ROS-responsive thioether-containing hyperbranched polymer micelles for light-triggered drug release

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Abstract
As a kind of promising drug carriers, smart polymers have attracted much attention due to the effective and controlled drug release in target cells. Herein, a reactive oxygen species (ROS)-responsive thioether-containing amphiphilic hyperbranched polymer prepared from MTPA and TMPTGE (HBPMT) is synthesized from 3-(methylthio)propylamine (MTPA) and trimethylolpropane triglycidyl ether (TMPTGE) by the amine-epoxy click reaction via A2 + B3 one-pot approach. Benefiting from its inherent amphiphilic nature, HBPMT can self-assemble into stable micelles in water. Triggered by H2O2, these micelles can be dissociated rapidly because hydrophobic thioether segments in their cores are oxidized into hydrophilic sulfoxide or sulfone groups. Additionally, the ROS produced by photosensitizer under light irradiation can also play the same role of H2O2. Such HBPMT micelles can be utilized to encapsulate anticancer drug paclitaxel (PTX) and photosensitizer chlorin e6 (Ce6) simultaneously for drug delivery and control release. The methyl thiazolyl tetrazolium assay toward MCF-7 tumor cells (a human breast adenocarcinoma cell line) indicates that these micelles encapsulated with PTX and Ce6 exhibit a significant combinational efficacy of cell proliferation inhibition, which means the promising potential for synergistic chemo-photodynamic cancer therapy. Such a novel nanocarrier based on amphiphilic to hydrophilic transition would provide a candidate for controlled drug release and cancer combination therapy.

KEYWORDS
drug delivery, hyperbranched polymer, photosensitizer, ROS-responsiveness, triggered drug release

1 | INTRODUCTION

In the past two decades, biocompatible and biodegradable polymeric nanoparticles have been widely used as anticancer drug delivery carriers since their great potential for prolonging drug blood circulation time and enhancing drug tumor accumulation, while reducing the systemic toxicity compared with the corresponding free drugs.1–4 However, these polymeric carriers commonly show inefficient drug release in tumor cells because of...
their inherent biodegradable behavior, resulting in decreased therapeutic efficacy. To address this issue, various stimuli-responsive polymeric nanoparticles have been developed as smart drug delivery systems for efficient drug release triggered by specific stimuli.5–7 These endogenous or external stimuli include pH,8,9 over-expressed enzymes,10 redox,11–13 temperature,14 magnetic field,15 ultrasound,16 and light.17,18 Among these stimuli, reactive oxygen species (ROS) has drawn considerable attention and an increasing number of ROS-responsive polymers have been exploited for target-specific drug delivery according to the different oxidation-sensitive moieties,19–24 such as the typical sulfur-,25–28 selenium- or tellurium-containing structures,29–32 phenylboronic acid/ester,33–35 thioketal-containing units,36 and so on.

Since the first report of oxidation-responsive polymeric vesicles formed from poly(propylene sulfide),25 increased follow-up studies focused on the development of different thioether-containing polymers used as smart nanocarriers for drug delivery.37–39 However, it was found that the limited amount of endogenous ROS in cancerous cells or at the pathological sites seemed not enough to oxidize the thioether-based polymers, which may limit their practical use. Recently, a few groups have reported that under light irradiation the encapsulated photosensitizer can generate high concentration of ROS to destroy the structures of the ROS-sensitive thioether-containing polymeric nanocarriers efficiently.40–42 However, these ROS-responsive thioether-containing polymers are limited to linear ones.

Hyperbranched polymers (HBPs), a class of highly branched polymers with linear units, dendritic units, and terminal units, have shown promising potential in biomedical applications, including drug/protein delivery, gene transfection, and biological imaging because of their good biocompatibility, biodegradability, and facile preparation.43–47 During the last decades, several ROS-responsive amphiphilic HBPs (e.g., HBPs consisting of selenide, diselenide, or thiolate units) have been exploited to fabricate smart drug delivery systems for cancer therapy.48–51 However, to the best of our knowledge, the ROS-responsive amphiphilic HBP containing thioether moiety for photo-triggered intracellular drug release has not yet been reported.

