PREPARATION AND CHARACTERIZATION OF 4-ARM STAR-SHAPED POLYLACTIDE-CO-POLY(ETHYLENE GLYCOL)

Tran Ngoc Quyen*, Nguyen Cuu Khoa

Institute of Applied Materials Science, VAST, 1 Mac Dinh Chi, Ho Chi Minh City

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Abstract

Four-arm star-shaped polylactide-co-poly(ethylene glycol) (4-arm PLA-PEG) was successfully synthesized via two steps. Firstly, ring-opening polymerization (ROP) of lactide with multifunctional initiator, pentaerythritol and stannous octoate ($SnOct_2$) catalyst was conducted at 120 °C. Secondly, star-shaped polylactide was conjugated to monomethoxy-poly(ethylene glycol)-succinic acid (MPEGa) via carbodiimide coupling agent. ^{1}H NMR spectroscopy results indicated that ROP method produced star-shaped polylactide containing a secondary hydroxyl end group in each arm. The molecular weights (GPC) of the resulting macromonomer linearly increased with the increase of the molar ratios of the lactide and pentaerythrytol in feed. The star-shaped macromonomer with hydroxy end groups was used as a macromonomer for block-coupling reaction with MPEGa. The molecular weight distributions of the macromonomers and block copolymers were rather narrow (Mw/Mn:1.1-1.2). The 4-arm polymers PLA-PEG could form gel network via physical bond when the concentration of polymers around 30 %. The gel network can act as a biomaterial for tissue regeneration application.

Keywords: Star-shaped, polylactide-co-poly(ethylene glycol), ring-opening polymerization

1. INTRODUCTION

Polylactide (PLA) has found extensively use in the medical materials and devices, in particular for controlled drug delivery systems, temporary tissue fixation and tissue engineering [1]. The polymer possesses advantageous properties such as biodegradability, biocompatibility and good mechanical strength. Due to the above advantages, PLA has been grafted or blocked with several synthetic and natural polymer forming several copolymers (PEG-PLA, Polysacharides-PLA, PLA-polyglycolide,…) in order to widen its biomedical application such as nanocarriers for drug delivery systems or solid and hydrogel scaffolds for tissue engineering [2, 3]. Moreover, major disadvantages of PLA including its inherent brittleness and low toughness could be improved via the modification. Many current PLA (its copolymer) synthesis methods employ stannous octoate, since it has been shown to be very effective. Especially, high molecular weight PLA can only be synthesized by the ring-opening polymerization of lactide [4].

Star-shaped (co)polymers are three-dimensional hyperbranched structures and thermoplastic elastomers in which linear arms with the same molecular weight or different molecular weights emanate from a central core. Several types of star-shaped (co)polymer have been shown to be nontoxic, so these polymers have recently attracted much attention for biomedical and industrial applications, where they are used as motor oil additives, paint additives, in inkjet printing, as drug-delivery carriers, and reinforcing materials [5-7].

In the study, we introduce synthetic method in two steps of 4-arm star-shaped PLA-PEG via ROP and use of carbodiimide-coupling agent. The obtained copolymer was well-characterized its structure and molecular weight by ^{1}H-NMR and GPC.

