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ARTICLE

Near-infrared light-sensitive liposomes for controlled release

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A photoresponsive amphiphilic lipid molecule with phosphatidylcholine as the headgroup and a near-infrared (NIR) light-responsive unit on the hydrophobic moiety were synthesized. Liposomes constituting the NIR-responsive lipid, cholesterol and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine, were constructed and applied as a photocontrolled release system. The precisely controlled release of the loaded cargo was demonstrated by adjusting the irradiation parameters and content of the photoresponsive species. The low cytotoxicity and good biocompatibility of the photoresponsive lipid was demonstrated by the MTT assay. This study provides us a new choice for developing a photoresponsive drug delivery system.

Introduction

Numerous nanoscale drug delivery vehicles have been developed[1] for preclinical and clinical studies. The control over the release of encapsulated drugs is the key to achieve desired success.[2–4] Liposomes represent one of the most widely explored drug delivery carrier. Stimuli responsiveness liposome-based drug delivery systems has attracted scientists' attention because they are easy-to-prepare and possess good biocompability.[5–9]

Photo irradiation can act as a viable strategy to externally control the release of the payloads. The photoactivation of liposomes can be realized by destabilizing the stability of the lipid bilayers. Photoinduced polymerization,[10] isomerization,[11] and photodegradation[12] have been applied to trigger cargo release from liposomes. However, most of these photoresponsive moieties were ultraviolet (UV)-responsive, the limited tissue penetration ability has restricted their applications. Recently, near-infrared (NIR) light was applied to trigger the on-demand release from drug-encapsulated cargos.[13–20] NIR light is more suitable for biomedical appplication as it can penetrate deeper into tissues (up to 10 cm) with less photodamage to cells and tissues comparing to UV or visible light. Though numerous NIR responsive drug carriers were reported in the past years, the incorporation of NIR responsive unit into liposome was seldom reported.[18]

Here, we designed a novel photolabile amphiphilic lipid by incorporating the NIR light-responsive 6-bromo-7-hydroxy-4-hydroxycoumarin (Bhc) unit into the lipid acyl chain.[21] The phosphocholine (PC) group was selected as the hydrophilic moiety since the PC-type lipid is the primary component of cellular membranes.[22] As a control, the amphiphilic lipid-containing UV-responsive unit was synthesized and investigated. Liposomes constituting photoresponsive amphiphilic lipids with and without 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC) were prepared, their photoresponsiveness, release behaviour, and biocompatibility were systematically studied.

Experimental

Materials

All of the reagents were purchased from Aldrich and Alfa Aesar Ltd in China. The solvents were purchased from Beijing Chemical Reagent Company and used without further purification. Deionized Millipore Milli-Q water (18.2 MΩ·cm^{-1}) was used in all of the experiments. The photoresponsive lipids were synthesized using the protocols shown in Figure 1 and Figure 2, the crucial intermediates and final products were purified by silica column chromatography. The cell line NIH3T3 was purchased from the Cell Bank of the Shanghai Institute for Biological Science, Chinese Academy of Sciences (Shanghai, China).

Instruments and Methods

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AMX 400 Spectrometer (400 MHz) at 298 K using partially deuterated solvents and the internal standard tetramethylsilane (TMS). Mass spectrometry (MS) spectra were obtained on an Agilent 6510 Q-TOF. UV measurements were performed on a Shimadzu UV2450 Spectrophotometer at 25°C. Fluorescence measurements were obtained on a Hitachi F2500 fluorescence spectrophotometer at 25°C. UV irradiation was performed on an AuLight CEL-HXF300 xenon light source with a UV band filter from 350–380 nm, and the modulation of power intensity was realized by adjusting the input voltage. NIR irradiation was performed using a Ti:sapphire regenerative amplifier (Hogan Inc) running at a 1 kHz repetition rate, which generated about 170 fs pulses at 808 nm. The laser beam was focused on the sample cell with a spot size of about 6 mm and an average power of 4 W. The cryo-sample was imaged with JEOL JEM-1400 TEM under 120 kV. The images were recorded on a Gatan multiscan CCD and processed with Digital Micrograph. DLS measurements were performed on a Malvern Zetasizer Nano ZS with a 173° scattering angle in a 45 µL quartz cuvette at 25°C, and all of the results were presented as the average of at least three repeats.

