Carbohydrate Polymers 103 (2014) 510–519

Contents lists available at ScienceDirect

Carbohydrate Polymers

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

Stimulus-responsive polymeric micelles for the light-triggered release of drugs

Bin Wang, Kefu Chen, Rendang Yang, Fei Yang*, Jin Liu

State Key Lab of Pulp and Paper Engineering, South China University of Technology, Guangdong Public Laboratory of Paper Technology and Equipment, Guangzhou, China

ARTICLE INFO

Article history:
Received 4 September 2013
Received in revised form 1 December 2013
Accepted 19 December 2013
Available online 6 January 2014

Keywords:
Ethyl cellulose
Light-responsive
ATRP
Drug loading
Light-controlled release

ABSTRACT

Ethyl cellulose macroinitiator was firstly synthesized by direct acylation of ethyl cellulose with 2-bromopropionyl bromide in a room temperature. And a light-responsive triblock copolymer of ethyl cellulose-g-poly(2-hydroxyethyl methacrylate)-g-poly(spiropyran ether methacrylate) (EC-g-PHEMA-g-PSPMA) was prepared by atom transfer radial polymerization. The amphiphilic structure of the copolymer enabled it to aggregate into spherical micelles in aqueous solution with an average diameter of 100 nm. The micelles exhibited light-responsive performance because of the SPMA monomer. The hydrophobic side chain of PSPMA became hydrophilic under UV light, which decreased the average size of the micelles. Additionally, the diameters of the micelles can be recovered when subsequently irradiated with visible light. The loading and light-triggered release profiles of model drugs were also investigated, and results showed that the release behavior can be controlled by changing the light wavelength.

1. Introduction

In drug delivery, therapeutic cargos including small molecules, peptides, proteins, nucleic acids, and living cells are used to treat various sicknesses. Materials for drug delivery packages can confer specific functions, such as enhanced solubility and accurate targeting. These materials can also resolve problems of premature degradation, permeable barriers, reduced dosage, and side effects (Farokhzad & Langer, 2009; Liu, Robinson, Tabakman, Yang, & Dai, 2011; Slowing, Trewyn, Giri, & Lin, 2007; Yoo, Irvine, Discher, & Mitragotri, 2011).

New technologies and methods have recently been used to study package materials for drug delivery, including nanoparticles, nanofibers, and polymer materials (Agasti et al., 2009; Cotí et al., 2009; Ferris et al., 2009; Fu, Xu, Yao, Li, & Kang, 2009; Lee, Larson, & Lawrence, 2009; Li & Keller, 2009; Uda, Hiraishi, Ohnishi, Nakahara, & Kimura, 2010). In the successful delivery of drugs to the human body, enhancing drug encapsulation package is needed to improve biocompatibility and stability. Drug packaging using polymeric carriers solves the above problem. Polymeric designs that avoid complex circulatory pathways enable the achievement of important goals. Optimized designs can provide new insights into better therapies.

Many designed biological carrier systems (Canelas, Herlihy, & DeSimone, 2009; Kutscher et al., 2010) have been developed. Biomimetic hydrogels well control biomolecular delivery from bone defects. Specifically, designed "biomimetic" scaffolds are inspired by natural extracellular matrices, using their body as a bioreactor to regenerate bone in regulating tissue regeneration (Martino et al., 2011). Micro-needles (Kim, Park, & Prausnitz, 2012) can penetrate onto the skin and traverse skin capillaries. Consequently, drugs can be delivered to diseased areas.

In seeking effective treatment, a variety of novel drug delivery systems have been actively investigated. Among them, personalized healthcare strategies are the most promising and exciting innovations. Personalized therapy selects the right dosage for the treatment of each patient to maximize therapeutic efficacy and reduce side effects. Healthcare strategies of personalized medicine for individual patients are different. Individual patient responses therapy efficacy is not the same because of the complexity and heterogeneity of diseases and patients (Sakamoto et al., 2010). Therefore, personalized medicine designs functional carriers and collects necessary molecular data to achieve its full potential.

