilic as that of PENS which would help supporting their micelle morphologies (as illustrated in Scheme 1). As expected, the diameters of the micelles in [0, 1] state were similar as those original ones except PENS$_6$ (Table 2). When changed to [1, 0] state, namely only upon light irradiation, the hydrophobic nitrobenzyl phototrigger was cleaved from the polymer but the crosslinked structure with disulfide bonds would physically prevent 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 in [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$_6$, it increased 13 times than 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 kept with single photo or GSH stimuli and only degraded when treated with both of the two stimulus. This huge variation for micelles made PENS$_7$ promising as carriers for constructing "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 39% calculated.

| Table 2 The “AND” logic responsive change in diameters (nm) of PENS with different P/N ratios. |
|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| [-hν, -GSH] 0  | [-hν, +GSH] 0  | [+hν, -GSH] 0  | [+hν, +GSH] 0  |
| PENS$_6$ | 194 | 193 | 308 | 892 |
| PENS$_7$ | 230 | 227 | 360 | 2980 |
| PENS$_8$ | 680 | 780 | 903 | 1763 |

Fig. 4 The TEM images of PENS$_7$ with different stimuli.

Fig. 5 DOX release from PENS$_7$ micelles with different stimuli in vitro.
from the UV absorption standard curve of DOX. Fig. 5 illustrated the drug release profiles of DOX loaded PENS 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. Only with GSH stimuli in [0, 1] state, the release of DOX was similar as those in [0, 0] state, suggesting no more drug was released in the presence of GSH. When changed to [1, 0] state with light irradiation, the DOX release amount was about 35% within 50 h. It should be attributed to the little increased diameters of the micelles in this state that induced some more release of drug. Only when the input signal turned to [1, 1], the DOX release achieved the highest and the release amount increased to 86% within 50 h. Although the drug release can’t be controlled in perfect ON and OFF state, this “AND” logic responsive release exhibited 4 times release efficiency than the ones without any stimuli. We can speculate that this controlled release system would work effectively in tumour cells, where the reduction state reach their thresholds, and the manipulation of light provide precise control for the release.

Conclusions

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

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Notes and references

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