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Polymeric micelles based on photocleavable linkers tethered with a model drug

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ABSTRACT

An amphiphilic block copolymer with photocleavable nitrobenzyl moieties in the side chain of the hydrophobic block was successfully synthesized by a combination of atom transfer radical polymerization (ATRP) and the Cu(I)-catalyzed 1,3-dipolar cycloaddition of azide and alkynes. 2-(Trimethylsilyloxy)ethyl methacrylate (HEMATMS) was polymerized from a poly(ethylene oxide) (PEO) macroinitiator via ATRP, leading to a well-defined block copolymer of PEO_{113}-*b*-$PHEMATMS_{45}$ with low polydispersity index (PDI = 1.09). After the polymerization, trimethylsilyl (TMS) groups were deprotected and then functionalized in-situ with 3-azidopropionic chloride to yield PEO-*b*-[2-(1-azidobutyryloxy)ethyl methacrylate] (PEO-*b*-PAzHEMA). Alkyne-functionalized pyrene with a photocleavable 2-nitrobenzyl moiety was added to the PEO-*b*-PAzHEMA backbone via click chemistry to produce the desired block copolymer with high fidelity. The resulting block copolymer was self-assembled in water to yield spherical micelles with an average diameter of 60 nm. Upon UV irradiation, 2-nitrobenzyl moieties were selectively cleaved, leading to the release of a model drug, 1-pyrenebutyric acid. Coumarin 102, another model drug that was physically encapsulated in the core of micelles during micellization in water, was also released at the same time. The general strategy presented herein can potentially be utilized for the preparation of polymeric vehicles that are capable of delivering multiple therapeutics under controlled individual release kinetics.

1. Introduction

Amphiphilic block copolymers have a unique chemical composition that is defined by a covalent linkage between hydrophilic and hydrophobic blocks [1–6]. In aqueous media, amphiphilic block copolymers self-assemble to form polymeric micelles, which are characterized by a well-defined core-shell structure with dimensions on the nanometer scale. Many important therapeutics are hydrophobic, rendering their delivery to desired biological targets quite challenging. Polymeric micelles have attracted interest due to their ability to solubilize hydrophobic drugs, which allows them to be potentially applied as nanocarriers for the controlled release of hydrophobic drugs [7–9].

Generally, hydrophobic interactions between hydrophobic drugs and a hydrophobic block are the driving forces for physical drug encapsulation. The release of drugs physically entrapped in micelles is diffusion-controlled and governed by the extent of interactions between the drug and the micelle core [10–12]. This simple method is versatile and thus, it may be applied for many hydrophobic drugs. However, the premature leakage of drugs from micelles during blood circulation cannot be avoided, which makes maximum drug release at the target site difficult [13,14]. In this regard, it is often advantageous to covalently conjugate a therapeutic agent that has been modified with a degradable linker. This can be achieved by employing stimuli-responsive systems in which endogenous or exogenous triggers can induce the release of tethered therapeutics. Several triggers, including pH, temperature, and light, have been extensively studied [15–22]. Among these stimuli, light holds great promise due to its selectivity in terms of the time and site of release [23–25]. Moreover, light-triggered release can be achieved even from outside of the system. For micelles built from photocleavable polymers in aqueous media, light stimulation leads to cleavage of the degradable linker and the subsequent release of cleaved drugs [26].

In this work, we report on the synthesis of a series of amphiphilic block copolymers tethered with photocleavable 2-nitrobenzyl

