Polymer 55 (2014) 4641–4650

Contents lists available at ScienceDirect

Polymer

journal homepage: www.elsevier.com/locate/polymer

Bioinspired photo-degradable amphiphilic hyperbranched poly(amino ester)s: Facile synthesis and intracellular drug delivery

Qiao Jin*, Yin Wang, Tongjiang Cai, Haibo Wang, Jian Ji**

MOE Key Laboratory of Macromolecule Synthesis and Functionalization of Ministry of Education, Department of Polymer Science and Engineering, Zhejiang University, Hangzhou 310027, China

ARTICLE INFO

Article history:
Received 15 April 2014
Received in revised form
26 June 2014
Accepted 26 July 2014
Available online 2 August 2014

Keywords:
Hyperbranched polymer
Photo degradable
Phosphorylcholine

ABSTRACT

A novel amphiphilic photo-degradable hyperbranched polymer was reported at the first time. The hyperbranched *o*-nitrobenzyl containing poly(amino ester)s (HPAE) were prepared by one-pot Michael addition polymerization. The photo-induced degradation of hyperbranched poly(amino ester)s was confirmed by gel permeation chromatography (GPC) and UV-*vis* spectra. Bioinspired phosphorylcholine grafted HPAE (HPAE-PC) was synthesized *via* thiol-ene click chemistry. HPAE-PC can self-assemble to micelles and the micelles could be disassembled under UV irradiation because of the photo-degradation of HPAE. HPAE-PC micelles were used to load anticancer drug Doxorubicin (DOX). *In vitro* drug release studies showed that the release of DOX was much faster in the presence of UV irradiation than that without UV irradiation. The fluorescence microscope results indicated that DOX-loaded micelles exhibited faster drug release in A549 cells after UV irradiation. Moreover, the DOX-loaded HPAE-PC micelles under UV irradiation exhibited better anticancer activity against A549 cells than that of the nonirradiated ones. The novel amphiphilic photo-degradable hyperbranched polymers can be used to construct spatiotemporal on-demand drug delivery system for cancer therapy.

© 2014 Elsevier Ltd. All rights reserved.

1. Introduction

Benefiting from the highly branched structure, hyperbranched polymers (HBPs) have recently received much attention due to their unique chemical and physical properties [1–3]. More recently, amphiphilic hyperbranched polymers are rapidly developed, which have displayed great potential in biomedical applications [4–9]. Amphiphilic HBPs have been confirmed to self-assemble into many supramolecular structures, such as micelles, vesicles, fibers, tubes, and membranes [7,10–13]. Compared to the amphiphilic linear copolymers, amphiphilic HBPs have demonstrated some unique characteristics in self-assembly, such as structural diversities, special self-assembly mechanism, smart responses and facile functionalization [7]. These properties make amphiphilic HBPs very useful to construct promising drug delivery systems with improved micellar stability and drug loading ability [12,14–17].

It is well-known that the degradability of HBPs is an important parameter for drug delivery applications [18]. Some degradable HBPs have already been developed. The researches are mainly focused on pH-, redox- and enzyme-degradable HBPs. Frey and coworkers introduced acid-degradable acetal moieties into hyperbranched polyether backbone. The acetal-containing hyperbranched polyethers were stable in aqueous solution at neutral pH (pH 7.0) but can be degraded at acid pH (pH 4.5) [19]. Yan and coworkers synthesized hyperbranched polyphosphates with good biocompatibility, biodegradability, and structural similarity to nucleic and teichoic acids. They can be degraded naturally into harmless low-molecular-weight products through hydrolysis or enzymatic digestion of phosphate linkages under physiological conditions [20]. For the above-mentioned endogenous triggered degradation (pH, redox potential, enzyme), it is still a considerable challenge to realize accurate controlled degradation because of the complex and still not fully understood physiological environment in cells, tissue and body liquids. Thus, it would be favorable to develop a new kind of externally triggered degradation of HBPs in vivo and/or in vitro. Photo is an especially attractive stimulus since it provides a possibility for realizing remote and spatiotemporal drug release by tuning the wavelength, energy, and site of irradiation [21–29]. Combination of photo and interventional therapy, site-specific drug release can be realized by taking advantage of optical fiber. Therefore, it will be of great interest to

