Ultrasonics Sonochemistry 30 (2016) 9–17

Contents lists available at ScienceDirect

Ultrasonics Sonochemistry

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

Ultrasound responsive block copolymer micelle of poly(ethylene glycol)–poly(propylene glycol) obtained through click reaction

Fayong Li, Chuan Xie, Zhengang Cheng, Hesheng Xia *

State Key Lab of Polymer Materials Engineering, Polymer Research Institute, Sichuan University, Chengdu 610065, China

ARTICLE INFO

Article history:
Received 4 October 2015
Received in revised form 24 November 2015
Accepted 24 November 2015
Available online 24 November 2015

Keywords:
"Click" chemistry
Block copolymer
Self-assembly
HIFU
Mechanochemical

ABSTRACT

The well-defined amphiphilic poly(ethylene glycol)-block-poly(propylene glycol) copolymer containing 1, 2, 3-triazole moiety and multiple ester bonds (PEG-click-PPG) was prepared by click reaction strategy. The PEG-click-PPG copolymer can self-assemble into spherical micelles in aqueous solution. It is found that high intensity focused ultrasound (HIFU) can open the copolymer PEG-click-PPG micelles and trigger the release of the payload in the micelle. The multiple ester bonds introduced in the junction point of the copolymer chain through click reactions were cleaved under HIFU, and leads to the disruption of the copolymer micelle and fast release of loaded cargo. The click reaction provides a convenient way to construct ultrasound responsive copolymer micelles with weak bonds.

1. Introduction

The molecular design for new stimuli-responsive amphiphilic block copolymer has gained a great interest in recent years [1,2]. When copolymer micelles suffer certain stimuli such as thermal [3], pH [4], light [5], magnetic [6] and ultrasound [7–10], the micelle structure can be broken physically or chemically, leading to the release of the encapsulated hydrophobic drugs. The synthesis of novel stimulus responsive copolymer and the design of new stimuli-responsive means are of equal importance. The major challenge is the realization of the optimized coupling interaction between physical or chemical stimulus means and the copolymer micelle microcontainer.

Ultrasound triggered drug release was firstly investigated by Pitt [7], Rapoport [11] and Hussein [12]. It was found that ultrasound could physically break the micelle and trigger the drug release. High intensity focused ultrasound (HIFU) is another promising external trigger for the drug release from polymer, which has the advantages such as focused tiny area, deep penetration, non-invasiveness and remote controllable properties [13–15]. Previously Xia and Zhao et al. [13–17] investigated HIFU induced release behavior of payload entrapped in polymer micelles containing weak bonds, and proposed a novel mechanism, i.e. breaking the copolymer micelle under HIFU by a mechanochemical way. In order to develop block copolymer micelles that can be rapidly and efficiently disrupted by HIFU, the copolymer should contain weak bonds, ideally mechano-labile ones that are sensitive to the mechanical effects associated with the ultrasonic cavitation. On the other hand, for drug delivery, HIFU intensity should be low to be acceptable by human body and HIFU time should be as short as possible.

Recently, a wide variety of mechanochemical reactions have been demonstrated through the deliberate incorporation of mechanophores into polymer chain, with the aim of developing mechanoresponsive polymers [18–25]. The exploring in new mechanophore structure and the routes to introduce the mechanophore into the polymer are the main directions [26,27]. The mechanophore concept could provide a novel approach to fabricate ultrasound responsive copolymer and its micelle system.

Click chemistry has emerged as an established robust and efficient method to link functional moieties with each other, which is especially interesting for the preparation of functional materials such as block copolymers. The orthogonal 1, 3-dipolar cycloaddition click reaction of azides and alkynes provides efficient route to synthesize amphiphilic block copolymer containing 1, 2, 3-triazole ring [28,29], such as $(PCL)_2$-$(PEG)_2$ miktoarm star copolymer [30] and PCL-*g*-PEG [31]. Click chemistry is also tried to introduce the mechanophore into the homopolymer, however, the mechanochemical ring-opening for the 1, 2, 3-triazole moiety under low frequency ultrasound in organic solvent is not successful [32].

Herein, we utilized the mechanophore-functionalization through click reaction of azides and alkynes for amphiphilic block copolymer to develop ultrasound responsive micelle. Previously we have confirmed that the irreversible release mechanism

* Corresponding author.
E-mail address: xiahs@scu.edu.cn (H. Xia).

http://dx.doi.org/10.1016/j.ultsonch.2015.11.023
1350-4177/

resulting from the cleavage of ester bonds as the "mechanophore" at the junction points of PEG and PPG blocks based on our designed Pluronic type copolymer PEG-COO-SS-PPG [17]. The robust click reaction route can introduce more ester bonds, i.e. mechanophore, into the junction points of PEG and PPG blocks, which may endow the copolymer rapid and efficient ultrasound responsiveness. Meanwhile, it is necessary to check whether HIFU can unlock the 1, 2, 3-triazole ring embedded in copolymer micelle in aqueous solution, and lead to the disruption of micelles and release of encapsulated hydrophobic drug.