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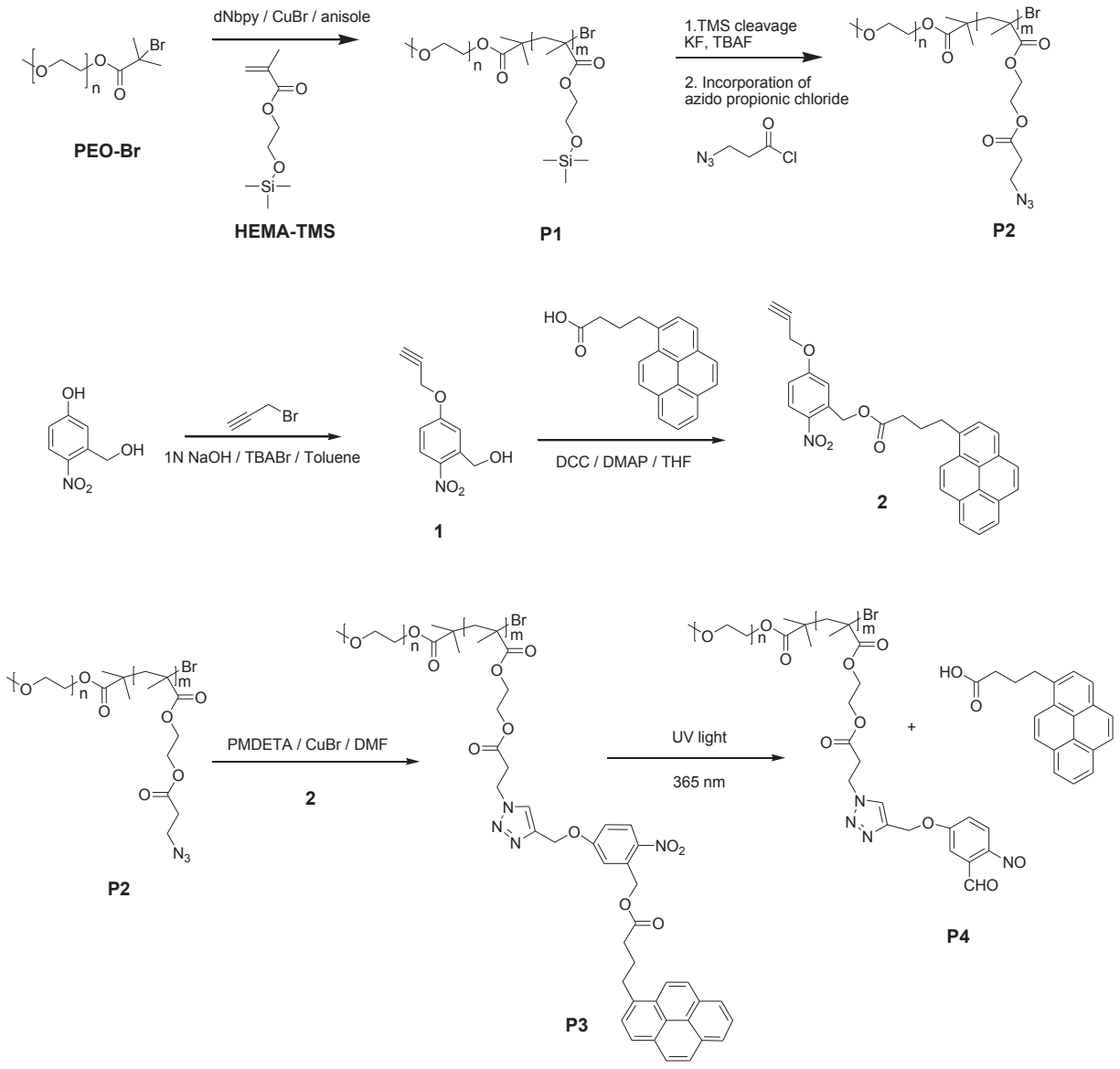

Scheme 1. Synthesis of amphiphilic block copolymers with photocleavable nitrobenzyl moieties to which 1-pyrenebutyric acid, a model drug, is covalently tethered.

moieties [27–30]. These nitrobenzyl groups are chemically conjugated with the side chain of the hydrophobic block in one end and 1-pyrenebutyric acid in the other end. 1-Pyrenebutyric acid was chosen as a model therapeutic agent, which has a COOH group for linkage to the polymer since there are many potential real drugs such as folic acid, captopril, and enalapril, featuring a COOH group that could be utilized for immobilization. Coumarin 102, another model drug, was physically encapsulated in the core of micelles during micellization in water. We demonstrated, for the first time as far as we know, that polymeric micelles prepared from the block copolymer with light-sensitive pendant groups were efficient to achieve controlled release of coumarin 102 physically entrapped in the micelles as well as photocleavable 1-pyrenebutyric acid.

2. Experimental

2.1. Material

2-Hydroxyethyl methacrylate (HEMA, 95%, Tokyo Chemical Industry; TCI) was purified by passing it through a column filled with basic alumina (Acros) so as to remove inhibitors. Triethylamine (TEA, 99.5%), tetrahydrofuran (THF, 99.9%), chloro-trimethylsilane (TMS-Cl, 99%), chloropropionic acid (98%), sodium azide (99.5%), dichloromethane (DCM, 99.9%), 5-hydroxy-2-nitrobenzaldehyde (98%), potassium fluoride (99%), tributylammonium fluoride (TBAF, 1.0 M in THF (~5 wt% water)), *N*,*N*-dimethylformamide (DMF, 99.8%), methyl alcohol (99.9%), sodium borohydride ($NaBH_4$, 99%), propargyl bromide solution (80 wt% in toluene), tetrabutylammonium bromide (98%), 1-pyrenebutyric acid (97%), *N*,*N*′-dicyclohexylcarbondimide (DCC, 99%), poly(ethylene glycol) methyl ether (average M_n ~5000), 2-bromoisobutyryl bromide (BIBB, 98%), 5-hydroxy-2-nitrobenzaldehyde, and CuBr (98%) were purchased from Aldrich with the highest purity and used as received without further purification. 4-Dimethylaminopyridine (DMAP), thionyl chloride (1.0 M in DCM), *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA), anisole (99%), and Coumarin 102 were purchased from TCI and used as received.