* Corresponding author. Tel.: +86 571 87953931.
** Corresponding author. Tel.: +86 571 87953729.
E-mail addresses: jinqiao@zju.edu.cn (Q. Jin), jijian@zju.edu.cn (J. Ji).

http://dx.doi.org/10.1016/j.polymer.2014.07.053
0032-3861/© 2014 Elsevier Ltd. All rights reserved.

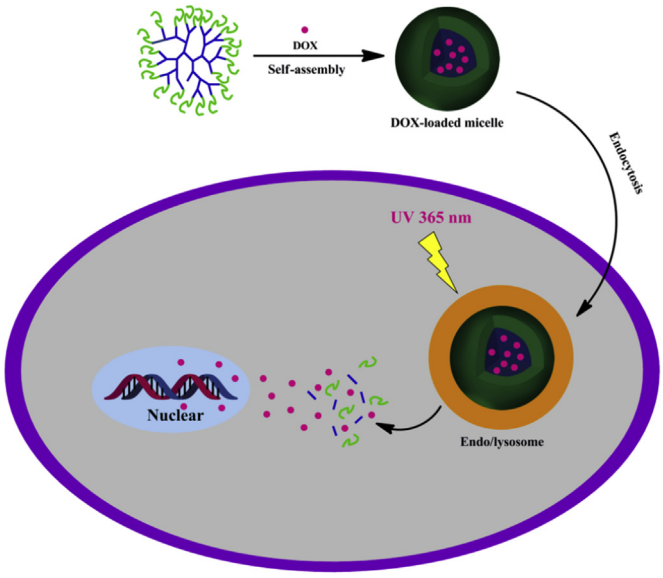
develop photo-degradable hyperbranched polymers since they have not been reported yet.

The construction of an artificial cell membrane structure based on phospholipid has been proved effective in preventing the occurrence of biological reactions at the surface [30–32]. In our previous research, zwitterionic phosphorylcholine modified nanoparticles and micelles were constructed and showed outstanding biostability and biocompatibility [33–35]. The bio-inspired phosphorylcholine provides a potential strategy for the surface tailoring of micelles. In this work, we attempted to synthesize hyperbranched o-nitrobenzyl containing poly(amino ester)s (HPAE) with tunable molecular weights and degrees of branching. Bioinspired phosphorylcholine was further grafted to HPAE via thiol-ene click chemistry. The nano-sized micelles were prepared by the self-assembly of phosphorylcholine grafted hyperbranched poly(amino ester)s (HPAE-PC). Finally, the hydrophobic anticancer drug Doxorubicin (DOX) was encapsulated into the micelles, and their performance as smart drug nanocarriers was also investigated in terms of the in vitro photo controlled drug release, anticancer activity in vitro, and the cellular internalization behavior (Scheme 1). To the best of our knowledge, it is the first time that photo-degradable amphiphilic hyperbranched polymers were designed.

2. Experimental

2.1. Materials

1,3-Dimethyl-2-nitrobenzene (TCI), potassium permanganate ($KMnO_4$, Sinopharm Chemical Reagent Co., Ltd), borane tetrahydrofuran complex solution (1.0 M, in THF, Shanghai darui finechemical Co., Ltd), 1-(2-aminoethyl)piperazine (AEPZ, Sigma–Aldrich), Doxorubicin hydrochloride (DOX•HCl, Zhejiang Hisun Pharmaceutical Co., Ltd.), 11-mercapto-1-undecanol (Sigma–Aldrich), 2-chloro-1, 3, 2-dioxaphospholane-2-oxide (Alfa Aesar) were used as received without further purification. 2-Nitro-1,3-benzenedimethanol was synthesized as described previously [28]. 11-Mercaptoundecylphosphorylcholine (HS-PC) was prepared according to the literature [31].



