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Self-assembly of cationic amphiphilic cellulose-g-poly (p-dioxanone) copolymers

Zhenzhen Liu[a], Mingjie Chen[b,*], Yanzhu Guo[a,*], Xing Wang[a], Li Zhang[a], Jinghui Zhou[a], Haiming Li[a], Qingshan Shi[b]

[a] Liaoning Key Laboratory of Pulp and Paper Engineering, Dalian Polytechnic University, 1#Ganjingzi District, Dalian, 116034, China
[b] State Key Laboratory of Applied Microbiology Southern China, Guangdong Provincial Key Laboratory of Microbial Culture Collection and Application, Guangdong Institute of Microbiology, No. 100, Martyrs Middle Road, Yuexiu District, Guangzhou, 510070, China

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ABSTRACT

Cationic amphiphilic cellulose copolymers were prepared through grafting hydrophobic poly (p-dioxanone) (PPDO) chains onto hydrophilic quaternized cellulose derivatives (QC) via ring-opening polymerization (ROP) reaction, which was performed in 1-butyl-3-methylimidazolium chloride (BmimCl) and using 4-dimethylaminopyridine (DMAP) or 1,8-diazabicyclo (5.4.0) undec-7-ene (DBU) as catalyst. Their chemical structures and physical properties were confirmed by FT-IR, ^{1}H-, ^{13}C-, 2D HSQC-NMR, X-ray diffraction (XRD), and thermal stability (TGA) techniques, while self-assembly behavior was characterized by dynamic light scattering (DLS), transmission electron microscopy (TEM) and fluorescence techniques. Both of the sizes and critical micelle concentration (CMC) values of micelles were decreased with increasing grafting contents of PPDO in the copolymers, which were in the ranges of 110–246 nm and 64–253 μg/mL, respectively. The ζ-potentials of micelles were cationic andranged from 39.1 mV to 45.4 mV. The highest encapsulation efficiencyof paclitaxel (PTX) into the micelles was 61.8% and 92.0% of loaded PTX was continuously released from micelles in phosphate buffered saline medium for 36 h.

1. Introduction

Amphiphili cpolymers (Dong et al., 2016; Yang, Guo, Sun, & Wang, 2016) have attracted increasing attentions due to their self-assemble behavior in solution phase, which makes them as an interesting host material for drug delivery, catalysis, imaging, and sensing application (Wang & Grayson, 2012). Amphiphilic polymers are generally composed of hydrophilic and hydrophobic segments (Visanko et al., 2014; Yang et al., 2016). They are able to self-assemble into the core-shell micelles in water. Typically, the cores of micelles are composed of hydrophobic segments, while the shells of micelles are formed by hydrophilic segments (Zhang, Zhao, Zhou, & Kondo, 2013).

Due to excellent properties of micelles, eg., solubilization, small sizes, enhanced drug bioavailability and reduced side effects of drugs, they are ideal carriers for hydrophobic drugs (Banerjee, Qi, Gogoi, Wong, & Mitragotri, 2016). Up to now, most of researches focus on synthetic linear block copolymers, which suffer from some drawbacks, such asbiotoxicity, undegradable, et al. (Joshi, Garg, Goyal, & Rath, 2016).

Amphiphilic polymers from natural polysaccharides have been attracting interests in the past decades, due to their outstanding advantages, such as abundant, cheap, safe, non-toxic, biocompatible, biodegradable and easily to be functionalization (Kumari et al., 2015). The most studied natural polysaccharides include chitosan (Chaw, Liu, Shih, & Huang, 2015), starch (Myburgh et al., 2012; Taylor et al., 2016), cellulose and cyclodextrin (Nowak et al., 2015; Valerón Bergh & Tønnesen, 2017). Cellulose is an attractive raw material to prepare amphiphilic polymers (Wang, Guo, Li, Chen, & Sun, 2012). Various kinds of cellulose-based amphiphilic polymers have been prepared via grafting hydrophobic groups into the mainchain of cellulose (Chen & Shi, 2015; Yang et al., 2016). However, the hydrophilic groups of these polymers are limited to nonionic and anionic groups, such as hydroxyl (Guo, Liu et al., 2013; Guo, Wang, Shen, Shu, & Sun, 2013; Zhong et al., 2017), hydroxypropyl (Pencheva et al., 2018), hydroxyethyl (Ge, Guo, Zhong, Wang, & Sun, 2015) and carboxymethyl groups (Yang, Kuang et al., 2008; Yang, Wu, & Liu, 2008). The applications of nanomicelles from such amphiphilic cellulose in the fields of drug delivery are limited to cationic bio-systems (Liu & Edgar, 2014), while numbers of organism have negative charged cell membrane. Therefore, developments of amphiphilic cellulose polymers with cationic surface charges

* Corresponding authors.
E-mail addresses: chan-mj@qq.com (M. Chen), guoyz@dlpu.edu.cn (Y. Guo).