In this study, the amphiphilic Pluronic type block copolymer PEG-click-PPG containing 1, 2, 3-triazole moiety and four ester bonds in the junction point was synthesized by click chemistry as shown in Scheme 1a, using azide-terminated PEG as the hydrophilic block and alkyne-terminated PPG as the hydrophobic block. Pluronic copolymer was selected because it is one of the few copolymer micelles which have been used as a FDA approved drug delivery system for the last decades. Base on this new copolymer, the HIFU triggered release of the copolymer micelle was expected. The proposed mechanism as illustrated in Scheme 1b includes HIFU-induced site-specifically mechanochemical degradation of the PEG-click-PPG chain containing weak bonds, and consequently the micelle disruption and controlled payload release.

2. Materials and methods

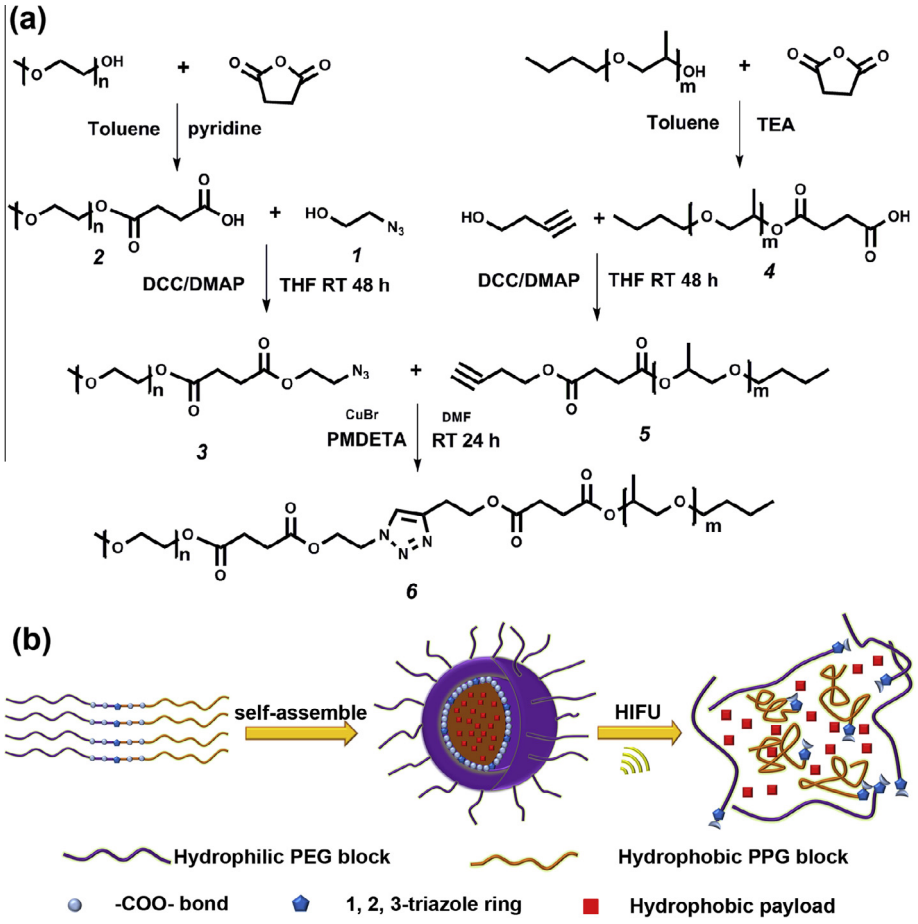
2.1. Raw materials

Poly(ethylene glycol) methyl ether (mPEG) (Mn = 2000), Poly(propylene glycol) monobutyl ether (PPG) (Mn = 2500), Succinic anhydride, dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), and Nile Red were obtained from Sigma–Aldrich Chemical Company and used without further purification. CuBr (99%; Maya) was purified by stirring overnight in acetic acid. Sodium azide (NaN_3), 3-Butyn-1-ol, Pentamethyldiethylenetriamine (PMDETA), 2-Bromoethanol and Sodium azide were purchased from Maya-Reagent. Diethyl ether (Et_2O), N, N-Dimethylformamide (DMF), Tetrahydrofuran (THF), dichloromethane (DCM), CaH_2, methanol, ethanol, and sodium were purchased from Chengdu Kelong Chemical Reagents Institute. THF and DCM were dried by refluxing over sodium wire and CaH_2 respectively, and distilled prior to use to remove the moisture and oxidative impurity. All other chemicals and solvents were used as received unless stated.

2.2. Sample preparation

2.2.1. Synthesis 2-Azidoethanol (1)

According to the reference [33], 2-bromoethanol (7.51 g, 60.5 mmol), NaN_3 (5.13 g, 122 mmol), and Tetrabutylammonium bromide (500 mg, 1.5 mmol) were added to a 50 mL flask, and stirred for 15 h at 110 °C. Then the mixture was cooled and the product was taken up with Et_2O (20 mL), and the precipitate was removed by filtration. The precipitate was washed with Et_2O (~20 mL). Evaporation of the solvents gave a yellow residue that was purified by distillation (bp 35 °C/1 Torr) to yield 5.0 g (95%) of 2-Azidoethanol as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.06 (m, —OH), 3.45 (m, —CH_2—N_3), 3.78 (m, —CH_2—OH). FTIR: ν = 3377.5, 2937.5, 2880.2, 2110 vs (—N_3), 1442.5, 1296.3, 1070.0 cm^{-1}.



Scheme 1. (a) Synthetic route of PEG-click-PPG copolymer. (b) Schematic illustration of HIFU responsive process of copolymer micelle containing mechano-labile ester bonds.