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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.

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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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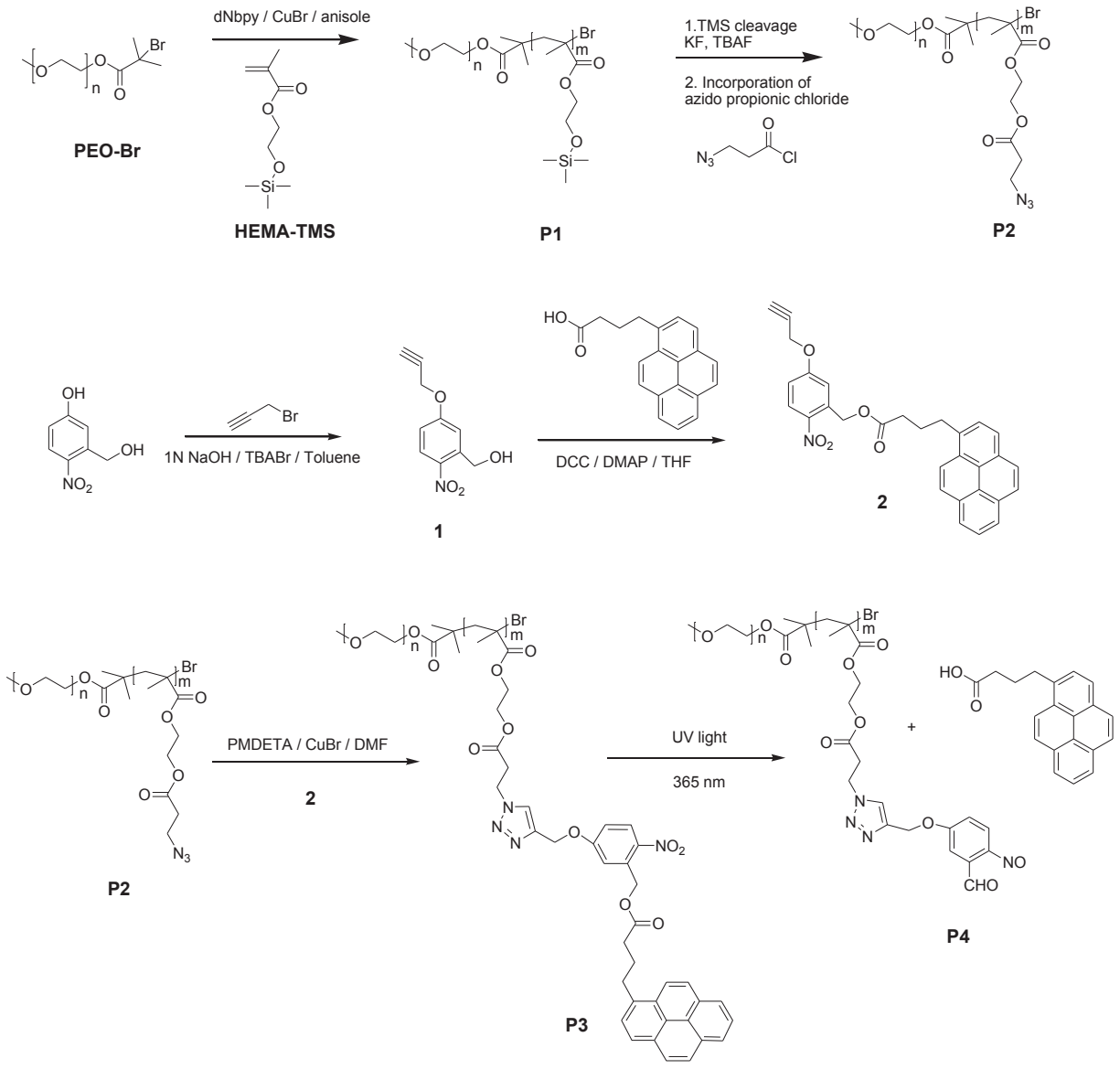

Scheme 1. Synthesis of amphiphilic block copolymers with photocleavable nitrobenzyl moieties to which 1-pyrenebutyric acid, a model drug, is covalently tethered.

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

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