Herein, we report a ROS-responsive amphiphilic HBP containing thioether units, which is synthesized via “A2 + B3” type polycondensations from 3-(methylthio)propylamine (MTPA) and trimethylolpropane triglycidyl ether (TMPTGE) by amine-epoxy click reaction at room temperature (Scheme 1). Driven by the hydrophilic–hydrophobic interaction, amphiphilic hyperbranched polymer prepared from MTPA and TMPTGE (HBPMT) can self-assemble into spherical

**Scheme 1** Synthetic route of amphiphilic hyperbranched polymer HBPMT and schematic illustration for preparation of (photosensitizer and drug)-loaded micelles (Ce6&PTX@HBPMT) and light-triggered drug release. HBPMT, hyperbranched polymer prepared from MTPA and TMPTGE.
micelles to coload photosensitizer chlorrin e6 (Ce6) and anticancer drug paclitaxel (PTX). Under the light irradiation, the ROS generated by Ce6 can oxidize the hydrophobic thioether segments into hydrophilic sulfoxide or sulfone groups, which results in the amphiphilic to hydrophilic change of HBPMT and further the disassembly of micelles to release PTX rapidly to inhibit the proliferation of cancer cells.

2 | EXPERIMENTAL SECTION

2.1 | Synthesis of HBPMT

HBPMT were synthesized by the amine-epoxy click reaction using MTPA as A2 monomer and TMPTGE as B3 monomer. TMPTGE (3.024 g, 0.01 mol), MTPA (1.683 g, 0.016 mol), ethanol (10 mL) were charged into 25 mL flask and allowed to stirred for 48 h at room temperature under N2 atmosphere, and then excessive MTPA monomer was added to consume all the unreacted epoxy groups to get the end-cap polymers. Then the polymer was purified by dialysis against dimethyl sulfoxide (DMSO) for 3 days (molecular weight cutoff [MWCO] = 7000 g/mol). After removing DMSO by dialyzing with deionized water, the colorless viscous product HBPMT was obtained by vacuum freeze-drying at ~50 °C.

2.2 | Preparation of HBPMT micelles

Briefly, 10.0 mg HBPMT was dissolved in 0.2 mL DMSO completely. Then the above solution was added dropwise into deionized water (5 mL) under the slight stirring for 10 min. Subsequently, the solution was transferred to dialysis bag (MWCO = 1000 g/mol) and dialyzed against deionized water for 12 h, during which the deionized water was renewed every 4 h. Finally, HBPMT micelle aqueous solution was obtained.

2.3 | Preparation of drug-loaded HBPMT micelles

The typical preparation of Ce6-loaded HBPMT micelles was as following: Ce6 (1 mg) and HBPMT (15 mg) were mixed with DMSO solution (0.2 mL). After stirring for 30 min, the mixture was slowly added into 5 mL of deionized water. After additionally stirring at room temperature for 20 min, the mixed solution was transferred into dialysis bag (MWCO = 1000 g/mol) and dialyzed against deionized water for 12 h. The Ce6-loaded HBPMT micelles were obtained and denoted as Ce6@HBPMT micelles, the unencapsulated Ce6 was removed by the use of a 0.45-μm Millipore filter. In addition, the Ce6 and PTX-loaded HBPMT micelles were denoted as Ce6&PTX@HBPMT micelles, which were prepared as aforementioned methods, only the Ce6 (1.0 mg) was changed to the mixture of Ce6 (1.0 mg) and PTX (1.0 mg). To determine the loading amount of drug, 1 mL drug-loaded solution was lyophilized and then dissolved in DMSO again. The total loading amount of Ce6 was determined by UV-Vis spectrophotometer and the loading amount of PTX was determine by the use of high performance liquid chromatography (HPLC). Drug loading content (DLC) and drug loading efficiency (DLE) were calculated according to the following equations:

\[
\text{DLC(\%)} = \frac{W_{\text{loaded}}}{W_{\text{polymer}} + W_{\text{loaded}}} \times 100\% \\
\text{DLE(\%)} = \frac{W_{\text{loaded}}}{W_{\text{total}}} \times 100\%.
\]

Here, \(W_{\text{loaded}}\), \(W_{\text{total}}\), and \(W_{\text{polymer}}\) representing the weight of the loaded drug, total drug and polymer, respectively. For Ce6@HBPMT micelles, the DLE and DLC of Ce6 were 61.8% and 3.96% respectively. For Ce6&PTX@HBPMT micelles, the DLE and DLC of Ce6 were 53.7% and 3.40% respectively, the DLE and DLC of PTX were 26.4% and 1.67%.