2.2. Instrumentation

^{1}H NMR spectroscopy (Bruker Avance 300 MHz, Varian) was employed with $CDCl_3$ and DMSO-d_6 as solvents. The apparent

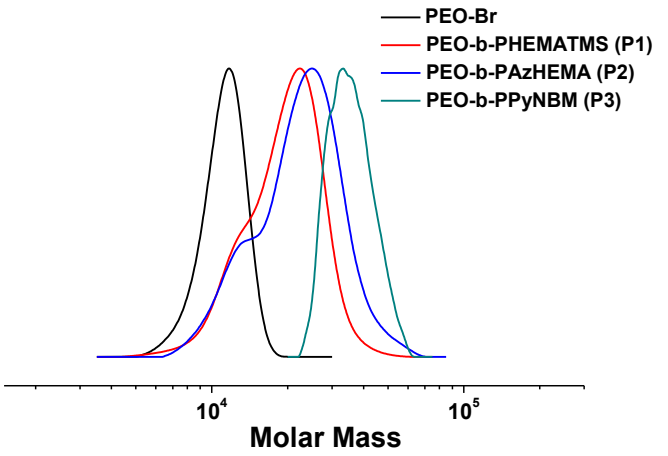

Fig. 1. Overlaid GPC traces of PEO-Br, PEO-*b*-PHEMATMS (P1), PEO-*b*-PAzHEMA (P2), and PEO-*b*-PPyNBM (P3) measured in DMF.

molecular weights and molecular weight distributions were measured by gel permeation chromatography (GPC, Agilent technologies 1200 series) using a poly(methyl methacrylate) standard and DMF as the eluent at 30 °C with a flow rate of 1.00 mL/min. UV–vis spectra were recorded using an OPTIZEN 3220 UV–vis spectrophotometer, while fluorescence spectra were acquired with a Fluoromax-4 Spectrofluorometer (HORIBA JOBIN YVON). For the irradiation experiments, the micelles were irradiated with UV light at 365 nm using a UV lamp (VILBER LOURMAT, *VL-4LC*, 4 W) operated at 365 nm.

2.3. Synthesis

2.3.1. 2-(Trimethylsiloxy)ethyl methacrylate

This was prepared as previously reported [31,32].

2.3.2. 3-Azidopropionic acid

3-Chloropropionic acid (11.8 g, 108.7 mmol) and sodium azide (14.1 g, 217.3 mmol) were dissolved in 50 mL of water. The solution was stirred for 15 h and then extracted with diethyl ether (3 × 50 mL). The organic layer was dried using anhydrous $MgSO_4$ to produce 3-azidopropionic acid in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 3.61–3.53 (2H, t, CH_2–CH_2–(C=O)); 2.66–2.58 (2H, t, N_3–CH_2–CH_2); 12.0–10.0 (1H, s, OH).

2.3.3. 3-Azidopropionyl chloride

3-Azidopropionic acid (4.5 g, 39 mmol) was dissolved in DCM (50 mL) and treated with a solution of thionyl chloride in DCM (1.0 M, 39 mL, 39 mmol). The reaction mixture was allowed to stir for 12 h at room temperature. The solvent was removed *in vacuo*, yielding 3-azidopropionyl chloride. ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm) 3.65–3.57 (2H, t, N_3–CH_2–CH_2); 3.16–3.07 (2H, t, N_3–CH_2–CH_2).

2.3.4. 2-Nitro-5-(2-propargyloxy) benzyl alcohol (**1**)

A solution of propargyl bromide (2 g, 17.7 mmol) in toluene (100 mL) was added dropwise to a solution of 5-hydroxy-2-nitrobenzyl alcohol (2.5 g, 14.8 mmol) and tetrabutylammonium bromide (0.48 g, 1.48 mmol) in 25 mL of 1 N NaOH at 60 °C. The reaction mixture was allowed to stir for 24 h at 60 °C. A yellowish white precipitate was obtained by cooling the mixture to room temperature. The organic layer was washed with distilled water (3 × 100 mL) and the solvent was removed *in vacuo*, yielding pale yellow crystals. The combined crude product was dissolved in 1,3-dioxane (5 mL) and precipitated in 1 L of distilled water. The precipitate was filtered and washed with distilled water until a white powder remained (1.06 g, 53%). ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 8.23–8.14 (1H, d, (C–O)–C*H*–CH–C–(NO_2)); 7.34–7.28 (1H, d, CH–C*H*–(C–O)); 7.02–6.94 (1H, doublet of doublet, CH–C*H*–C–(NO_2)); 5.04–4.95 (2H, s, CH–CH_2–OH); 4.95–4.75 (2H, d, O–CH_2–CH); 2.60–2.54 (1H, t, CH–C*H*); 2.53–2.43 (1H, s, OH).

