Materials Science & Engineering C 91 (2018) 688–695

Contents lists available at ScienceDirect

Materials Science & Engineering C

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

Stereocomplexed micelle formation through enantiomeric PLA-based Y-shaped copolymer for targeted drug delivery

Wenqiang Li[a,b], Xiaoshan Fan[a], Xiaokun Wang[a], Xiaohong Shang[a], Qi Wang[b], Juntang Lin[b], Zhiguo Hu[a,*], Zibiao Li[c,*]

[a] Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang 453007, China
[b] The Second Affiliated Hospital of Xinxiang Medical University, Henan Key Lab of Biological Psychiatry of Xinxiang Medical University, China
[c] Institute of Materials Research and Engineering, A*STAR (Agency for Science, Technology and Research), 2 Fusionopolis Way, Innovis, #08-03, Singapore 138634, Singapore

ARTICLE INFO

Keywords:
Stereocomplex
Enantiomeric PLA
Y-shaped
Block copolymer
Drug delivery

ABSTRACT

In this study, a novel stereocomplexed micelle system was prepared from the self-assembly of enantiomeric PLA-based Y-shaped copolymers, i.e. folic acid-adamantane/β-cyclodextrin-*b*-[poly(D-lactide)]$_2$ (FA-AD/CD-*b*-(PDLA)$_2$) and poly(2-dimethylaminoethyl methacrylate)-*b*-[poly(L-lactide)]$_2$ (PDMAEMA-*b*-(PLLA)$_2$) in aqueous solution. The newly designed Y-shaped copolymer FA-AD/CD-*b*-(PDLA)$_2$ was prepared by a combination of "click" reaction and host guest interaction between FA-AD and CD-*b*-(PDLA)$_2$. In addition, enantiomeric Y-shaped PDMAEMA-*b*-(PLLA)$_2$ copolymer was synthesized through ring-opening polymerization (ROP) of L-lactide using three-head initiator with bromo and –OH at distal ends, followed by atom transfer radical polymerization (ATRP) of DMAEMA to obtain the desired macromolecular architecture. The resultant copolymers and their intermediates were characterized by ^{1}H nuclear magnetic resonance (^{1}H NMR) and gel permeation chromatography (GPC) techniques. Due to the strong stereocomplexation interaction, FA-AD/CD-*b*-(PDLA)$_2$ and PDMAEMA-*b*-(PLLA)$_2$ mixture could self-assemble into stable mixed micelles in aqueous solution. Further, the stereocomplexed micelles exhibited excellent biocompatibility as revealed in the cytotoxicity assay. Together with the intrinsic biodegradability of PLA, it is envisioned that the stereocomplexed micelles developed in this study can be used as a promising nanocarrier for targeting drug delivery.

1. Introduction

Over the past few decades, polymeric micelles derived from amphiphilic copolymers have attracted tremendous interest due to their potential applications in the field of drug delivery, bioengineering, material science, and so forth [1–8]. Largely driven by hydrophobic interaction, conventional amphiphilic block copolymer form self-assemblies above their critical micelle concentration (CMC). So, the formed micelles present the instablly thermodynamic aggregations of multi polymer chains above CMC and might disassociate into free polymer chains as being subject to high dilution, shear forces and other parameters, such as pH, temperature and ionic strength [9, 10]. As a consequence, this drawback may heavily hinder the applications of polymeric micelles. Especially as the drug carrier, the disassociation of the polymeric micelles results in the premature release of the encapsulated therapeutic drugs before they reach the targeted disease sites and even lead to undesirable systemic toxicity [11–14].

