Carbohydrate Polymers 136 (2016) 216–223

Contents lists available at ScienceDirect

Carbohydrate Polymers

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

Amphiphilic graft copolymers with ethyl cellulose backbone: Synthesis, self-assembly and tunable temperature–CO_2 response

Weizhong Yuan*, Hui Zou, Jin Shen

School of Materials Science and Engineering, Key Laboratory of Advanced Civil Materials of Ministry of Education, Tongji University, 201804, People's Republic of China

ARTICLE INFO

Article history:
Received 7 July 2015
Received in revised form 21 August 2015
Accepted 16 September 2015
Available online 21 September 2015

Keywords:
Graft copolymers
CO_2-responsive
Temperature-responsive
Self-assembly
Micelles

ABSTRACT

Amphiphilic ethyl cellulose-*graft*-poly(N,N-dimethylaminoethyl methacrylate) (EC-*g*-PDMAEMA) and ethyl cellulose-*graft*-poly(2-(2-methoxyethoxy)ethyl methacrylate-*co*-N,N-dimethylaminoethyl methacrylate) (EC-*g*-P(MEO_2MA-*co*-DMAEMA)) graft copolymers were easily synthesized by atom transfer radical polymerization (ATRP). The micelles self-assembled from the copolymer presented switchable temperature–CO_2 dually responsive properties. The value of lower critical solution temperature (LCST) for the copolymer micelle solutions could be adjusted by CO_2/Ar. Moreover, due to the alteration of the ratio of DMAEMA to MEO_2MA, the LCST values of the micelle solutions decreased with the increase of MEO_2MA in copolymer. The temperature–CO_2 dually responsive properties of the copolymer were reversible and could be accomplished through altering the temperature and bubbling CO_2/Ar. The hydrodynamic radius (R_h) of the copolymer micelles was also influenced by the ratio of DMAEMA to MEO_2MA and the stimuli of temperature and CO_2/Ar. As a drug release system, the copolymer micelles could achieve the control release of doxorubicin (DOX) by changing the temperature and alternatively bubbling CO_2/Ar.

1. Introduction

Considerable attention has been paid to the stimuli-responsive polymers due to their potential applications in nano-smart materials and biomedical fields, such as nano-sensor, nano-reactor, and drug/gene delivery system (Bertrand, Poggi, Gohy, & Fustin, 2014; Blum et al., 2015; Dai, Ravi, & Tam, 2009; Ganivada et al., 2014; Huo, Yuan, Tao, & Wei, 2014; Jochum & Theato, 2013; Li & Keller, 2009; Mori, Kato, & Endo, 2009; Schattling, Jochum, & Theato, 2014; Song, Du, & Li, 2014; Theato, Sumerlin, O'Reilly, & Epps, 2013; Yang et al., 2015). A great many of stimuli-responsive polymers have been extensively investigated, including temperature, pH, light, ionic strength, redox-responsive polymers and so on (Alarcón, Pennadam, & Alexander, 2005; Amin, Ahmad, Halib, & Ahmad, 2012; Bai et al., 2012; Ganta, Devalapally, Shahiwala, & Amiji, 2008; Gao et al., 2014; Gil & Hudson, 2004; Ha, Yu, Song, Chen, & Shi, 2014; Hamner et al., 2013; Hua, Yuan, Britt, Mays, & Hong, 2013; Roy, Cambre, & Sumerlin, 2010; Zhang et al., 2013; Zou & Yuan, 2015a, 2015b). Furthermore, novel type stimuli-responsive polymers, such as carbon dioxide (CO_2)-responsive polymers have attracted great attention owing to the availability, nontoxicity, biocompatibility, low cost and abundance of CO_2. Up to now, some CO_2-responsive polymeric micelles, vesicles, organogels, and organic–inorganic hybrid nano-materials have been investigated (Che et al., 2015; Guo et al., 2014; Liu et al., 2014; Nagai, Suzuki, Maki, & Takeno, 2011; Yan & Zhao, 2014; Zou & Yuan, 2015a, 2015b). Most CO_2-responsive polymers contain amidine functional groups that could react with CO_2 in water to form charged amidinium bicarbonates and would be recovered upon CO_2 removal. The amidine functional groups in CO_2-responsive polymers represent a general means to render the polymer CO_2-response, however, the synthesis of the amidine-containing polymers is demanding, and meanwhile this kind of polymers may be hydrolytically unstable (Jessop et al., 2011). Recently, Zhao et al. revealed that poly(N,N-dimethylaminoethyl methacrylate) (PDMAEMA) could react with CO_2 in water to form protonated PDMAEMA without functionalization with amidine, and the protonation of PDMAEMA would lead to the increase of its lower critical solution temperature (LCST) drastically (Han, Tong, Boissière, & Zhao, 2012; Han, Boissière, et al., 2012; Yan & Zhao, 2013).