2.4 | In vitro light-triggered drug release

2 mL of Ce6&PTX@HBPMT micelles solution (1 mg/mL) was transferred into dialysis bag (MWCO = 1000 g/mol). With or without irradiating by 660 nm laser for 5 min, the dialysis bags were immersed in 30 mL phosphate-buffered saline (PBS) in a shaking water bath at 37 °C. At predetermined time intervals, 3 mL external buffer solution was withdrawn and replaced with 3 mL fresh PB, respectively. The cumulative released amount of PTX with or without light irradiation was determined using the HPLC measurement. All PTX-released experiments were carried out in triplicate and the results are shown as the average data with standard deviations.

2.5 | In vitro anticancer activity of Ce6&PTX@HBPMT micelles

MCF-7 cells were seeded in 96-well plates at a cell density of \(6.0 \times 10^3\) cells per well. After incubation overnight, the culture medium was removed and replaced with 200 μL of medium containing serial dilutions of Ce6&PTX@HBPMT micelles from 1.5 to 120 μg/mL and the corresponding different dilutions of PTX from 0.025 to 2 μg/mL (Ce6: from 0.063 to 4.06 μg/mL) in the
absence or presence of Vitamin C (Vc, 1.0 mmol/L). Vc was used as a ROS scavenger to eliminate intracellular ROS. After treatment for 12 h, the cells were treated with PBS twice and then were irradiated under 660 nm laser for 10 min. After incubation for another 48 h, the cell viabilities were measured by methyl thiazolyl tetrazolium (MTT) assay according to the protocol.

3 | RESULTS AND DISCUSSION

To obtain the expected HBPMT effectively, the molar ratio of A2–B3 was set as 1.6:1 and the reaction was carried out in ethanol at room temperature. After the reaction was completed, the polymer was purified by dialysis with DMSO. The final HBPMT was characterized by gel permeation chromatography (GPC) and nuclear magnetic resonance (NMR) techniques. Figure 1A shows the molecular weight and the molecular weight distribution of HBPMT analyzed by GPC measurement. The number-averaged molecular weight ($M_n$) and molecular weight distribution index ($M_w/M_n$) of HBPMT were 4900 and 2.88, respectively, which suggested that the polymerization on the base of amine-epoxy click reaction was successful. The $^1$H NMR spectrum of HBPMT was shown in Figure 1B and all of the proton signals were assigned to the corresponding protons in its chemical structure. The chemical structure of HBPMT was also confirmed by fourier transform infrared technique (Figure S1). In addition, thermal gravimetric analysis and differential scanning calorimetry (DSC) measurements were used to evaluate the thermal properties of HBPMT and the results were exhibited in Figure S2. As seen from Figure S2A, the thermal stability of HBPMT is relatively high and the initial decomposition temperature is approximate to 246 °C. According to the DSC curve in Figure S2B, the glass transition temperature of HBPMT was about −10 °C. All the above experimental results verified that HBPMT was synthesized successfully.

Due to the amphiphilic molecular structure, HBPMT could spontaneously self-assemble into polymeric aggregates in water. In detail, a DMSO solution of HBPMT was slowly dropped into water to form a bluish solution of polymeric aggregates and then dialyzed in water to remove DMSO. The final concentration of HBPMT in polymeric aggregates solution was 1 mg/mL. The dynamic light scattering (DLS) and transmission electron microscopy (TEM) were utilized to determine the diameter and morphology of the polymeric aggregates. Figure 1C shows the formed aggregates with an average hydrodynamic diameter of approximate 70.4 ± 4.6 nm and a polydispersity indexes (PDI) of 0.165. The TEM photo in Figure 1D indicates that the HBPMT can form spherical micelles with an average diameter of approximate 56.3 ± 5.4 nm, which is a little smaller than that tested by DLS. This may be ascribed to both radius overestimation by DLS and shrinkage of micelles during TEM preparation. In addition, the stability of HBPMT

![Figure 1](image-url)
micelles was monitored by DLS measurement at different time intervals and the result was shown in Figure 1E. Obviously, the diameter and PDI of HBPMT micelles remained nearly the same in 21 days.