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Electronic Supplementary Information (ESI) available: Cryo-TEM of the liposome before and after irradiation, synthesis data, ^{1}H NMR and MS spectra of compounds are available free of charge. See DOI: 10.1039/x0xx00000x

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Liposome Preparation

2 mmol lipid (photo-responsive lipid, POPC and cholesterol) was well dissolved in a mixture solvent consisting 9 mL $CHCl_3$ and 1 mL MeOH in a 50 mL round-bottom flask. The solvent was removed by rotary evaporation under reduced pressure to form a thin layer on the flask's wall. The flask was kept under vacuum overnight to remove the residue organic solvent. Then 5 mL HEPES buffer (pH 7.4) containing 10 mmol·L^{-1} HEPES, 100 mmol·L^{-1} NaCl, 1 mmol·L^{-1} EDTA, and 100 mmol·L^{-1} 5(6)-carboxyfluorescein (CF) were added, and the flask was shaken in a water bath (60°C). After all of the lipid films were dispersed, the suspension was transferred to a plastic centrifuge tube and subjected to freeze-thaw cycles by alternately placed in liquid nitrogen (−195.6°C) and a water bath (60°C) for four cycles to disrupt the large multilamellar vesicles and to anneal any structure effects.[23] Liposomes of the desired size were obtained by 30 times extrusion through a 100 nm polycarbonate membrane mounted in the mini-extruder (Avanti Polar Lipids) at 25°C. Non-entrapped carboxyfluorescein (CF) was removed by eluting through a Sephadex G100 column with HEPES buffer as the eluent. The liposome-containing fraction was collected and kept in the dark.

Photocontrolled Release

Release of the entrapped CF molecule from vesicles was studied by fluorescence dequenching at 25°C. [2, 4]The aqueous solution of CF-loaded vesicles was stored in a 1 mm quartz cuvette and exposed to the NIR laser (808 nm, 4W) or UV light (50 mW·cm^{-2}) with a band path filter (350–380 nm) at different time points. After irradiation, the sample was incubated at 25°C for additional 5 min in the dark. The change in fluorescence emission intensity at 517 nm (excited at 492 nm) was tracked on a Hitachi F2500 fluorescence spectrophotometer, as a function of irradiation time. The release of CF (%) was calculated using the following equation:

$$\text{CF release } (\%) = \frac{I_t - I_0}{I_\infty - I_0}$$

where I_0 is initial fluorescence intensity, I_t is fluorescence intensity at time t, and I_∞ is fluorescence intensity when all CF molecules were released from the vesicles, which occurred upon addition of 0.4% (the final concentration) Triton X-100 and heating for an additional 30 min. As 0.4% Triton X-100 had negative effects on the fluorescence intensity of CF (20% suppression), the I_∞ value was corrected accordingly. The procedure for the control experiment was similar to the method outlined above.

Cytotoxicity against Mammalian Cells

The cytotoxicity of photoresponsive liposomes in mammalian cells was determined with the MTT assay. [24, 25] Briefly, NIH3T3 mouse embryonic fibroblasts were pre-seeded on sterilized 96-well plates at a density of 2 × 10^4 cells in 100 μL medium containing 10% HEPES. Then the plates were incubated for 24 h at 37°C in an atmosphere containing 5% CO_2. Aliquots (100 μL) of different concentrations of liposome solutions were added to the wells (well without cells served as controls), and the cells were incubated for an additional 24 h. Subsequently, a 20 μL aliquot of MTT solution (5 mg·mL^{-1}) was added to each well and the plates were incubated for 4 h at 37°C. The precipitated formazan was dissolved in 200 μL DMSO. The absorbance at 570 nm was measured using a microplate autoreader (Molecular Devices, M^{2}e).Cell survival percent was expressed as the percent ratio of NIH3T3 cells without liposome.

Results and discussion

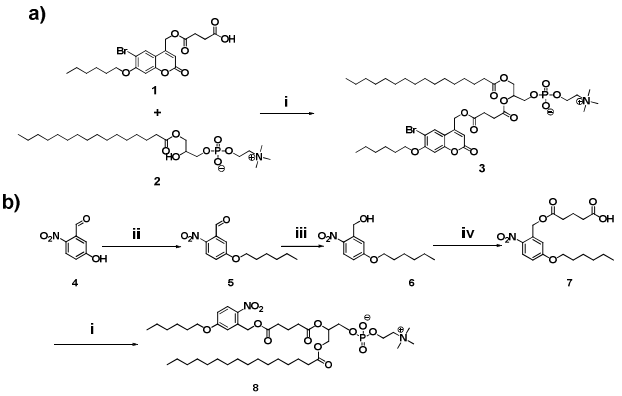

Figure 1. Synthesis route of Bhc-PC and NB-PC. i) palmitoyl-lysophosphatidylcholine, DCC, DMAP, CH_2Cl_2, 24 h. ii) 1-bromohexane, K_2CO_3, acetone, reflux, 6 h; iii) $NaBH_4$, THF, 1 h; iv) glutaric anhydride, triethylamine, CH_2Cl_2, 12 h.

