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Synthesis and micellization of amphiphilic biodegradable methoxypolyethylene glycol/poly(D,L-lactide)/polyphosphate block copolymer

Qiuhua Wu [a], Chuang Wang [a], Dan Zhang [b], Ximing Song [a], Francis Verpoort [c], Guolin Zhang [a,*]

[a] Liaoning Province Key Laboratory for Green Synthesis and Preparative Chemistry of Advanced Materials, College of Chemistry, Liaoning University, Shenyang 110036, PR China
[b] Fushun New and High-Tech Industry Development Zone Management Committee, Fushun 113004, PR China
[c] Department of Inorganic and Physical Chemistry, Laboratory of Organometallic Chemistry and Catalysis, Ghent University, Krijgslaan 281(S-3), 9000 Ghent, Belgium

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ABSTRACT

A new amphiphilic biodegradable methoxypolyethylene glycol/poly(D,L-lactide)/poly(ethyl ethylene phosphate) (MPEG-*b*-PLA-*b*-PEEP) block copolymer was synthesized by ring-opening polymerization of ethyl ethylene phosphate (EEP) with methoxypolyethylene glycol/poly(D,L-lactide) (MPEG-*b*-PLA) as a macroinitiator, which was prepared by ring-opening polymerization of D,L-lactide (LA) initiated by methoxypolyethylene glycol (MPEG) using stannous octoate as catalyst. The structures of the block copolymers were confirmed by IR, ^{1}H NMR and GPC analysis. Fluorescence measurements were applied to determine the critical micelle concentration (CMC) of the copolymer micelle solutions. The diameter and the distribution of micelles were characterized by dynamic light scattering (DLS) and the shape was perceived using transmission electron microscopy (TEM). The results prove that the copolymers can self-assemble into nano-micelles in aqueous solutions. The CMC of the copolymer solutions increased and the size of the micelles reduced with increasing of the proportion of PEEP segments. TEM images demonstrate that all micelles are spherical.

1. Introduction

Amphiphilic block copolymers with the ability to self-assemble have extensively investigated for biomedical applications [1]. They can be used as controlled release agents of drugs, proteins, etc. because their biodegradability and amphiphilicity [2,3]. Lipophilic drug molecules can be incorporated into the hydrophobic core of polymeric micelles by physical entrapment, while the hydrophilic shell composed of flexible polymers provides steric protection [4].

Polylactide (PLA), which is most commonly synthesized by the ring opening polymerization of lactide [5,6], is a biodegradable polyester having good biocompatible properties. As a consequence, it has been utilized as a valuable bio-absorbent in medical and pharmaceutical fields [7–11]. Because PLA is hydrophobic and degrade very slowly by simple hydrolysis under the human body conditions, hydrophilic segment was usually introduced into the PLA polymer chain.

Recently, polyphosphoester (PPE) becomes of interest for biological and pharmaceutical applications because of their biocompatibility and structural similarities to natural occurring nucleic and teichoic acids [12]. PPE represents a class of biodegradable polymers with repeated phosphoester attachments in the backbone, which degrades under the physiological conditions via hydrolysis or enzymatic cleavage of the phosphoester bonds [13–17]. The degradation rates and other physico-chemical properties of these polymers are controllable by the chemical structure in the backbone and side chain [18]. More recently, PPE has received substantial interest in a wide range of applications from drug and gene delivery to tissue engineering [19–22]. Furthermore, poly(ethyl ethylene phosphate) (PEEP), a typical hydrophilic polyphosphoester, also received considerable attention in biomedical applications due to its biodegradability and good biocompatibility. If the PLA chain is combined with PEEP to prepare an amphiphilic biodegradable polymer, its hydrophilicity and biodegradability can be regulated, and thus its applications may extend widely.

In this paper, a new amphiphilic biodegradable methoxypolyethylene glycol/poly(D,L-lactide)/poly(ethyl ethylene phosphate) (MPEG-*b*-PLA-*b*-PEEP) block copolymer was synthesized by ring-opening polymerization of cyclic ethyl ethylene phosphate (EEP) with methoxypolyethylene glycol/poly(D,L-lactide) (MPEG-*b*-PLA) as a macroinitiator. Its structure was characterized and the self-assembling properties of the copolymer were investigated.

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* Corresponding author. Tel.: +86 24 62207795; fax: +86 24 62202380.
E-mail address: glzhang@lnu.edu.cn (G. Zhang).

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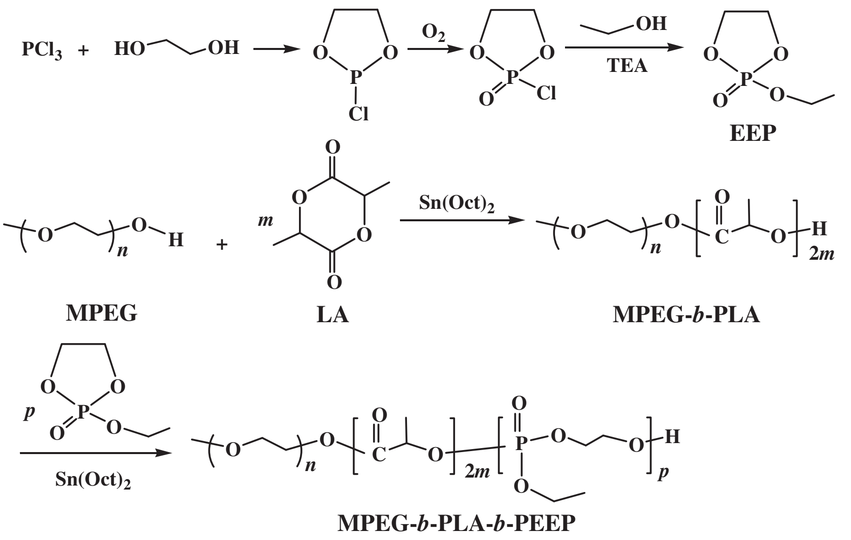

Scheme 1. The synthesis of MPEG-*b*-PLA-*b*-PEEP block copolymer.