To address the issue associated with the polymeric micelle structure instability above, many approaches have been proposed (i) the chemically cross-linking the core or shell or both of the prepared micelles [15–18], (ii) the polymer-polymer complex formation mediated by noncovalent interactions between blocks [19–22] and (iii) the development of unimolecular micelles, each of which is formed by a single amphiphilic macromolecules [23–27]. As for the chemical cross-linking strategy, the biodegradability of the micelles and the encapsulation or release of a guest molecule might be compromised [28, 29]. The intrinsic covalent linkage between the compositional units endows the unimolecular micelles excellent stability, while the architecture of polymer for forming unimolecular micelles is usually complex, which will elevate the synthetic difficulties. In comparison, the use of noncovalent interactions that are still dynamic is a relative simple and versatile approach to stabilized micelles. Up to now, a few examples of stabilized micelles driven by noncovalent interactions have been well investigated, including polyelectrolyte complex, hydrogen-bonding

* Corresponding authors.
E-mail addresses: zghu@htu.edu.cn (Z. Hu), lizb@imre.a-star.edu.sg (Z. Li).

https://doi.org/10.1016/j.msec.2018.06.006
Received 5 March 2018; Received in revised form 11 May 2018; Accepted 8 June 2018
Available online 10 June 2018

complex and so on [19, 30, 31].

Polylactides (PLA), a thermoplastic aliphatic polyester derived from renewable resources, have great current and potential applications in many fields due to its number of desirable properties, such as biodegradability, biocompatibility and excellent mechanical properties [32–36]. PLA has three isomeric forms, that is, optically active poly(L-(-)-S-lactide) (PLLA) and poly(D-(+)-R-lactide) (PDLA) and racemic poly(DL-lactide) (PDLLA), as lactide monomers have two stereoisomers, L- and D-compounds. It has been reported that PLLA/PDLA mixture can form a racemate, so-called stereocomplexes in either the melt or solution via hydrogen-bonding between L-lactyl and D-lactyl unit sequences. As compared with the individual enantiomers, PLA stereocomplexes exhibit better physical and chemical properties, such as higher mechanical properties, higher melting point and improved thermal and hydrolytic stability [37–42]. In recent years, PLA stereocomplex interaction-assisted polymeric micelles have attracted increasing attention. As compared with the conventional micelles formed via hydrophobic interaction, stereocomplex micelles were endowed with some improved characteristics, such as enhanced stability, reduced degradation rate, and so forth. Furthermore, there is no need for introducing special functional groups into the blocks to stabilize the formed micelles in comparison with other noncovalent interactions. The above-mentioned advantages combining with the good biocompatibility make the PLA stereocomplex micelles with great promising applications in the field of drug delivery [20, 22].

In this study, stable mixed micelles consisting of a biodegradable core and a mixed shell were prepared from a mixture of two block copolymers PDMAEMA-*b*-$(PLLA)_2$ and FA-AD/CD-*b*-$(PDLA)_2$, as depicted in Fig. 1. PLLA and PDLA enantiomers were employed to constitute the hydrophobic core of the micelles as the peculiarly strong stereocomplexation between them can well stabilize the formed micelles. Specially, we expected that the unique V-shaped structure of PLLA or PDLA segments on the copolymers CD-*b*-PL(D)LA_2 could facilitate the stereocomplexation formation as compared with the conventional linear counterpart. The poly(2-dimethylaminoethyl methacrylate) (PDMAEMA) chains and CD segments on the hydrophilic shell play the role to improve the solubility of the formed micelles in aqueous solution, while the CD segments near the core also provides the possibility to conjugate some special molecules via host-guest interaction. Herein, the folic acid (FA) moiety, one of the mostly employed targeting molecules, was introduced into the copolymer CD-*b*-$(PDLA)_2$ through the host-guest interaction to form the copolymer FA-AD/CD-*b*-$(PDLA)_2$. The presence of the FA moieties endows the stereocomplex micelles derived from the mixture of FA-AD/CD-*b*-$(PDLA)_2$ and PDMAEMA-*b*-$(PLLA)_2$ with the targeting properties. In a word, the proposed drug delivery system possesses the following innovation and advantages: biodegradability, biocompatibility, targeting property and the good stability derived from the stereocomplexation of novel "Y"-shaped copolymers. Due to these combined good properties, the as-developed mixed micelles are promising candidates as drug delivery nanocarriers.

2. Experimental section

Materials: L-lactide and D-lactide monomers (99.5%) were purchased from Sinobiom and used as received. 2-(Dimethylamino)ethyl methacrylate (DMAEMA) (98%, Alladin) was passed through a short column with neutral alumina oxide just before use to remove the inhibitor. Mono-6-deoxy-6-azido-β-cyclodextrin (β-CD-N_3) was synthesized according to the procedure reported in the literature [43]. The three-head initiator trimethylolpropane propargyl ether used to initiate polymerization of D-lactide (DLA) was synthesized according to the previously reported procedure. Other reagents were purchased from Alladin Chemical Co., Ltd.