The photoactive lipid was synthesized by covalently conjugating a photocleavable Bhc with lyso PC. [26-28] Cleavage of the Bhc group by UV light or NIR laser induced destabilization of the lipid membrane and the consequent release of the encapsulated cargo. As shown in Figure 1, the Bhc-PC (compound **3**) and NB-PC (2-nitrobenzyl containing PC, compound **8**) were obtained by coupling the photoresponsive carboxylic acid and palmitoyl-lysophosphatidylcholine (LPC, compound **2**) via esterification (Fig. 1a). The Bhc-containing carboxylic acid (compound **1**) group was synthesized according to a previous study.[29] NB-containing carboxylic acid **7** was synthesized from 5-hydroxy-2-nitrobenzaldehyde through esterification to **5**, reduction to **6**, followed by opening of glutaric anhydride to the photocleavable carboxylic acid **7**, in a yield of 53% (Fig. 1b). All of the intermediates and final products were purified by column chromatography. Their molecular structures and purities were confirmed by ^{1}H NMR and electrospray ionization mass spectrometry (ESI-MS).

Liposomes of 100–200 nm in diameter exhibited a prolonged circulation half-life in the blood and excellent enhanced permeability and retention (EPR) effects toward solid tumours. In our study, these unilamellar liposomes with desired size were prepared by extrusion through a polycarbonate membrane. Cholesterol was added to improve the tendency for liposome formation by improving hydrophobic interactions in the bilayer, it could increase the fluidity and stability of the liposome.[30-33] As shown in Table 1, liposomes containing 33% cholesterol, varying percentages of Bhc-PC (22%, 44%, 66%) and POPC were prepared. The NB-PC liposome was used as the control and the POPC cholesterol-based liposome was selected as the blank.

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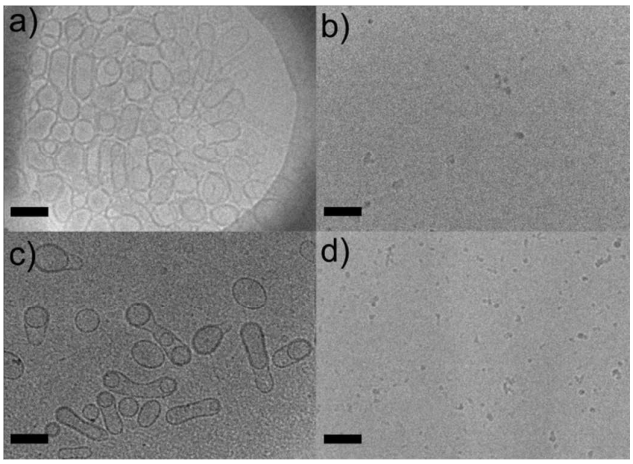

Figure 2. Cryo-TEM image of liposome. a) Liposome 3 before NIR irradiation; b) Liposome 3 after NIR irradiation; c) Liposome 6 before UV irradiation; d) Liposome 6 after UV irradiation (bar = 100 nm).

	POPC	Cholesterol	Bhc-PC	NB-PC
Control	**66%**	**34%**	**-**	**-**
Liposome 1	**44%**	**34%**	**22%**	**-**
Liposome 2	**22%**	**34%**	**44%**	**-**
Liposome 3	**-**	**34%**	**66%**	**-**
Liposome 4	**44%**	**34%**	**-**	**22%**
Liposome 5	**22%**	**34%**	**-**	**44%**
Liposome 6	**-**	**34%**	**-**	**66%**

Table 1. The mole-composition of cholesterol, Bhc-PC, NB-PC, and POPC in the liposomes

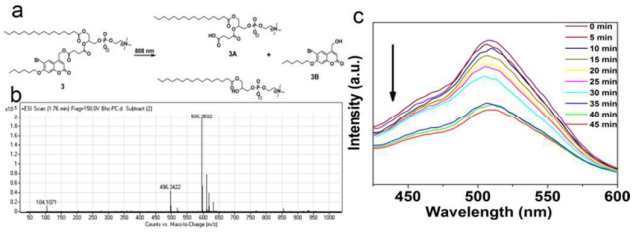

Figure 3. a) Photolysis route of Liposome 3 upon NIR irradiation (808 nm, 4W); b) ESI-MS data of photolyzed product from Bhc-PC; c) Fluorescence emission spectra (λ = 380 nm) of liposome 3 exposed to NIR light (808 nm, 4W).