The critical micellization concentration (CMC) of HBPMT in water was determined by using Nile red (NR) as a fluorescent probe according to our previously reported method. The fluorescence intensity of NR versus the concentration of HBPMT was displayed in Figure 1F. When the concentration of HBPMT is low, the intensity of NR remains nearly unchanged, suggesting the typical characteristic of NR in water. With increasing the concentration of HBPMT, the fluorescence intensity of NR enhanced dramatically, which meant the formation of micelles and the loading of NR into the hydrophobic region of micelles. Accordingly, the CMC of HBPMT was about 6.75 μg/mL according to the inflection of the curve.

It was reported that the hydrophobic thioether units can be oxidized to the hydrophilic sulfoxide or sulfone moieties under strong oxidative condition. Here, H2O2 was used to as an oxidant to investigate the oxidation-responsive behavior of HBPMT micelles. First, the aqueous solutions of HBPMT micelles were treated by the H2O2 solution with the different concentration from 0 to 200.9 mmol/L. After incubation for 12 h, the transmittance of HBPMT micelles aqueous solutions was measured by UV-Vis spectrophotometer. Figure 2A indicates the transmittance of mixture solution increases to ~100% at a H2O2 concentration of 13.6 mmol/L or more, suggesting that the micelles disassemble completely at such H2O2 concentrations. The similar result can be observed clearly in the photos of the mixture solution (Figure 2B).

Additionally, the diameter changes of HBPMT micelles were detected by DLS and shown in Figure 2C. It is clear that the diameter of HBPMT micelles decrease significantly with the increase of H2O2 concentration, which also verifies the disaggregation of HBPMT micelles. Comparison with the TEM images of HBPMT micelles before (Figure 2D) and after (Figure 2E) oxidation, no micelles can be observed after HBPMT micelles are incubated with 100.5 mmol/L H2O2 for 12 h. These results could be ascribed to the oxidation of the hydrophobic thioether groups into the hydrophilic sulfoxide or sulfone groups at the high concentration of H2O2, causing the transition of HBPMT from amphiphilic to hydrophilic.

To prove the above deduction, the samples of HBPMT after oxidation with H2O2 were freeze-dried and then measured by 1H NMR (Figure 2F). The two proton signals at 2.11 (1') and 1.76 ppm (3') associating to methyl (–SCH3) and methylene (–CH2CH2SOCH3) disappeared gradually with increasing the H2O2 concentration. Meanwhile, the two new proton signals gradually appeared at 2.61 (1') and 1.91 ppm (3') ascribed to methyl (–SOCH3) and methylene (–CH2CH2SOCH3), respectively, which further confirmed the oxidation of thioether groups. Then the oxidation extent was quantitatively calculated by use of the following equation, and the result is shown in Figure 2G.

\[
\text{Oxidation extent} = \frac{I(–SOCH_3)}{I(–CCH_2C_H_3)} \times 100%.
\]

When treated with H2O2 at a concentration of 2.9 mmol/L, and 6.1 mmol/L, the oxidation extent of HBPMT was calculated as 15.3% and 34.9%, respectively. After adding 13.5 mmol/L of H2O2, the oxidation extent increases dramatically to 83.5%. When the concentration of H2O2 increased to 25.7 mmol/L or higher, almost 100% of thioether group was oxidized, which is in accordance with the results of UV-Vis and DLS measurements.

Aside from H2O2, ROS also can oxidize the thioether group of HBPMT, which is produced by photosensitizers under the irradiation of light with a fixed wavelength. Here the photosensitizer Ce6 was loaded into HBPMT micelles and irradiated with 660 nm laser to generate ROS. After irradiation for different time intervals, the Ce6@HBPMT micelles were freeze-dried and analyzed in CDCl3 by 1H NMR spectrum. As seen from Figure 3A, similar behavior could be observed that the proton signals at 2.09 and 1.74 ppm disappeared gradually and new signals at 2.59 and 1.91 ppm emerged. The oxidation extents of different irradiation times were calculated and shown in Figure 3B. It was obviously watched that the oxidation extent increased with the prolongation of irradiation time. Only irradiation for 5 min, the thioether groups of HBPMT were oxidized completely. These results verify that light irradiation with the help of Ce6 can produce ROS in a short time and oxidize the hydrophobic thioether units to hydrophilic sulfoxide or sulfone moieties, leading to the shrinkage of HBPMT micelles and release of loaded drugs. The similar result could be observed from the TEM images of Ce6@HBPMT micelles with irradiation by 660 nm laser at different time intervals (Figure 3C). Stimulus-responsive micelles are potentially used as smart vehicles to deliver anticancer drugs to the target and control drug release.