2.3.5. 2-Nitro-5-(2-propargyloxy)benzylpyrene butyrate (**2**)

1-Pyrenebutyric acid (0.093 g, 0.323 mmol), 2-nitro-5-(2-propargyloxy) benzyl alcohol (**1**) (0.056 g, 0.27 mmol), and DCC (0.084 g, 0.41 mmol) were dissolved in 6 mL of THF in a 1 L round-

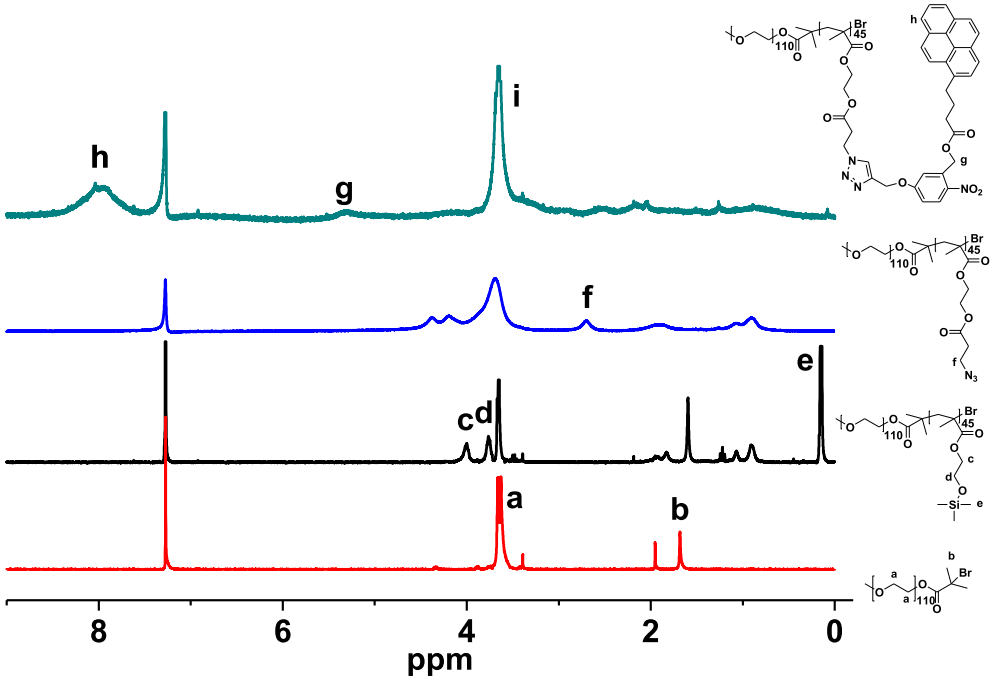

Fig. 2. Overlaid ^{1}H NMR spectra of PEO-Br, PEO-*b*-PHEMATMS (P1), PEO-*b*-PAzHEMA (P2), and PEO-*b*-PPyNBM (P3).