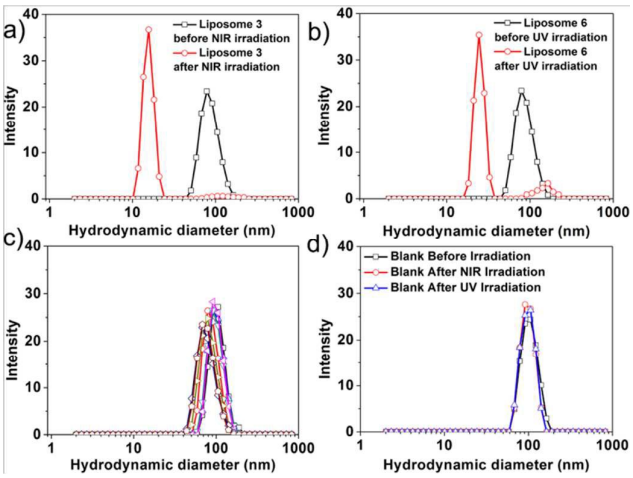

Figure 4. a) Hydrodynamic diameter distributions of liposome 3 before and after NIR irradiation; b) Hydrodynamic diameter distributions of liposome 6 before and after UV irradiation; c) Hydrodynamic diameter distributions of liposome 1 (balck open square, □) and 2 before (blue open uptriangle, △ and after NIR irradiation (red open circle, ○ and cyano open downtriangle ▽), and liposomes 4 and 5 before (megenta solid square ■ and navy open diamond ◇)and after UV irradiation (dark yellow solid circle● and wine open star☆); d) Hydrodynamic diameter distributions of the blank liposome before and after NIR irradiation.

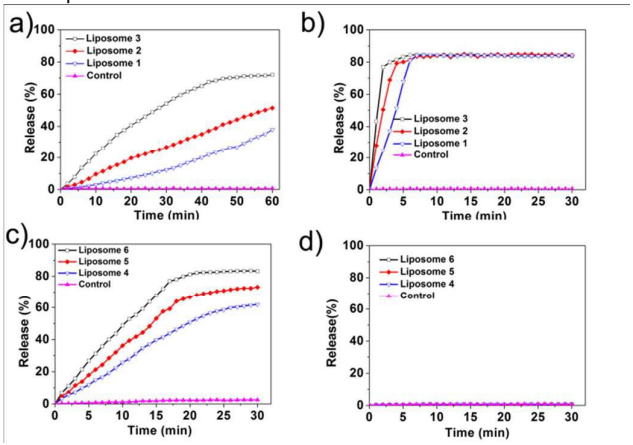

Figure 5. a) Release profiles of CF from liposomes containing Bhc-PC upon 808 nm laser irradiation (4 W); b) Release profiles of CF from liposomes containing Bhc-PC upon UV irradiation (50 mW/cm^2); c) Release profiles of CF from liposomes containing NB-PC upon UV irradiation (50 mW/cm^2); d) Release profiles of CF from liposomes containing NB-PC upon 808 nm laser irradiation (4 W).

Cryo-TEM was used to characterize the morphology of the liposomes. The microscopic images indicated that liposomes had a diameter of about 100 nm (Fig. 2a, 2c). Introduction of the photo responsive unit into the lipid structure did not affect the liposome's stability and morphology. The elongated or tube-shaped liposomes implies the possible segration of cholesterol and lipid components. Liposomes constituted of different ratio of photo-responsive lipid (Liposome 1, 2, 4 and 5)exhibited similar morphology (Fig. S1). Moreover, the cryo-TEM images showed an obvious contrast between the periphery and central area of the sphere, indicating liposome formation. After light irradiation, the liposomes disappeared and aggregates around 20 nm were observed (Figs.2b, 2d, 4a, 4b). We presumed that these aggregates consisted of

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cleaved species of the photoresponsive lipid and cholesterol. The morphology of the POPC-containing liposome (liposomes 1, 2, 4, 5) was preserved after irradiation (Figs. 4c, 4d, S1), suggesting that the POPC maintains the basic frame of the liposome.