Herein, PTX was chose as a model drug and encapsulated into HBPMT micelles with Ce6 simultaneously. The release profiles of Ce6&PTX@HBPMT with or without 660 nm laser irradiation were shown in Figure 4. The cumulative release of PTX from Ce6&PTX-loaded HBPMT micelles without light irradiation was only about 35.4% in 24 h, whereas the cumulative release of PTX significantly increased to 74.8% in 24 h under the irradiation of 660 nm laser. This
can be attributed to the ROS, which is produced by Ce6 with the irradiation of 660 nm laser, to oxidize the hydrophobic thioester moieties into hydrophilic sulfone units and accelerate the disassembly of HBPMT micelles to release PTX rapidly.

The cytotoxicity of HBPMT was evaluated by MTT assay against normal cells and the results were shown in Figure S6. It is obvious that the cytotoxicity of blank HBPMT micelles is extremely low and the cell viability is up to 90% even at the high concentration of HBPMT micelles. Furthermore, flow cytometry and confocal laser scanning microscopy (CLSM) were used to investigate whether Ce6&PTX@HBPMT micelles can enter cells efficiently. As exhibited in Figure 5A, the fluorescence intensity of the cells is enhanced gradually with the increase of incubation time. As seen from Figure 5B, after incubating with Ce6&PTX@HBPMT micelles for 1 h, the red fluorescence of Ce6 in MCF-7
cells is mainly located in cytoplasm according to the merged image. Thereafter, to verify whether Ce6&PTX@HBPMT micelles could produce ROS upon 660 nm laser irradiation in cells, intracellular ROS generation was detected by ROS assay kits against MCF-7 cells. Strong green fluorescence was observed in MCF-7 cells after treatment with Ce6&PTX@HBPMT micelles with (L+) 600 nm laser irradiation, while almost no green fluorescence could be seen in the cells without (L-) irradiation, which demonstrated that Ce6&PTX@HBPMT micelles could generate a great amount of ROS inside the cells under 660 nm laser irradiation.

The intracellular ROS generation should be able to enhance therapeutic activity effectively. To demonstrate this, the proliferation inhibition of Ce6&PTX@HBPMT micelles against MCF-7 cells was evaluated. MCF-7 cells were treated with Ce6&PTX@HBPMT micelles and then irradiated with 660 nm laser or not. In addition, the cells treated with Ce6&PTX@HBPMT micelles and V_c plus light irradiation were used as a control. As displayed in Figure 5D, Ce6&PTX@HBPMT micelles showed the lower anticancer activity at each concentration without irradiation of 660 nm laser. On the contrary, the anticancer activity of Ce6&PTX@HBPMT micelles to MCF-7 cells was remarkably enhanced. However, after addition of V_c, the anticancer effect of Ce6&PTX@HBPMT micelles was moderately reduced, suggesting that the ROS produced by Ce6 under the irradiation of 660 nm laser not only triggered the release of PTX but also induced cell apoptosis directly. The similar results were obtained with other cancer cell lines such as HeLa and A549 cells (Figure S7). Such Ce6&PTX@HBPMT micelles could be utilized for cancer chemo-photodynamic synergistic therapy.

**FIGURE 3** (A) $^1$H NMR spectra of HBPMT after irradiation with different times with 660 nm laser. (B) Oxidation extent of HBPMT at various irradiation times with 660 nm laser. (C) TEM images of Ce6@HBPMT micelles at different irradiation time intervals under 660 nm laser. Scale bar: 200 nm. HBPMT, hyperbranched polymer prepared from MTPA and TMPTGE

**FIGURE 4** In vitro PTX release profiles from Ce6&PTX@HBPMT micelles with or without laser irradiation at 660 nm. PTX, paclitaxel
4 | CONCLUSION

In summary, we synthesized a novel ROS-responsive amphiphilic HBPMT successfully from MTPA and TMPTGE via amine-epoxy click reaction. HBPMT can self-assemble into stable micelles in water. HBPMT micelles loaded with Ce6 and PTX can enter cancer cells efficiently and display significantly chemophotodynamic synergistic anticancer efficacy against MCF-7 cells under the irradiation of 660 nm laser. Such ROS-responsive amphiphilic hyperbranched polymer would be a promising candidate for drug delivery and light-triggered release.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

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