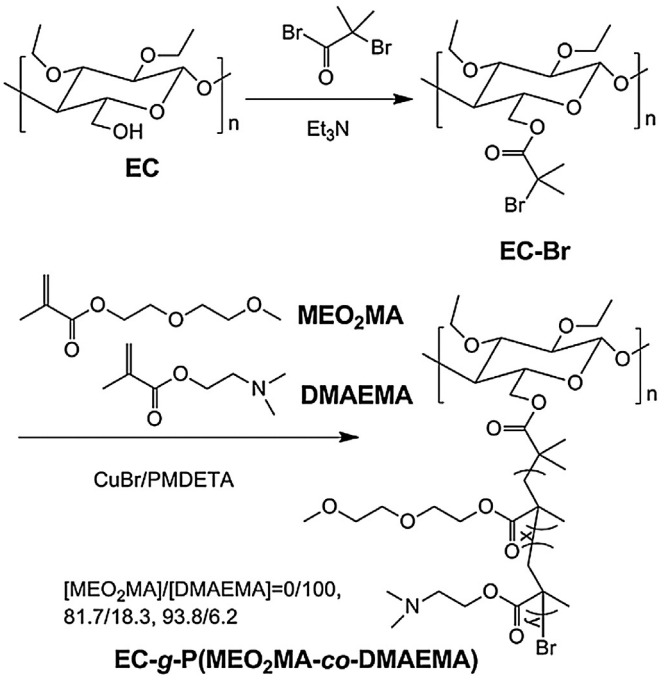
PDMAEMA is used to design thermoresponsive materials due to its LCST property in aqueous solutions (Car et al., 2014; Guo et al., 2010; Han et al., 2013; Huang, Hsu, & Wang, 2014; Yuan,

* Corresponding author.
E-mail address: yuanwz@tongji.edu.cn (W. Yuan).

http://dx.doi.org/10.1016/j.carbpol.2015.09.052
0144-8617/

Zou, Guo, Wang, & Ren, 2012). Meanwhile, PDMAEMA can react with CO_2 in water, which means it can be used to prepare CO_2-responsive polymers. In addition, it is more important that DMAEMA can be copolymerized with lots of non-CO_2-responsive polymers (such as poly[2-(2-methoxyethoxy)ethyl methacrylate] ($PMEO_2MA$)) and act as a CO_2-sensitive trigger to endow the copolymer with CO_2-responsive property (Lutz, 2011). LCST is a key property for thermo-switchable polymers. Therefore, introducing a CO_2-switchable LCST to the polymers is of great importance, which would make it possible to use CO_2 to trigger reversible structural changes of smart materials. The LCST of these polymers can be changed and recovered by bubbling CO_2 or Ar. As a result, such polymers can establish the connection of temperature and CO_2 responses. The CO_2–temperature dual responsive system deserves further investigation.

Cellulose is the most abundant and renewable bio-polymeric material in the nature. It has been widely used in membranes and pharmaceuticals owing to its nontoxicity, biocompatibility, and mechanical strength (Credou & Berthelot, 2014; Eichhorn, 2011; Gupta & Sahoo, 2001; Khan, Sakaguchi, Shiotsuki, Nishio, & Masuda, 2006; Moon, Martini, Nairn, Simonsen, & Youngblood, 2011; Utsel et al., 2012). With the increasing demands in various areas such as smart nano micelles or vesicles, biological gel, and antibacterial surface, it is essential to modify the structure and enhance the function of cellulose or its derivatives by grafting polymerization (Joubert, Musa, Hodgson, & Cameron, 2014; Kang et al., 2006; Liu et al., 2009; Roy, Semsarilar, Guthrie, & Perrier, 2009; Sui et al., 2008; Wang et al., 2011; Yan et al., 2009; Yu, Qin, Wang, & Zhou, 2012; Yuan, Yuan, Zhang, & Xie, 2007; Zhu, Dong, Wang, & Wang, 2010). The preparation and self-assembly behavior of amphiphilic cellulose-based graft copolymers have attracted much interest. Grafting hydrophilic CO_2-responsive copolymers to hydrophobic ethyl cellulose (EC) backbone will create amphiphilic CO_2-responsive cellulose-based graft copolymers, and these copolymers can self-assemble to micelles which could be used in the smart drug delivery field.