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are very important to find application in negative charged bio-systems (Khatri, Mayakrishnan, Hirata, Wei, & Kim, 2013; Zhu et al., 2015). However, the preparation of cationic amphiphilic cellulose-based polymers has scarcely been reported.

Aliphatic polyester, poly (p-dioxanone) (PPDO) (Li et al., 2015), is an advanced material for drug delivery (Dash & Konkimalla, 2012; Guo, Liu et al., 2013; Guo, Wang et al., 2013), bone graft substitutes (Kurd et al., 2015) and tissue engineering (Cui, Zhou, & Chang, 2010; Holzapfel, Wagner, Thibaudeau, Levesque, & Hutmacher, 2015), due to its excellent biocompatibility, biodegradability, low immunogenicity, mechanical properties, nontoxicity and thermoplastic. It is conventionally prepared through ROP of p-dioxanone (PDO) with metallic catalysts, such as stannous octoate ($Sn(Oct)_2$), triethylaluminum ($Al(Et)_3$) and so on (Huang et al., 2005). However, the metallic catalysts are toxic to organism and unavoidable remain in the polymers to some extent. Organocatalytic ROP is believed to be an alternative to prepare PPDO and its copolymers for bio-systems application (Kamber et al., 2007). Simple organic molecules, eg., DMAP and DBU have been shown to promote ROP of cyclic monomers in the presence of hydroxyl groups in cellulose or hemicelluloses as nucleophilic initiator (Ge et al., 2015; Sánchez, Mauricio, Paredes, Gamero, & Cortés, 2017; Vasylevskyi et al., 2017; Zhang, Chen, Liu, Zhang, & Sun, 2015). Zhang et al. (2016) prepared cellulose-g-PPDO in BmimCl medium via ROP, which was catalyzed by DMAP. A comparative study showed that DMAP showed higher catalytic activity than ($Sn(Oct)_2$) for preparing cellulose-g-PPDO via ROP reaction (Guo, Liu et al., 2013; Guo, Wang et al., 2013). As well, amphiphilic cellulose polymers were prepared using PPDO as hydrophobic group via ROP using hydroxyethyl cellulose as initiator (Guo, Liu et al., 2013; Guo, Wang et al., 2013). However, these studies are limited to the preparation of nonionic/anionic amphiphilic cellulose, while cationic amphiphilic cellulose is mandatory for the application in anionic bio-systems. Meanwhile, the surface charge of these reported cellulose-based micelles, in versus of ζ-potential value, was relatively low, which was not beneficial to get a stable micelles aqueous solution.

In this work, cationic amphiphilic cellulose copolymers were prepared with quaternary ammonium groups and PPDO as hydrophilic and hydrophobic groups, respectively. Firstly, quaternized cellulose (QC) derivatives were homogeneously synthesized in NaOH/urea aqueous solution, and then PPDO was grafted onto QC mainchain via ROP in BmimCl using DMAP/DBU as catalyst. Their chemical structures and physical properties of QC-g-PPDO copolymers were analyzed using FT-IR, ^{1}H-, ^{13}C-, 2D HSQC-NMR, XRD and TGA techniques, while their self-assembly behaviors were characterized by DLS, TEM and fluorescence techniques. Moreover, the drug loading capacities of the QC-g-PPDO micelles were studied using PTX as a model drug and in vitro drug release behaviors of PTX-loaded QC-g-PPDO micelles were further determined. The aim of this study was to develop the cellulose-based micelles with positive surface charge and excellent stability in aqueous solution, whose ζ-potential values were desired to be more than 30 mV.

