European Polymer Journal 45 (2009) 1190–1197

Contents lists available at ScienceDirect

European Polymer Journal

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

A water-soluble PPDO/PEG alternating multiblock copolymer: Synthesis, characterization, and its gel–sol transition behavior

Xiu-Li Wang, Yu-Rong Mou, Si-Chong Chen, Jing Shi, Yu-Zhong Wang *

Center for Degradable and Flame-Retardant Polymeric Materials, College of Chemistry, State Key Laboratory of Polymer Materials Engineering, Sichuan University, Chengdu 610064, China

ARTICLE INFO

Article history:
Received 21 March 2008
Received in revised form 9 December 2008
Accepted 16 December 2008
Available online 31 December 2008

Keywords:
Poly (*p*-dioxanone)
Poly (ethylene glycol)
Alternating multiblock copolymer
Temperature-sensitive gel–sol transition

ABSTRACT

Biodegradable and nontoxic alternating multiblock copolymers based on poly (*p*-dioxanone) (PPDO) and poly (ethylene glycol) (PEG) were synthesized by the coupling reaction of two bifunctional prepolymers, a dihydroxyl-terminated PPDO and dicarboxylated PEG. The prepolymers and the resulting PPDO/PEG multiblock copolymers were characterized by various analytical techniques such as FT-IR, ^{1}H NMR, GPC, DSC and TG. At high concentration levels above critical gelation concentration (CGC), the aqueous solution of copolymers formed a gel. Temperature-sensitive gel to sol transition behaviors were investigated by the test tube inverting method. Dynamic light scattering (DLS) was used to investigate the micelle of copolymers, whose association probably caused the gelation of the system. Therefore, this novel copolymer has a great potential in injectable drug-delivery system for long-term delivery of drugs.

1. Introduction

Amphiphilic block copolymers have attracted so much attention as they exhibit complex and interesting micellization [1–6] and gelation behaviors [7–13] in aqueous solution. Poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) (PEO–PPO–PEO) triblock copolymer, well known as Pluronic or Poloxamer, is one of the earliest and most widely investigated amphiphilic block copolymers. The aqueous solution of PEO–PPO–PEO triblock copolymers showed micellization, sol-to-gel and gel to sol transition behaviors depending on their molecular structure, concentration and temperature [14–17]. It has been advocated that PEO–PPO–PEO triblock copolymers can be used for drug controlled delivery system [18,19] and for the prevention of post-surgical tissue adhesions [20]. Unfortunately, PEO–PPO–PEO triblock copolymers are nonbiodegradable and have been reported to induce hyperlipidemia rats [21], limiting its use in human body.

Therefore more and more efforts have been paid to developing biodegradable and nontoxic block copolymers for biomedical applications, requiring no surgical removal after use. PEG, accepted by US Food and Drug Administration (FDA) [22], is widely used as a hydrophilic block into a copolymer. And many temperature-sensitive copolymers based on PEG and PCL (polycaprolactone), PLA (polylactide) or PLGA (poly (lactic-co-glycolide)) with different structures were reported, such as diblock, triblock, multiblock and star-shaped block copolymers. Lu et al. [7] investigated the micellization and gelation of aqueous solutions of star-shaped PEG–PCL block copolymers by atomic force microscopy (AFM). The micelles showed a core-corona spherical structure, while the gel showed a mountain-chain-like morphology picture. Jeong et al. [23] reported the thermo-sensitive, biodegradable hydrogels consisting of poly (ethylene oxide) and poly (L-lactic acid) as injectable drug-delivery systems. Alternating multiblock copolymers of poly (L-lactic acid) and poly (ethylene glycol), which showed reverse thermal gelation, were studied by Lee et al. [9]. Park et al. [24] synthesized the star-shaped PLLA–PEO block copolymers with temperature-sensitive

* Corresponding author. Tel./fax: +86 28 85410259.
E-mail address: yzwang@email.scu.edu.cn (Y.-Z. Wang).

0014-3057/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.eurpolymj.2008.12.038

sol–gel transition behavior, having possibility to be used as injectable drug-delivery system for long-term delivery of bioactive agents. Temperature-sensitive reversible gelation of PEG–PLGA–PEG and PLGA–PEG–PLGA triblock copolymers in aqueous solution was studied by Jeong et al. [25] and Ghahremankhani et al. [26], respectively. Loh et al. [27] studied the correlation between the protein release characteristics of the thermgelling poly(PEG/PPG/PHB urethane) copolymers and their hydrolytic degradation, suggesting that the release rate could be tuned by the formulation and copolymer composition.