Several biological polymers that possess a stimulus-responsive ability are called "smart materials", which can solve personalized therapy problems. Stimulus-responsive nanocarriers deliver vehicles corresponding to external signals and "load-and-release" functions. These materials are sensitive to viruses, tumor cells, or other environmental diseases and respond to drug delivery systems. Delivery of same drug suits individual patients differently. Stimulus-responsive nanocarriers could improve drug properties

* Corresponding author. Tel.: +86 20 87110084; fax: +86 20 87111072.
E-mail address: yangfei@scut.edu.cn (F. Yang).

0144-8617/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.carbpol.2013.12.062

by changing their response to environmental pH (Chen, Meng, Cheng, & Zhong, 2010; June, Gogoi, Eguchi, Cui, & Dowdy, 2010; Liu et al., 2011; Makhlof, Tozuka, & Takeuchi, 2009, 2011; Yuba, Harada, Sakanishi, Watarai, & Kono, 2013;Yuba et al., 2013), and temperature (Chen, Amajjahe, & Stenzel, 2009; He et al., 2011; Jiang, Li, Liu, Hennink, & Zhuo, 2012; Santos, Alves, & Mano, 2010), or through remotely applied external stimuli such as magnetic fields (Jiang et al., 2012; Lin et al., 2012; Wang et al., 2013), ultrasound (Zhang, Xia, Wang, & Li, 2009; Zhao, Du, Lu, Jin, & Ge, 2013), and light (Fan, Cheng, Ho, & Yeh, 2012; Kang et al., 2011; Knežević, Trewyn, & Lin, 2011; Lai et al., 2010). Among these stimuli, light is the most suitable for use in delivery systems because it can be manipulated with extremely high spatial and temporal precision. Additionally, the release of drugs can be rapidly accomplished at a specific time and location by specific wavelengths of light irradiation. The parameters of light intensity, wavelength, and exposure time can be established in drug delivery systems. UV light, visible light, and near infrared (NIR) can be adjusted in a treated area to induce drug release (Fomina, Sankaranarayanan, & Almutairi, 2012). Light-induced reactions do not require any chemical environmental change and can be repeated several times.

Photosensitive nanocarriers can be fabricated from a variety of biocompatible and non-toxic molecules combined with a chromophore to modulate release by switching construct properties. The therapeutic agents can be released from nanocarriers upon light exposure. Different nanocarrier including micelles, polymeric nanoparticles, hollow metal nanoparticles, and liposomes are used in respective photochemical reactions in order to facilitate release of the encapsulated bioactive agent. All light-induced reactions depending on their molecular chromophore can be divided into three: photo-isomerization, photo-cleavage, and photo-dimerization. The properties of reversible and reproducible photo-isomerization processes make chromophores attractive and be functionalized as "on–off" switch nanocarriers. Common photo-isomerization chromophore mainly include azobenzene, stilbene, and spiropyran (Tomatsu, Peng, & Kros, 2011).

Spiropyran (SP) is a structure which can control hydrophobic/hydrophilic interactions by light conversion. The hydrophobic spiropyrane state can transform into hydrophilic merocyanine state under UV light irradiation. Apart from this property, spiropyran-based materials have been widely applied in many fields, such as data storage, optical and electrical switching, and light-actuated nanovalves. SP has also been introduced into polymers to develop light-responsive micelles (Haque, Kakehi, Hara, Nagano, & Seki, 2013; Ivashenko, van Herpt, Feringa, Rudolf, & Browne, 2013; Renkecz, Mistlberger, Pawlak, Horváth, & Bakker, 2013). For example, Chen et al. reported a novel spiropyran-based block copolymer which was used to fabricate thermo- and light-responsive micelles and reverse micelles (Chen et al., 2012). Spiropyran reactions can lead to a change in the nanocarrier assembly directly or indirectly, which leads to release of drug from the nanocarrier.

A challenge in light-responsive nanocarriers is to optimize material responses and introduction into drug delivery systems to ensure that biomaterials achieved their application potential. Thus, several materials have been studied by multidisciplinary research teams in an attempt to solve such problems. These materials have been designed and engineered considering their bulk properties.