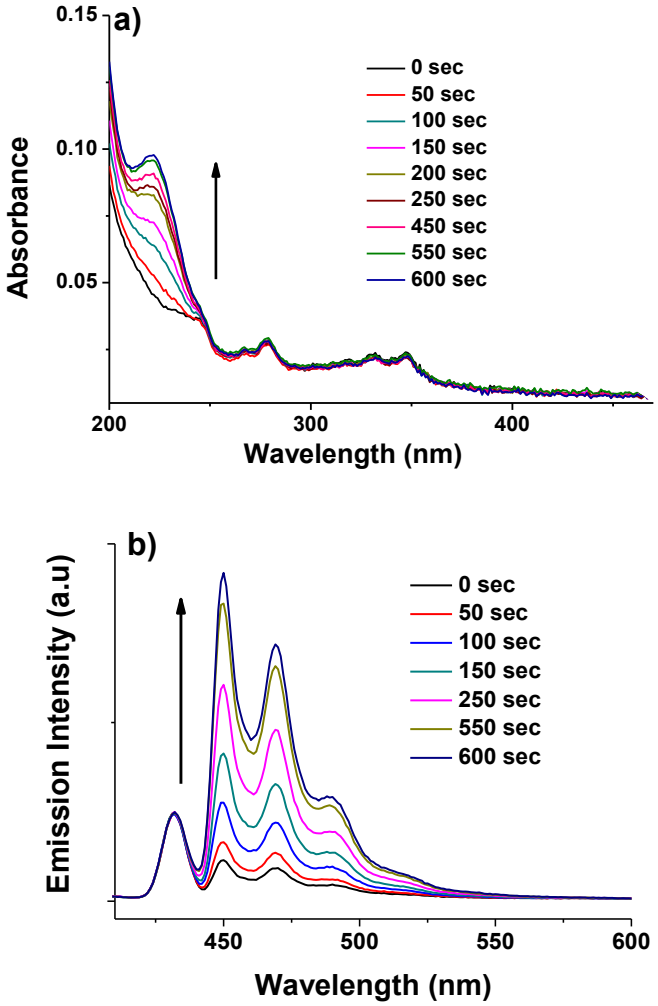

Fig. 3. (a) UV–vis and (b) emission spectra of a 0.01 wt% aqueous solution of P3 after UV irradiation at 365 nm.

bottomed flask at 0 °C. DMAP (2.06 mg, 0.0169 mmol) in 1 mL of THF was added dropwise to the flask over 0.5 h. The reaction mixture was allowed to stir for 40 h at room temperature, allowing insoluble DCC urea to precipitate out of the solution. After filtration, the resulting solution precipitated in cold diethyl ether. The product was ultimately filtered and dried under vacuum at room temperature for 48 h (yield: 90%). ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 9.53–7.80 (9H, m, pyrene); 7.10–6.99 (2H, s, C–*CH*–(C–O)); 6.97–6.95 (1H, d, (NO_2)–C–CH_2–CH); 5.58–5.42 (2H, t, O–CH_2–C–C–(NO_2)); 4.71–4.67 (1H, d, O–CH_2–CH–CH); 3.45–3.38 (2H, t, pyrene–CH_2–CH_2); 2.61–2.54 (2H, t, CH_2–CH_2–(C=O)); 2.50–2.41 (1H, d, –CH–*CH*); 2.35–2.14 (2H, m, CH_2–CH_2–CH_2–(C=O)).

2.3.6. PEO_{113}-Br

PEO_{113}-Br was prepared as previously reported [33].

2.3.7. PEO-b-PHEMATMS (**P1**)

HEMATMS (4.06 g, 20 mmol), PEO-Br (1.0 g, 0.2 mmol), dNbpy (0.041 g, 0.1 mmol), and anisole (10.0 mL) were added to a 25 mL Schlenk flask equipped with a magnetic stir bar. Oxygen was removed by three freeze–pump–thaw cycles, and CuBr (0.0143 g, 0.1 mmol) was added under argon. The polymerization was conducted at 70 °C for 10 h. The reaction was stopped by opening the flask to air when monomer conversion reached 45%. The catalyst was removed by passing the solution through a neutral alumina column. The polymer was precipitated by adding the solution to cold diethyl ether, at which point the product was dried overnight under vacuum at room temperature (DP of PHEMATMS = 45, as determined by ^{1}H NMR). M_n = 18 000 g/mol, M_w/M_n = 1.13. ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 4.09–3.98 (2H, d, –O–CH_2–CH_2–O–TMS); 3.93–3.67 (2H, d, –O–CH_2–CH_2–O–TMS); 3.67–3.55 (110H, s, PEO part); 0.16–0.01 (9H, s, Si–C(CH_3)$_3$).

2.3.8. PEO-b-PAzHEMA (**P2**)

PEO-*b*-PHEMATMS (0.5 g, assuming 1.6 mmol of -OTMS groups), KF (0.092 g, 1.6 mmol), and dry THF (25 mL) were placed in a 50 mL round-bottom flask. The flask was then sealed and flushed with argon. A solution of tetrabutylammonium fluoride in THF (1.0 M, 0.016 mL, 0.016 mmol) was added dropwise to the flask, followed by the slow addition of APC (0.25 g, 1.9 mmol in 5 mL of THF) over the course of 5 min. The reaction mixture was stirred overnight at room temperature and precipitated into cold diethyl ether. The separated precipitate was redissolved in $CHCl_3$ (10 mL), re-precipitated into cold diethyl ether, and dried under vacuum at 25 °C for 24 h (yield: 80%). M_n = 20,200 g/mol, M_w/M_n = 1.17. ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm) was as follows: 4.48–4.26 (2H, d, –O–CH_2–CH_2–O–(C=O)); 4.24–4.02 (2H, d, –O–CH_2–CH_2–O–(C=O)); 3.67–3.55 (110H, s, PEO part); 2.95–2.45 (2H, d, O–CH_2–CH_2–N_3); 2.30–1.80 (2H, d, O–CH_2–CH_2–N_3).