Scheme 1. Preparation of DOX-loaded HPAE-PC micelles and intracellular drug release triggered by UV irradiation.

2.2. Synthesis of (2-nitro-1,3-phenylene)bis(methylene) diacrylate (NPDA)

NPDA was synthesized by reacting 2-nitro-1,3-benzenedimethanol (8.27 g, 45 mmol) with acryloyl chloride (14.7 mL, 180 mmol) in the presence of triethylamine (25 mL) in dichloromethane (150 mL) at 0 °C for 12 h. The mixture was filtered and the solvent evaporated. The crude mixture was purified by silica gel chromatography using n-hexane/ethyl acetate as elute. ^{1}H NMR ($CDCl_3$): δ 5.30 (s, 4H), δ 5.88 (d, 2H), δ 6.12 (m, 2H), δ 6.2 (s, 2H), δ 6.42 (m, 2H), δ 7.51 (m, 3H).

2.3. Synthesis of hyperbranched poly(amino ester)s (HPAE)

The hyperbranched HPAE with different molecular weights and degrees of branching were synthesized by Michael addition polymerization as shown in Scheme 2. Typically, 0.87 g of NPDA (3 mmol) was added into a solution of AEPZ (196 μL, 1.5 mmol) in DMSO (5 mL) and H_2O (0.5 mL). The polymerization was performed at 50 °C under an argon stream in the dark. After the reaction was performed at 50 °C for 24 h, the solution was precipitated into diethyl ether under vigorous stirring. The polymer was then collected and dried in high vacuum at 40 °C.

2.4. Synthesis of phosphorylcholine grafted hyperbranched poly(amino ester)s (HPAE-PC)

In a typical procedure for the synthesis of HPAE-PC, 0.5 g of HPAE and 0.5 g of HS-PC were added into 5 mL of methanol. The solution was stirred at room temperature under an argon stream in the dark. After 24 h, the crude produce was dialyzed against distilled water for 5 days (MWCO 3500) and lyophilized.

2.5. Photo-degradation of HPAE

The photo-degradation of HPAE was monitored by means of GPC. Briefly, 4 mg of HPAE was dissolved in 10 mL of THF. The solution was then irradiated with UV light (365 nm, 8 W). After 30 min, the molecular weight of the solution was measured by GPC.

2.6. Preparation of blank micelles, coumarin 102-loaded micelles and DOX-loaded micelles

The blank HPAE-PC micelles were prepared by a typical cosolvent approach. Briefly, 10 mg of HPAE-PC was dissolved in 2 mL of methanol and stirred for 1 h. 2 mL of distilled water was added dropwise. After that, the resulting mixture was kept stirring for another 2 h and further purified by dialysis (MWCO 3500) in water for 48 h.

For the preparation of coumarin 102-loaded micelles, 20 mg of HPAE-PC was dissolved in 3 mL of methanol, followed by addition of 0.2 mg coumarin in 3 mL THF dropwise into the solution. After stirring for 1 h, 6 mL of water was added. After stirring for another 3 h, the solution was dialyzed against water for 48 h.

DOX-loaded micelles were prepared in a similar way. At first, 3 mg of Doxorubicin hydrochloride was dissolved in 2 mL of methanol. 20 μL of triethylamine was added to obtain hydrophobic Doxorubicin (DOX). 15 mg of HPAE-PC was then added into the solution and stirred for 2 h. The solution was dialyzed against water for 48 h. In order to determine the total loading of DOX, the DOX loaded micelles solution was lyophilized and then dissolved in methanol. The fluorometric measurement was used to determine the total loading amount. Excitation and emission were set at 480 and 560 nm, respectively, with slit width of 10 nm. Drug loading content (DLC) was calculated according to the follow equation.

Download English Version:

https://daneshyari.com/en/article/5181035

Download Persian Version:

https://daneshyari.com/article/5181035

Daneshyari.com