2. EXPERIMENTAL SECTION

2.1. Materials

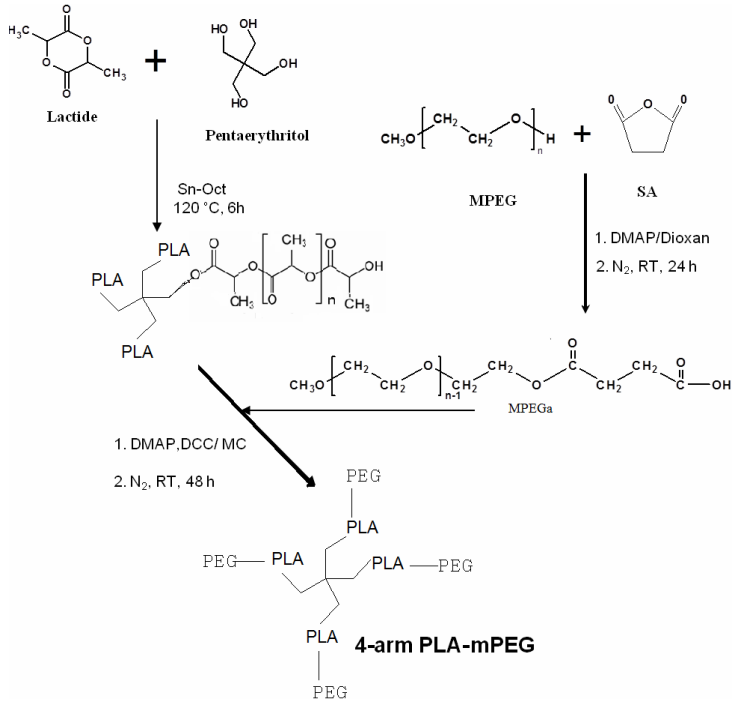
Lactide was supplied by Purac (Gorinchem, Netherland). Dicyclohexyl carbodiimide (DCC) was purchased from Sigma. Stannous octoate (Sn-Oct_2), pentaerythrytol (PTOL), dimethylamonium pyridine (DMAP) and succinic anhydride (SA) were purchased from Acros Organics. Monomethoxy polyethylene glycol (MPEG; *M*w 2000 g/mol) was obtained from Polyscience Inc. All other chemicals and solvents were used without further purification.

2.2. Synthesis of 4-arm PLA and its copolymer (scheme 1)

The 4-arm star-shaped polymer was prepared by ROP method. Brieftly, pentaerythritol (0.85 g, 6.25 mmol), lactide (12.5 g, 86.8 mmol) and Sn-Oct_2 (20 mg) were added to ampoule. The ampoule was connected with a Schlenkline, where an exhausting-refilling process with nitrogen occurred 3 times and sequently sealed under vacuum. The ampoule was put into an oil bath at 120 °C for 6 h. The system was cooled. The resulting product was dissolved in CH_2Cl_2 and poured dropwise into an excess of diethyl ether. The purified polymer was dried in a vacuum to obtain PLA macromonomer. ^{1}H NMR ($CDCl_3$)/ppm: δ = 1.60 (s, -CH_3, LA); 4.18 (-CH_2-, PTOL); 4,38 (-CH-, LA, next to the secondary hydroxyl end group); 5.16 (-CH-, LA). The resulting polymer was obtained in high yield around 88 %.

Synthesis of MPEGa: MPEG (10 mmol) was esterified with succinic anhydride (1.1 mmol) using DMAP catalyst and dioxin solvent at room temperature for 24 hr. The resulting product was concentrated and dropwised into an excess of diethyl ether. The purified polymer was dried in a vacuum to obtain MPEGa. ^{1}H NMR ($CDCl_3$)/ppm: δ = 2.60 (-CH_2-CH_2-, SA); 3.38 (s, -CH_3, MPEG); 3.62 (-CH_2-CH_2-, PEG); 4.20 (-CH_2-, next to SA).

4-arm star-shaped PLA-PEG was synthesized from the macromonomer and MPEGa by use of carbodiimide coupling agent. Brieftly, MPEGa (6 mmol) was activated for 5 min with DCC in dioxan. 4-arm PLA (5 mmol) and DMAP were added to the mixture and stirred at room temperature for 48 hr. The resulting product was concentrated and dropwised into an excess of diethyl ether. The purified polymer was dried in a vacuum to obtain 4-arm-PLA-PEG. ^{1}H NMR ($CDCl_3$)/ppm: δ = 1.58 (s, -CH_3, LA); 2.64 (-CH_2- CH_2-, SA); 3.62 (-CH_2-CH_2-, PEG); 4.21 (-CH_2-, PEG, next to SA ester group); 5.17 (-CH-, LA).