2.3.9. PEO-b-PPyNBM (**P3**)

The ratio of reagent [PEO-*b*-PAzHEMA]/[compound **2**]/[CuBr]/[PMDETA] was 1/2/0.2/0.2. The click reaction between PEO-*b*-PAzHEMA (14.2 mg, 0.02 mmol) and compound **2** (0.19 g, 0.04 mmol) was conducted in 2 mL of DMF using CuBr/PMDETA as a catalyst. After 5 h, the polymer solution was exposed to air, diluted with DMF, and passed through neutral alumina to remove the copper catalyst. The resulting polymer was precipitated in diethyl ether and dried in a vacuum oven for 24 h. M_n = 34,800 g/mol, M_w/M_n = 1.14. ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm) was as follows: 8.70–7.51 (9H, m, pyrene); 5.80–4.95 (2H, t, O–CH_2–C–C–(NO_2)); 4.48–4.26 (2H, t, –O–CH_2–CH_2–O–(C=O)); 4.24–4.02 (2H, m, –O–CH_2–CH_2–O–(C=O)); 3.67–3.55 (110H, s, PEO part); 2.95–2.45 (2H, d, O–CH_2–CH_2–N_3); 2.70–2.39 (2H, d, N–C–CH_2–O); 2.30–1.80 (2H, d, O–CH_2–CH_2–N_3).

3. Results and discussion

A schematic of the strategy employed in this study is shown in Scheme 1. The hydrophobic PHEMATMS block was extended from a hydrophilic poly(ethylene oxide) (PEO) macroinitiator via atom transfer radical polymerization (ATRP) [34,35]. Anisole was used as a solvent, and a CuBr/dNbpy catalyst system was employed for the block copolymerization of HEMATMS. The initial ratio of monomer to PEO-Br macroinitiator was 100:1, and the polymerization was stopped when monomer conversion reached 45% (DP_{theory} of PHEMATMS = 45). The molecular weight and molecular weight distribution of PEO-*b*-PHEMATMS (P1) were obtained on a GPC DMF line using PMMA standards (M_n = 18 000 g/mol, M_w/M_n = 1.13) (Fig. 1). The experimental molecular weight of P1 was obtained from ^{1}H NMR spectroscopy ($M_{n,\ NMR}$) by calculating the integration area of the TMS signals at 0.11 ppm and the signals at 3.6 ppm of the PEO repeat unit (–OCH_2CH_2–) (DP_{NMR} of PHEMATMS = 48) (Fig. 2). After polymerization, TMS groups were deprotected in the presence of potassium fluoride and then functionalized in-situ with 3-azidopropionyl chloride in THF to yield PEO-*b*-PAzHEMA (P2). The ^{1}H NMR spectra provided evidence of the successful synthesis of azido-functionalized