However, as far as we know, little information on the gelation of polymers based on poly PPDO has been reported [28]. PPDO is one of the biodegradable and biocompatible aliphatic polyether ester and has received the approval of FDA to be used as a suture material [29–31]. And the degradation of PPDO occurs mainly by hydrolytic scission, resulting in low molecular weight species, which are in accordance with the human metabolites and can be metabolized or bioabsorbed by the body [29,31]. The purpose of this research is to synthesize biodegradable and nontoxic PPDO/PEG alternating multiblock copolymers, which are expected to form micelles and to exhibit temperature-sensitive gel–sol transition behaviors. In order to tailor the block length and distribution in copolymers, coupling approach is used to produce PPDO/PEG copolymers by using well-defined prepolymers in an alternating manner, which is different from the general ring-opening polymerization of PDO.

2. Experimental section

2.1. Materials

p-Dioxanone (PDO) was provided by the Pilot Plant of the Center for Degradable and Flame-Retardant Polymeric Materials (Chengdu, China), and was dried over CaH_2 for 48 h, distilled under reduced pressure before use. PEG (M_n = 4000) was purchased from Sinopharm (Shanghai, China) and was dried under vacuum at 70 °C overnight before use. Stannous octoate ($SnOct_2$) ($\geqslant$95%) was purchased from Sigma (USA) and used without any further purification. After diluted with dry toluene, $SnOct_2$ solution was stored in glass ampoules under argon. 1, 4-butanediol (BD) was distilled under reduced pressure immediately before use. 1, 4-dioxane was dried over sodium and chloroform was distilled from calcium chloride. All other chemicals and solvents were reagent grade and used as received.

2.2. Synthesis of PPDO prepolymers

Dihydroxyl-terminated PPDO was prepared by typical bulk ring-opening polymerization of PDO using BD as an initiator, and $SnOct_2$ as a catalyst. When the polymerization was completed, the crude polymers were dissolved in chloroform and precipitated with methanol. After eliminating the residual solvent by vacuum at 40 °C, the white PPDO powder was obtained. The molar ratio of PDO to BD ([P]/[B]) was varied with 6, 8, 10 and 12 to give PPDO3, 4, 5 and 6, respectively. The molar ratio of BD to $SnOct_2$ was fixed at 400.

2.3. Dicarboxylation of PEG

Dicarboxylated PEG was synthesized according to Zalipsky et al. [32]. The typical procedure was as follows: dried PEG (2 mmol) was dissolved in anhydrous dioxane, and then succinic anhydride (5 mmol), 4-(dimethylamino) pyridine (DMAP) (4 mmol) and triethylanine (TEA) (4mmol) were added. The solution was stirred for 24 h at room temperature under nitrogen. The dioxane was evaporated in vacuum, and then the residue was taken up in carbon tetrachloride, filtered. The filtrate was precipitated into an access amount of cold diethyl ether, and the obtained solid was dried in vacuo.

2.4. Synthesis of PPDO/PEG multiblock copolymers

PPDO and equimolar PEG-COOH (2 mmol) were dissolved in anhydrous chloroform, to which DMAP (0.5 mmol) and dicyclohexylcarbodiimide (DCC) (5 mmol) were added, and the solution was kept 24 h at room temperature under nitrogen. When the precipitated dicyclohexylurea (DCU) was filtered off as a reaction byproduct, the filtrate was precipitated in the mixture of diethyl ether and methanol (8:2 in volume fraction).

2.5. Characterization

The FT-IR spectra were recorded as KBr tablet using a Nicolet FT-IR 170SX infrared spectrophotometer. And the ^1H NMR spectra were recorded with Bruker AV400 spectrometers (Bruker, Germany) at 400MHz in $CDCl_3$, using tetremethyl silane (TMS) as an internal reference. GPC analysis was performed on a Waters 1515-717-2414 apparatus equipped with a refractive index detector, using monodispersed polystyrene standards to get a calibration curve. The elution solvent was chloroform at a flow rate of 1 mL/min at 30 °C. DSC analysis was carried out with DSC Q20 V23.12 Build 103 under a steady flow of ultrahigh purity nitrogen. Samples were heated to 150 °C for 5 min to erase all the previous thermal history and then were cooled to −50 °C at a rate of 10 °C/min. The samples were heated again at the same rate up to 150 °C. TG measurements were conducted with SDT Q600 V20.4 Build 14 at a heating rate of 10 °C/min at temperatures ranging from 30 to 500 °C under a nitrogen atmosphere.

2.6. Gel–sol transition

The gel–sol transition behavior of the aqueous copolymer solution was investigated by a test tube inverting method [8]. A given concentration of copolymer sample was prepared by dissolving the copolymer in doubly distilled water in a 5 mL tightly capped vial at 80 °C. After equilibrated at 4 °C for 15 h, the 5 mL vials containing 0.5 mL of PPDO/PEG multiblock copolymer aqueous solutions were immersed in a water bath, and then the temperature was elevated with a temperature increment of 1 °C per 10min. The gel–sol transition temperature was determined