Scheme 1: Synthesis of 4-arm PLA-PEG via ROP and use of carbodiimide coupling agent

2.3. Characterizations

Nuclear magnetic resonance (NMR) data was collected using $CDCl_3$ as solvent on a Bruker AC 500 MHz spectrometer. The average molecular weights of 4-armPLA and its copolymer were collected from Gel Permeation Chromatography (GPC) technique using Agilent 1100-GPC system. Tetrahydrofuran was used as an eluent at a flow rate of 1 mL/min.

3. RESULTS AND DISCUSSION

3.1. Structural assignment of 4-arm PLA-PEG

Figurre 1 shows the ^{1}H NMR spectrum of a 4-arm PLA. A signal appeared at 4.19 ppm that was referred to methylene proton of PTOL. Two signals at 5.16 ppm and 1.6 ppm were assigned to a methine proton and methyl protons of the PLA block, respectively. Another methine proton signal (b', next

to the secondary hydroxyl end group of 4-arm PLA) appeared at 4.38 ppm. These indicate success in ring-opening polymerization of the lactide. According to several studies, ROP has been shown to be very effective for synthesis of PLA, especially, high molecular weight PLA.

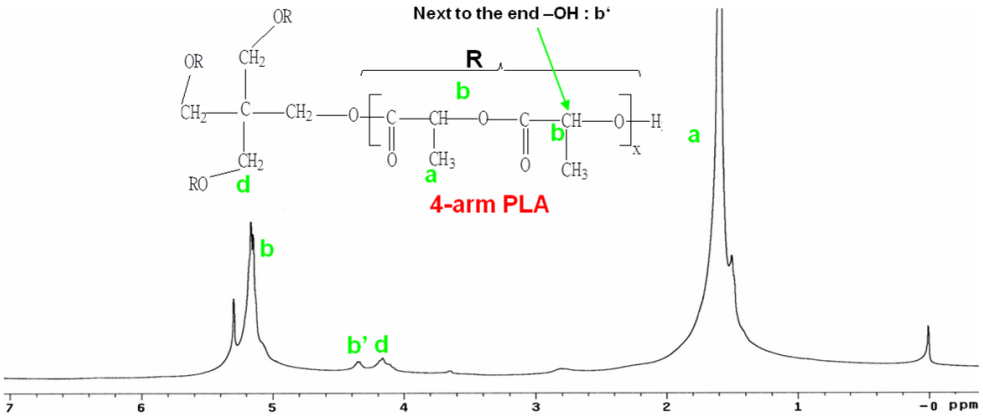


Figure 1: ^{1}H-NMR spectrum of 4-arm PLA

Structure of MPEGa and 4-arm PLA-PEG were also well-defined by ^{1}H-NMR spectra as shown in Fig. 2. Beside of several proton signals appearing in ^{1}H-NMR spectrum of 4-arm PLA, A signal at 3.62 ppm was derived from the methylene protons of oxyethylene, indicating the presence of a PEG chain. Successful coupling reaction between 4-arm PLA and MPEGa by using carbondiimide agent could be seen in the Fig. 2, in which, the methine proton signal (next to the secondary hydroxyl end group of 4-arm PLA) disappeared in 4-arm PLA-PEG.