2.1. Preparation of the inclusion complex FA-AD/CD-$(PLLA)_2$ via host-gust interaction (Scheme 1A)

As shown in Scheme 1, a V-shaped poly(D-lactide) with one alkyne group on the conjugating point (Alkyne-$(PDLA)_2$) was first synthesized via a three-head initiator initiating ring-opening polymerization of D-lactide. The detail procedure is as following: To a Schlenk flask (50 mL) treated with several repeated exhausting/refilling with nitrogen gas processes, D-lactide (4.0 g, 0.028 mol) was added, followed by another three repeated exhausting/refilling with nitrogen gas processes. Then, 1 mL of the dioxane solution of the three-head initiator (0.18 g, 1.15 mmol) was charged into the system. The reaction vessel was immersed into an oil bath preheated to 130 °C to start the polymerization. The reaction was allowed to proceed for 24 h under vigorous stirring. After being cooled down to the room temperature, the product was dissolved with chloroform and poured into an excess of ether. The as-purified polymer alkyne-$(PDLA)_2$ was obtained as a white solid after filtration and being dried under vacuum at 35 °C. ($M_{n,NMR}$ = 4720 g mol^{-1}, $M_{n,GPC}$ = 4550 g mol^{-1}, Mw/Mn = 1.17).

CD-*b*-$(PDLA)_2$ was obtained via click chemistry of alkyne-$(PDLA)_2$ as-prepared above with β-CD-N_3. To a dried Schlenck flask with 12 mL freshly distilled *N*,*N*-dimethylformamide (DMF), β-CD-N_3 (0.6 g, 0.52 mmol) and the polymer alkyne-$(PDLA)_2$ (1.5 g, 0.434 mmol) were added. After all of substrates were dissolved completely, PMDETA (0.11 mL, 0.52 mmol) was added and the solution was subsequently degassed thoroughly by bubbling with nitrogen flow. After 40 min, CuBr (0.08 g, 0.52 mmol) was added followed by bubbling with nitrogen flow for another 15 min. Then, the flask was put into an oil bath preheated to 45 °C. The reaction lasted for 48 h. After the reaction was completed, appropriate amount of EDTA aqueous solution was added into the solution and stirred for 30 min. Then, the solution was dialyzed against deionized water using a dialysis tube (MWCO, 2000 Da) for

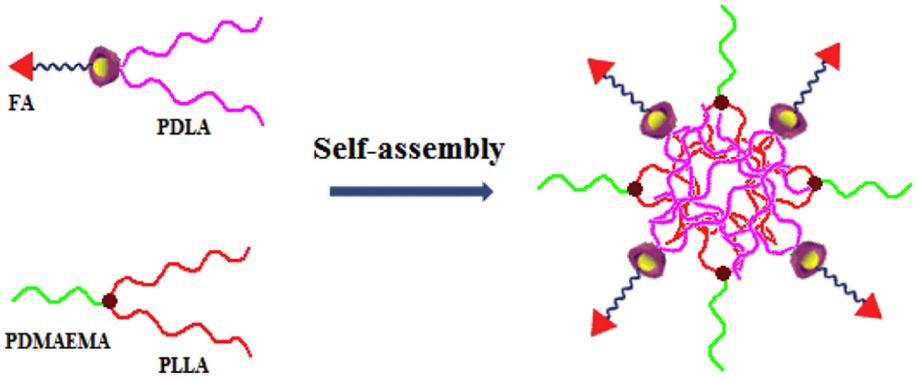

Fig. 1. Illustration showing the formation of FA modified micelles stabilized via stereocomplexation from folic acid-adamantane/β-cyclodextrin-*b*-[poly(D-lactide)]$_2$ (FA-AD/CD-*b*-$(PDLA)_2$) and poly(2-dimethylaminoethyl methacrylate)-*b*-[poly(L-lactide)]$_2$ (PDMAEMA-*b*-$(PLLA)_2$).