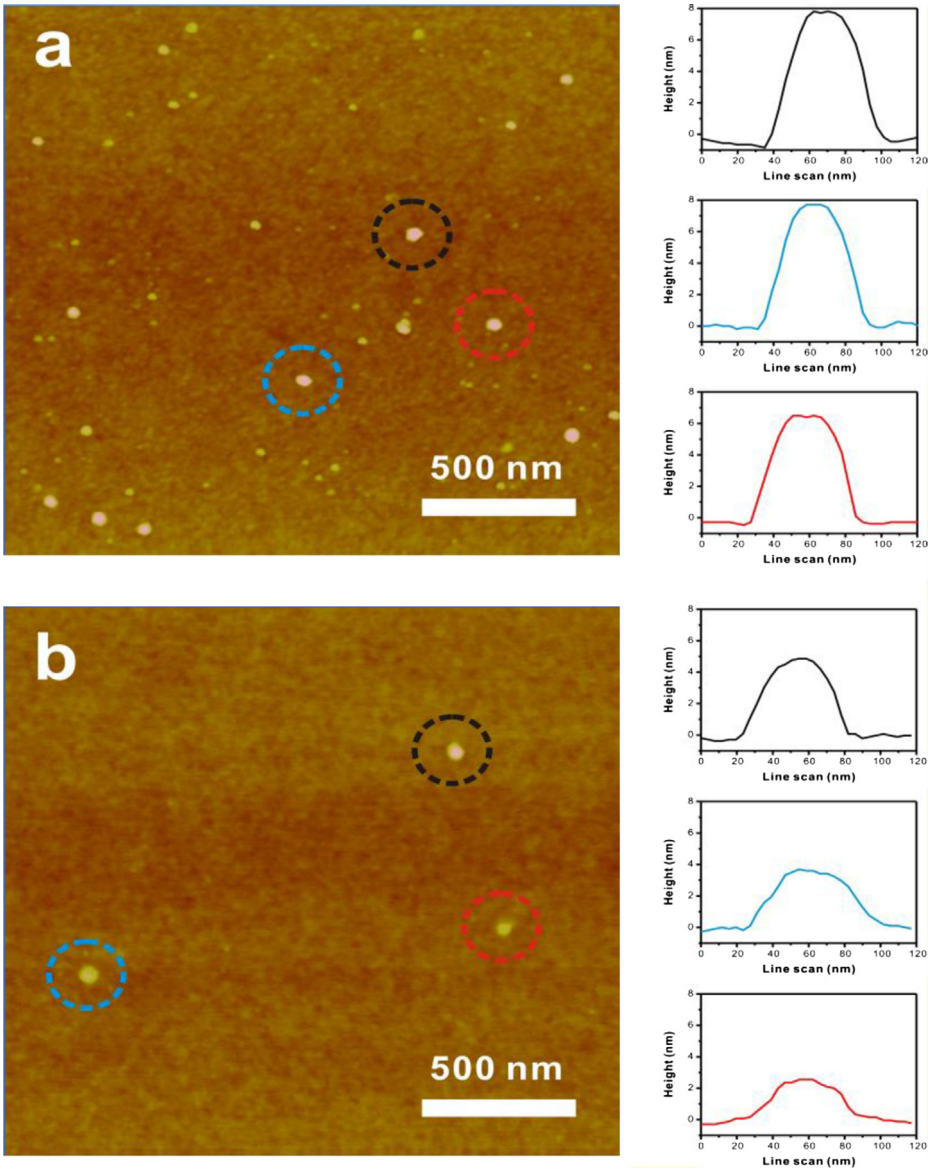

Fig. 4. Representative AFM images of P3 with corresponding line scan profiles (a) before and (b) after UV irradiation.

polymers (P2). A new peak (f) representing the proton next to the azido group appeared at 2.6 ppm, whereas a TMS peak (e) disappeared completely. The GPC traces in Fig. 1 also show that there was no significant change in the apparent molecular weight for P2 when compared to P1. Through the use of high fidelity click reactions, pyrene-containing photolabile 2-nitrobenzyl groups can be introduced on every repeating unit of the hydrophobic PAzHEMA block of P2. Compound **2** was successfully added to the P2 backbone in DMF with a CuBr/PMDETA complex at room temperature using click chemistry. To ensure 100% conversion, two-fold molar excess of compound **2** over azido groups of the P2 backbone was used. The successful introduction of pyrene-containing photolabile groups by click reaction was confirmed by ^{1}H NMR spectra (Fig. 2). A broad peak (f) representing the aromatic protons of the PPyNBM block appeared at 7.5–8.5 ppm. The click reaction was quantified by calculating the ratio of integration area of the aromatic signals (h) and the PEO signals (i) (1.2:1.0), indicating near-quantitative functionalization. The apparent molecular weight of P3 increased due to the introduction of bulky side groups (Fig. 1).

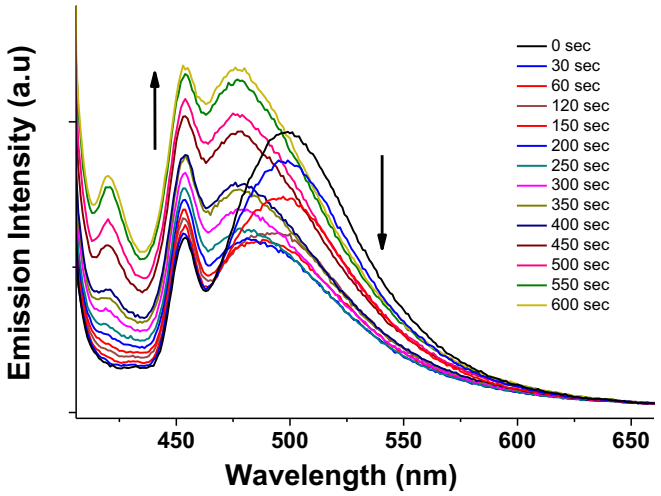

Fig. 5. Emission spectra of an aqueous micellar solution of P3 with encapsulated coumarin 102.

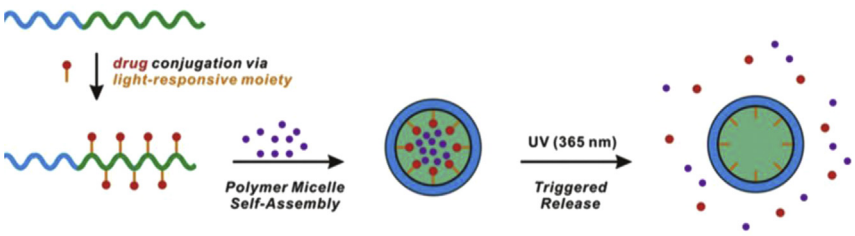

Fig. 6. Schematic representation of drug conjugation to the hydrophobic block through photocleavable linkers, encapsulation of a dye within the hydrophobic core of a polymeric micelle on micellization, and the subsequent release of physically entrapped dyes and photo-dissociated dyes by UV irradiation.