To assess the photolysis behavior of Bhc-PC, Liposomes 3 without CF was exposed to NIR light. The ESI-MS results was utilized to study the photolysis pathway. Upon light irradiation, the signal of 3A and the hydrolysized product 2 was observed in ESI-MS, which coincide with our assumption. Compound 3B was not detected due to its poor solubility in aqueous solution (Fig. 3b). Photolysis of Liposome 3 under NIR light irradiation was also evidenced by changes in fluorescence emission intensity of the coumarin groups. Figure 3c shows the fluorescence emission spectra of liposome 3 recorded as a function of cumulative NIR exposure time. The emission intensity gradually decreased as a function of NIR irradiation time, indicating the generation of compound 3B, which was insoluble in aqueous medium and had partly quenched fluorescence. The photolysis of Liposome 6 was also investigated by UV-vis absorption, the decreased absorption at 320 nm and increased absorption around 270 nm and 370 nm indicated the disappearing of *o*-NB and formation of 2-nitrosobenzaldehyde (Fig. S2a). ESI-MS results illustrate the main constituents is compound 7A and 2 (Fig. S2c), which meet the results of UV-vis absorption.

After confirming the efficiency of the photocleavage, we characterized the release profiles of the liposomes under light irradiation. The water-soluble fluorophore CF was selected to mimic the drug encapsulated in the interior cavity of the liposome, and its release was examined by the increase of fluorescence intensity at 517 nm. We observed that the encapsulated CF was smoothly released from Bhc-PC containing liposomes (liposomes 1–3) upon NIR irradiation, and release was accelerated when the Bhc-PC content in the liposome was increased (Fig. 5a). A 60% release was observed after 1 h of irradiation. As a comparative experiment, CF release kinetics were examined under UV irradiation, the release demonstrated a relatively steep trend at the start of irradiation that reached a plateau in a short period of time (Fig. 5b). This could be attributed to the fact that the NIR two-photon process is slow and less efficient than the photocleavage obtained with UV irradiation. These findings demonstrate that the Bhc-containing liposome exhibited responsiveness to NIR laser as well as UV light, and its on-demand release can be regulated by irradiation time as well as liposome composition.

We also studied the release of CF from NB-PC containing liposomes (Liposomes 4-6) under UV and NIR irradiation. As expected, release ender UV irradiation gradually increased with time and plateaued after 15 min of UV irradiation (Fig. 5c), which was consistent with changes in the UV-visible absorption spectra (Fig. S2). The release of CF from liposomes 1–3 was barely observed when they were irradiated with NIR (Fig. 5d), due to the low two-photon absorption cross section of 2-nitrobenzyl. The results illustrates the Bhc-containing liposome have better performance than NB-PC containing liposome upon NIR irradiation.

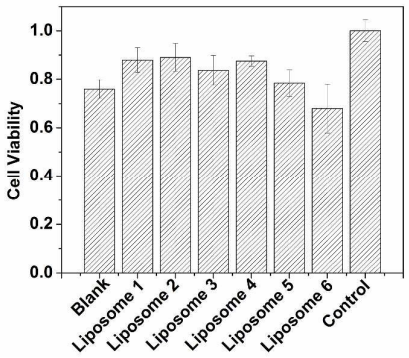

Figure 6. MTT assay of liposomes 1–6 and the blank liposome.

To evaluate the cytotoxicity of the photoresponsive liposomes, the MTT assay was performed. As shown in Figure 6, the metabolic activity of the cells was slightly higher after incubation with Bhc-PC-containing liposomes (liposome 1–3) for 48 h. Similar results were observed when liposomes containing 22% and 44% (liposomes 4 and 5, respectively) of NB-PC were utilized, but slightly lower metabolic activity of the cells was noted as the NB-PC content increased to 66% (liposome 6). An acceptable level of cell viability (> 75%) was observed. Taken together, these findings demonstrate that liposomes containing Bhc-PC exhibit low toxicity towards mammalian cells.

Conclusions

A novel photoresponsive PC-type lipid molecule with a Bhc moiety on the acyl chain was designed and synthesized. The large unilamellar liposome composed of cholesterol and the photoresponsive lipid, POPC, encapsulated the hydrophilic molecule in the interior cavity of the liposome, and released the cargo upon NIR and UV irradiation. The release behaviors were controlled either by adjusting the percentage of photoresponsive lipid or by irradiation time and intensity, demonstrating an important controlled release process. The combination of being easy-to-prepare, being NIR-responsive, and having low toxicity in cells indicates that these liposomes may be developed into efficient tools for drug and gene delivery.

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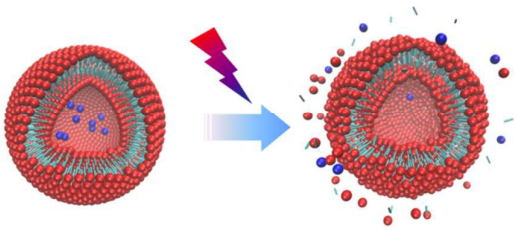

A 6-Bromo-7-hydroxy-4-hydroxymethylcoumarin containing amphiphilic lipid was synthesized and applied as near-infrared light triggered controlled release system.