Scheme 1. Synthesis of EC-*g*-P(MEO_2MA-*co*-DMAEMA) graft copolymer by ATRP.

Herein, we designed and synthesized amphiphilic ethyl cellulose-*graft*-poly(N,N-dimethylaminoethyl methacrylate) (EC-*g*-PDMAEMA) copolymer and ethyl cellulose-*graft*-poly(2-(2-methoxyethoxy)ethyl methacrylate-*co*-N,N-dimethylaminoethyl methacrylate) (EC-*g*-P(MEO_2MA-*co*-DMAEMA)) copolymer by atom transfer radical polymerization (ATRP). The synthesis route is shown in Scheme 1. PDMAEMA or P(MEO_2MA-*co*-DMAEMA) side chains are hydrophilic and endowed with thermo-CO_2 dual responses, while the EC backbone is hydrophobic. The amphiphilic copolymers can self-assemble to micelles with CO_2–temperature dual responses. The LCST transition of the micelle solutions can be adjusted through the alteration of ratio of DMAEMA to MEO_2MA. The controlled release behavior of the loaded drug from the copolymer micelles has also been investigated.

2. Materials and methods

2.1. Materials

The details for materials are provided in ESI.

2.2. Characterization

The details for this part are provided in ESI.

2.3. Synthesis of EC-Br

EC (2.264 g, containing 7 mmol of hydroxyl groups) was dissolved in anhydrous tetrahydrofuran (40 mL) under stirring and triethylamine (1.06 g, 10.5 mmol) was added into the solution under argon at room temperature. The mixture was stirred and cooled to 0 °C with ice bath. Then 2-bromoisobutyryl bromide (4.828 g, 21 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise to the mixture within 30 min. The reaction mixture was stirred for 48 h at room temperature before it was washed with saturated $NaHCO_3$ aqueous solution and deionized water. EC-Br was obtained by filtration and dried in vacuum.

ATR FT-IR (cm^{-1}): 2975 (ν_{C-H}), 2816–2927 (ν_{C-H}), 1742 ($\nu_{C=O}$). ^1H NMR (δ, ppm, $CDCl_3$): 2.85–4.41 (*CH* and CH_2 in EC backbone), 1.94 ($C(CH_3)_2Br$), 1.15 (CH_3 in EC backbone).

2.4. Synthesis of EC-g-PDMAEMA graft copolymer

The detail procedure of preparing EC-*g*-PDMAEMA was as follows. EC-Br (0.4876 g, 0.318 mmol of Br groups) was added to flask (100 mL) dissolved in anhydrous toluene (20 mL). Then, DMAEMA (2.5 g, 15.9 mmol) and CuBr (45.5 mg, 0.318 mmol) were added to the flask. The flask was degassed with three freeze–evacuate–thaw cycles. PMDETA (0.11 g, 0.636 mmol) was deoxygenated by bubbling dry argon before injection into the reaction system by syringe. The molar ratio of [DMAEMA]:[EC-Br]:[CuBr]:[PMDETA] was 50:1:1:2. The polymerization reaction was performed at 60 °C for 48 h. After being cooled to room temperature, the reaction flask was opened to air, and the crude product was diluted with THF and passed through a neutral oxide alumina column to remove the copper catalysts. The copolymer was obtained by precipitation in cold *n*-hexane and dried *in vacuo* for 48 h.

ATR FT-IR (cm^{-1}): 2734–2981 (ν_{C-H}), 1726 ($\nu_{C=O}$). ^1H NMR (δ, ppm, $CDCl_3$): 0.89 (CH_3 in EC backbone), 0.99–1.24 ($C(CH_3)CH_2$), 1.75–2.00 ($C(CH_3)CH_2$), 2.30 ($N(CH_3)_2$), 2.57 (CH_2CH_2N), 4.06 (CH_2CH_2N).

2.5. Synthesis of EC-g-P(MEO2MA-co-DMAEMA) graft copolymer

The typical procedure of preparing EC-*g*-P(MEO_2MA-*co*-DMAEMA) was as follows. EC-Br (0.4876 g, 0.318 mmol of Br