When properly designed, the amphiphilic block copolymer (P3) would form self-assembled aggregates in an aqueous solution. Here, a hydrophobic photolabile PPyNBM block forms the inner core of the aggregates, while the outer shell of the structures is composed of hydrophilic PEO. UV light irradiation (365 nm) leads to the dissociation of 2-nitrobenzyl groups and the subsequent release of 1-pyrenebutyric acid. Since the resulting PEO-*b*-PNBM (P4) is still amphiphilic, the block copolymer would be expected to retain the micellar structure. As a control experiment, photochemical cleavage of the 2-nitrobenzyl groups of compound 2 was carried out so as to evaluate the photolytic cleavage behavior. A solution of compound 2 (0.02 wt% in THF) was exposed to UV light (365 nm). As shown in Fig. S1, an increase in the absorbance of the pyrene unit was observed with an increase in UV irradiation. Moreover, the emission intensity increased while the wavelength of maximum emission shifted gradually from 475 nm to 444 nm. The completion of photolytic cleavage, as determined from the point when a photostationary state was reached (Fig. S2), was achieved in 140 s.

Having demonstrated the light-induced cleavage of the nitrobenzyl groups of compound 2, we attempted to apply this system for the light-triggered release of a model therapeutic, 1-pyrenebutyric acid, from amphiphilic block copolymer P3. An aqueous micellar solution (0.01 wt%) was prepared by adding water to a solution of the polymer in THF. Briefly, a 1.0 mg sample of P3 was dissolved in 1 mL of THF, and then 10 mL of water was added dropwise overnight to form micelles while the THF was allowed to evaporate completely. The solution was filtered through a 0.22-mm filter before use. The solution was subsequently irradiated with UV light (365 nm) until a photostationary state was reached.

Upon UV irradiation, a strong absorption band characteristic of free 1-pyrenebutyric acid in aqueous solution appeared at 220 nm (Fig. 3a). The resulting solution also showed strong emission with a maximum at 455 nm, indicating the successful photochemical cleavage of 2-nitrobenzyl groups, which in turn leads to the release of the model therapeutic, 1-pyrenebutyric acid.

The photoinduced cleavage of nitrobenzyl groups was further confirmed by atomic force microscopy (AFM), which revealed that morphological changes of the micelles had occurred. The samples were prepared from solutions with the same concentrations as those employed for the UV–vis and fluorescence investigations. AFM images of the samples deposited on a silicon wafer directly after micellization showed the presence of uniform, well-dispersed individual globular micelles with an average diameter of 60 nm (Fig. 4a). The micelle solution of P3 was then exposed to 365 nm UV light for 5 min and quickly spin-coated onto a silicon surface for AFM analysis. It is anticipated that the globular shape of the micelles is retained even after UV irradiation since there would be no change in the hydrophobic character of the hydrophobic block. As expected, the characteristic globular micelles still appeared, but the average diameter of the particles became relatively larger with a smaller height profile, indicating the release of free 1-pyrenebutyric acid.

In addition to the light-triggered release of covalently attached molecules, the simultaneous release of a non-covalently encapsulated model hydrophobic drug is also of interest. This way, two kinds of drugs can be delivered at the same time from only one vehicle. In this study, coumarin 102 was chosen as a model hydrophobic drug. To incorporate coumarin 102 into the core of the micelles, 1.0 mg of P3 and 0.1 mg of coumarin 102 were dissolved in 1 mL of THF followed by the dropwise addition of water (10 mL) overnight. Photochemical control of the release of 1-pyrenebutyric acid and coumarin 102 was assessed by fluorescence spectroscopy (Fig. 5). The initial micellar solution showed two emission bands, one from coumarin 102 with a maximum at 500 nm and another from the pyrene unit with a maximum at 455 nm. After UV irradiation for 200 s, the emission intensity of coumarin 102 decreased drastically while that of 1-pyrenebutyric acid increased slowly. During this period of time, the release of coumarin 102 was completed. Further exposure to UV light led to the continuous release of 1-pyrenebutyric acid, which eventually reached a photostationary state at 600 s. A schematic of the entire process is depicted in Fig. 6.

4. Conclusions

We have successfully synthesized an amphiphilic block copolymer that has photocleavable 2-nitrobenzyl moieties in the side chain of the hydrophobic block. 1-Pyrenebutyric acid was covalently attached to the hydrophobic block through a photocleavable linker. Coumarin 102, another model drug, was physically encapsulated in the core of micelles during micellization in water. UV irradiation induced a cleavage of the nitrobenzyl groups and the subsequent release of coumarin 102 and 1-pyrenebutyric acid from the micelle core. It was demonstrated that two kinds of model drugs can be co-delivered from a single polymeric vehicle at the same time.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.polymer.2014.01.026.

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