Peng et al. (Han et al., 2013) reported on amphiphilic diselenide-containing block copolymers micelles. Additionally, stable nanospheres controlled by red light can release encapsulated cargo into polymeric micelles. NIR light-responsive drug delivery platforms (Kang et al., 2011) coated with DNA cross-linked polymeric shells have been constructed. Drug delivery systems remotely controlled by NIR light can carry drugs.

In general, avoiding micellar cross-linking requires diblock copolymer micelles to be prepared in a very dilute solution. By contrast, ABC triblock polymer micelles can be achieved at higher micelle concentrations. Xu, Flores and McCormick (2011) recently synthesized the pH-responsive triblock copolymer PEO-PAPMA-PNIPAM through aqueous RAFT polymerization. Such "pH-triggered" release behavior demonstrated that triblock copolymers can be used as therapeutic nanocarriers.

In the present work, we designed and synthesized a stimulus-responsive ABC triblock polymer. First, acrylic acid-based spiropyrane monomer (SPMA) was synthesized using carboxyl-containing Sp (Sp-COOH) and hydroxyethyl methylacrylate (HEMA). The ATRP initiator was then immobilized covalently onto ethyl cellulose (EC) surface followed by 2-bromopropionyl bromide. Finally, HEMA and SPMA were grafted onto the ethyl cellulose backbone (Scheme 1). EC-g-PHEMA-g-PSPMA exhibited multiple functions resulting from its special architectures with a hydrophilic HEMA unit and a photo-responsive hydrophobic SPMA group. Considering the amphiphilic and light-responsive properties of ABC triblock polymer, they are expected to self-assemble into micelles that respond to light. The behaviors of loading and light-controlled release of drug (probe pyrene) were also investigated by irradiation at different wavelengths of light. Light-responsive triblock polymers have potential applications in controlled drug delivery.

2. Experimental

2.1. Materials

EC (M_n = 29,100 g/mol; degree of ethyl substitution = 2.1) was obtained from Aladdin and dried at 35 °C in a vacuum for 72 h before use. HEMA (Acros; 97%) was passed through a neutral aluminum oxide (250 mech) column to remove stabilizing agents.

CuBr (Acros; 97%) was purified by stirring with acetic acid and washed with methyl alcohol three times until the washings were clear. CuBr was then dried in a vacuum oven at 50 °C for 48 h. 2-Bromopropionyl bromide (BPB; 98%), Me_6tren (99%), and 2,2′-bipyridine (BPY; 98%) were purchased from Aldrich and used as received. Tetrahydrofuran (THF; Sigma, 99.9%) was dried overnight over CaH_2 and distilled under reduced pressure before use.

All other chemicals were analytical reagent grade and used without further purification. Water (18.2 MΩ) was purified with a Millipore Milli-Q system. UV and visible light irradiation were conducted at 8 W UV (354 nm) and 8 W white light (620 nm) lamps.

2.2. Synthesis of allyl-functionalized spiropyrane monomer (SPMA)

Exactly 3.84 g of SPCOOH (10 mmol), 2.68 g of HEMA (20 mmol), and 0.24 g of DMAP (2 mmol) were dissolved in 70 mL of tetrahydrofuran (THF). The solution was mixed in a three-neck flask, cooled to 0 °C in an ice–water bath, and purged with gaseous Ar. A solution containing 2.06 g (10 mmol) of dicyclohexyl carbodiimide in 30 mL of THF was added dropwise to the mixture. The following reaction was performed in the dark: the mixture was placed in an ice salt bath for 2 h and then stirred at room temperature for 24 h. Residual salt produced from the reaction was removed by filtration. The product was purified by concentration, water precipitation, benzene washing, and petroleum ether re-precipitation. The final product (3.19 g; 52% yield) was obtained using vacuum dryer.

2.3. Synthesis of an EC-Br initiator

An EC-Br macroinitiator was prepared based on the procedure shown in Scheme 1. In a typical procedure, 2.02 g (unit of