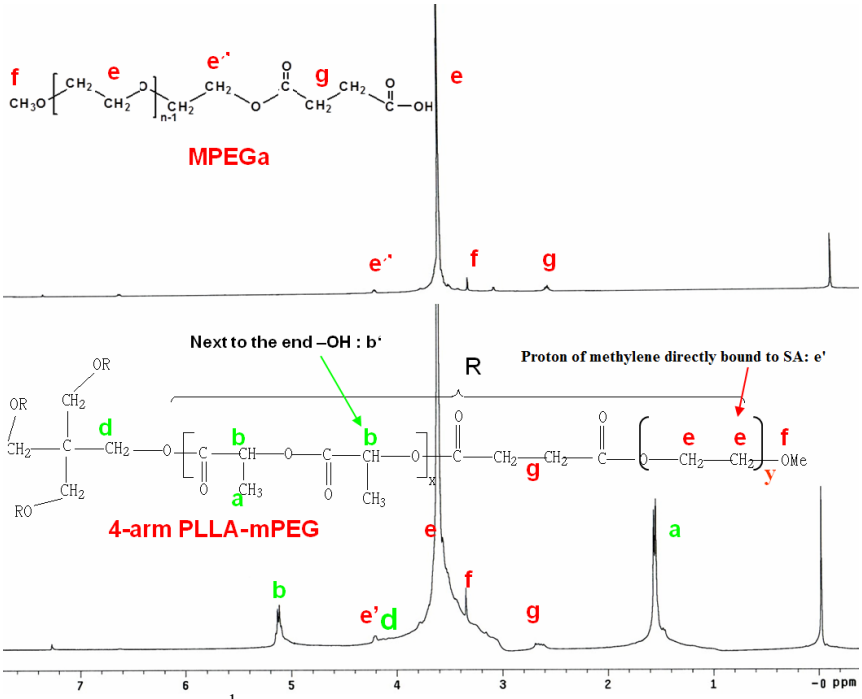


Figure 2: ^{1}H-NMR spectra of MPEGa and 4-arm PLA-PEG

3.2. Conversion of 4-arm PLA-PEG by ROP and carbodiimide-coupling reaction

For 4-arm PLA, The GPC results revealed that the molecular weights linearly increased with the increase of the molar ratios of the lactide and pentaerythrytol in feed. Table 1 summarizes the feed amounts and synthetic results of the 4-arm PLA and 4-arm PLA-PEG copolymers. The chain lengths of the PLA block were tailored by varying the feed

amounts in accordance with the feed ratios of lactides.

According to resulting GPC of copolymers, grafting degree of MPEGa in copolymers was over 75 %, meaningly, more than of 3 MPEG chains were grafted to 4-arm of PLA. The polydispersity indices (PDI, Mw/Mn) of all copolymers were also maintained at ranging 1.1-1.2, indicating the monodisperse properties of the synthesized copolymer chains.

Table 1: The feed amount and synthetic results of the 4-arm PLA-PEG block copolymers

No	PTOL	Lactide	Feed mol (L:PTOL)	Sn-Oct$_2$	Mn	Mw	Mw/Mn
1	0.85 g	12.5 g	28	0.02 g	4900	5300	1.27
2	0.85 g	18.75 g	42	0.02 g	6000	7400	1.23
3	0.85 g	25 g	56	0.02 g	8800	11400	1.29
	Mn (4-arm PLA)		Mw (4-arm PLA)	MPEGa			
1	4900		5300	2000	12100	14800	1.13
2	6000		7400	2000	12700	16100	1.27
3	8800		1140	2000	17200	19500	1.13

3.3. Solubility and gelability of the copolymer

It is well-known that PLA is a hydrophobic polymer and insoluble in water. So in several applications, the polymer is blocked or grafted with water soluble polymers such as PEG, polysaccharides, etc. In this study, when increasing molecular weight of PLA domain increase resulted in a hydrophobic copolymer (insoluble in water) as shown in figure 3. Moreover, the copolymer could form hydrogel in water when it was used at copolymer concentration over 30 %.

No	Mn	MPEGa	Water solubility	Gelation
1	12100	2000	Soluble (<30%)	+
2	12300	2000	Soluble (<30%)	+
3	17215	2000	Insoluble	-

Figure 3: Effect of synthetic results on water solubility and gelability

The obtained results from the study could be background to synthesize many kinds of star-shaped PLA-based copolymer matching with each typical application in biomedical and industrial application.

4. CONCLUSION

4-arm star-shaped PLA-PEG copolymers were synthesized via ROP and use of carbodiimide-coupling agent. The obtained copolymer was well-characterized its structure and molecular weight by ^{1}H-NMR and GPC, which could indicate that ROP and the coupling reaction are two effective methods to synthesize star-shaped PLA-PEG copolymer. These methods should be extensively studied to obtain several novel materials for biomedical and industrial applications.

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Corresponding author: **Tran Ngoc Quyen**
Institute of Applied Materials Science, VAST,
1 Mac Dinh Chi, Ho Chi Minh City
Email: tnquyen@iams.vast.vn.