2. Experimental

2.1. Materials

D,L-lactide (LA) was purchased from Daigang Biotechnology Co., Ltd. (Shandong, China) and recrystallized from dry ethyl acetate prior to use. Methoxypolyethylene glycol (MPEG, $M_n = 5000$) (Fluka Chemical Reagent Co., Ltd.) was distilled with toluene (azeotropic) before use. Stannous octoate ($Sn(Oct)_2$) was purchased from Sigma–Aldrich Chemical Reagent Co., Ltd. Ethylene glycol (analytical grade), triethylamine (analytical grade), ethanol (analytical grade) and CH_2Cl_2 (analytical grade) were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China), dried and distilled prior to use. Phosphorus trichloride (analytical grade) was purchased from Guangfu Fine Chemical Research Institute (Tianjin China). Toluene (analytical grade) was purchased from Baishi Chemical Reagent Co., Ltd. (Tianjin, China), dried and distilled before use. Other chemicals are all analytical reagents made in China and used without further purification.

2.2. Preparation of ethyl ethylene phosphate (EEP)Scheme 1

Ethyl ethylene phosphate (EEP) was prepared according to the procedure [23]. Briefly, to a stirred mixture of 274.66 g (2 mol) of phosphorus trichloride and 250 mL of dry CH_2Cl_2, 124.14 g (2 mol) of ethylene glycol was added drop wise. After complete addition of ethylene glycol, the solution was stirred at room temperature for another 0.5 h and CH_2Cl_2 was evaporated under vacuum. The residue was distilled under reduced pressure to give 123.2 g of 2-chloro-1,3,2-dioxaphospholane (yield: 49%, b.p. 42–45 °C/1600 Pa).

The oxidation of 123.2 g 2-chloro-1,3,2-dioxaphospholane was carried out by bubbling O_2 through the toluene solution at 40 °C for 48 h. After removal of toluene, the residue was distilled under reduced pressure to give 77.9 g colorless liquid of 2-chloro-2-oxo-1,3,2-dioxaphospholane(yield: 56%, b.p. 88–90 °C/107 Pa).

To a stirred and cooled mixture (−5 °C) containing 77.9 g (0.55 mol) of 2-chloro-2-oxo-1,3,2-dioxaphospholane and 250 mL dry toluene, a mixture of 25.3 g (0.55 mol) dry ethanol and 61.6 g (0.605 mol) dry triethylamine was added drop wise, and then the resulting mixture was stirred at room temperature for another 2 h. Thereafter, the triethylamine hydrochloride was filtered off and the filtrate was concentrated. The residue was distilled under reduced pressure to give 90.5 g colorless liquid of ethyl ethylene phosphate (EEP) (yield: 61%, 95–97 °C/107 Pa).

2.3. Synthesis of methoxypolyethylene glycol/poly(D,L-lactide)(MPEG-b-PLA) macroinitiator

MPEG-*b*-PLA was prepared according the literature [24]. In brief, 0.505 g (0.1 mmol) of MPEG, 2.954 g (20.5 mmol) of LA and 0.009 g (0.02 mmol) of $Sn(Oct)_2$ were transferred to a 10 mL ampoule and after six cycles of evacuation–purging with purified nitrogen the ampoule was sealed. The polymerization reaction was performed in an oil bath at 140 °C and terminated after 48 h. After being cooled to room temperature, the resulting polymer was dissolved in 15 mL anhydrous CH_2Cl_2 and precipitated in 150 mL ethyl ether twice. The precipitate was dried under reduced pressure at 35 °C for 24 h giving the MPEG-*b*-PLA macroinitiator as pale yellow solid, yield: 40% (Scheme 1). The copolymers were characterized by IR, ^{1}H NMR and GPC analysis. M_n is 22,424 (determined by ^{1}H NMR). The copolymers gave a broad absorption in the 3200–3600 cm^{-1} region due to terminal hydroxyl groups. Furthermore, the peak at 1757 cm^{-1} was assigned to the stretch vibration $\nu_{C=O}$ from the PLA segment, the typical absorption of the lactide monomer at 935 cm^{-1} had completely disappeared (Fig. 1A). ^{1}H NMR ($CDCl_3$, δppm): 1.56 (3H, —CH$\mathbf{H_3}$ of PLA), 3.40 (3H,

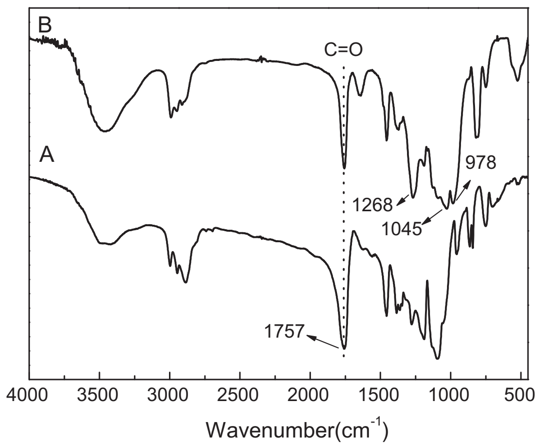

Fig. 1. IR spectra of MPEG-*b*-PLA (A) and MPEG-*b*-PLA-*b*-PEEP**2** (B) block copolymers.