2. Materials and methods

2.1. Materials

The α-cellulose with a particle size of 90 μm (Aladdin Industrial Inc, Shanghai, China) was vacuum dried at 45 °C for 48 h before use. 2,3-epoxypropyltrimethylammonium chloride (CHPTAC, 95% purity) was purchased from Oudu Trading Company (Jinan, China) and used without further purification. 1-*N*-butyl-3-methylimidazolium chloride (BmimCl, 99% purity) was supplied by Cheng Jie Chemical Co., Ltd. (Shanghai, China). DMAP (99% purity) and DBU (99% purity) were provided from Aladdin-reagent Inc (Shanghai, China). The p-dioxanone with a purity of 99.5% was obtained fromJitela Chemical Co., Ltd (Jiaxing, China). Paclitaxel (PTX, 98% purity) was purchased from Beijing Solarbio Science & Technology co., Ltd (Beijing,China). The dialysis membranes (MWCO 3000 Da and 5000 Da) were obtained from Shanghai Yuanye Bio-Technology Co., Ltd (Shanghai, China). All other reagents were of analytical grade and used without further purification.

2.2. Synthesis of QC

Firstly, 2 g cellulose was completely dissolved in 100 g NaOH/urea aqueous (7 wt%/12 wt%) solutions. Desired amount of CHPTAC (10:1 M ratio of CHPTAC to anhydroglucose unit (AGU)) was slowly added into the above cellulose-NaOH/urea solutions under vigorous mechanical stirring. The quaternization of cellulose was performed for 24 h by magnetic stirring at room temperature. After neutralizing with HCl solution, the reaction mixture was dialyzed against deionized water until no precipitates were found after adding several drops of silver-nitratesolution into the dialyzed water. The deionized water was refreshed every 6 h. After freeze-dried for 3 days, the water-soluble QC was obtained. Nitrogen contents (N%) of QC was measured with SKD-800 Kjeldahl analyzer (Shanghai Pei Ou Analytical Instrument Co., Ltd., China). The DS value of QC was determined by nitrogen content and calculated using the following equation (Song, Sun, Zhang, & Zhang, 2008).

$$DS = 162 \times N\% / (14–151.5 \times N\%)$$

2.3. Synthesis of QC-g-PPDO copolymers

The 5% (w/w) QC/BmimCl solutions were prepared by dissolving 0.5 g QC into 10 g BmimCl at 80 °C for 2 h under protection of nitrogen. Definite amounts of monomer p-dioxanone and catalyst DMAP or DBU were slowly added into the QC/BmimCl solutions. The ROP was performed by magnetic stirring the solutions at 80 °C for 12 h. After cooling to room temperature, the resultant solutions were dialyzed (MWCO 5000) against deionized water for 72 h. The crude QC-g-PPDO copolymers were obtainedafter lyophilizing the dialysis solutions for 72 h. In order to remove the homo-PPDO polymers, the crude copolymers were immersed into 250 mL dichloromethane for 24 h. The precipitates were obtained by centrifugation of the above mixtures at 4000 rpm for 10 min. Dichloromethane washing process was repeated for 3 times. The purified copolymers were vacuum dried at 60 °C for 48 h.

2.4. Characterization of QC and QC-g-PPDO copolymers

The molecular weight (M_w) and polydispersity of the copolymers were determined by a gel permeation chromatography (GPC) instrument equipped with a SB-802.5 HQ column (Agilent Technologies Inc, America) and eight angle laser light scattering apparatus (BI-MWA).The measurements were performed with sodium phosphate buffer containing NaCl as the eluent at a flow rate of 0.8 mL/min at 25℃. The FT-IR spectra of QC-g-PPDO copolymers were collected on a Fourier spectrometer (Frontier I, PerkinElmer, America) at room temperature. The ^{1}H-NMR, ^{13}C-NMR and 2D HSQC-NMR analysis was carried out on a Bruker AV-III 400 M spectrometer (Germany) using tetramethylsilane (TMS) as the internal standard. The thermogravimetric analysis (TGA Q500, TA, USA) was performed by heating 10 mg copolymers from room temperature to 600 °C at a rate of 10 °C min^{-1}. The XRD patterns of copolymers were determined by a 6100 X-ray diffractometer (Rigaku, Japan) using the Cu Ka radiation source (30 kV, 30 mA) with a scanning range of 10° to 70°.

2.5. Preparation and characterization of QC-g-PPDO self-assembled nanomicelles

10 mg QC-g-PPDO samples were dissolved into 10 mL distilled water, and the solution was ultrasonic treated for 15 min with a power of 75 W and every 2 s working time for 1 s break time. The DLS and ζ-potential of micelles were measured on a Nano-ZS ZEN90 (Malvern Instruments Ltd., UK) at 25 °C. Each test was repeated at least five times