

Synthesis of amphiphilic poly(*N*-vinylpyrrolidone)-*b*-poly(ϵ -caprolactone) block copolymers by a combination of ROP and RAFT

Y. C. Yu, H. W. Kang, D. W. Lee, B. R. Ki, J. H. Youk*

Department of Advanced Fiber Engineering, Division of Nano-Systems,
Inha University, Incheon, South Korea

* youk@inha.ac.kr

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1 Introduction

Amphiphilic block copolymers composed of biocompatible hydrophilic and hydrophobic blocks have been attracted great attention as nano-sized carriers for poorly water-soluble drugs.[1-5] In our previous study,[6] synthesis of a biocompatible amphiphilic block copolymer of poly(*N*-vinylpyrrolidone)-*b*-poly(ϵ -caprolactone) (PVP-*b*-PCL) by a combination of cobalt-mediated radical polymerization and ring-opening polymerization (ROP) was investigated. Well-defined PVP-*b*-PCL block copolymer with $M_n=18,000$ ($M_w/M_n=1.35$) was successfully synthesized, and its critical micelle concentration was determined to be 0.015 mg/mL.

In this study, synthesis of biocompatible PVP-*b*-PCL block copolymers by a combination of ROP and reversible addition-fragmentation chain transfer (RAFT) polymerization was investigated. PCL synthesized by ROP was first modified into macro-chain transfer agent (PCL-CTA), and then the RAFT polymerization of *N*-vinylpyrrolidone (VP) was consecutively conducted using PCL-CTA. It was found that this method also could successfully produce PVP-*b*-PCL block copolymers with very narrow molecular weight distributions without any residual metal impurities.

2 Experimentals

2.1 Materials

VP (Aldrich >99%), ϵ -caprolactone (CL, Aldrich, 99%) were purified by passing through a column filled with neutral alumina, and distilled prior to use. Tin(II) 2-ethylhexanoate ($\text{Sn}(\text{EH})_2$, Aldrich, 95%), 2,2'-azobis(4-methoxy-2,4-dimethyl valeronitrile) (V-70, Wakko, 96%), potassium ethyl xanthogenate (Aldrich, 96%) were used as received.

2.2 Synthesis of PCL-OH

PCLs with various molecular weights were synthesized using different feed ratios of butanol/CL. PCL ($M_n=5,100$ g/mol, $\text{PDI}=1.21$) was synthesized as follows: Butanol (0.1g, 1.3 mmol), CL (7.47 mL, 0.0675 mol), and $\text{Sn}(\text{EH})_2$ was dissolved in 7.47 mL of toluene. After three freeze-pumping-thaw cycles, the vial was sealed under vacuum and heated at 90 °C for 24 h. The product was precipitated in diethyl ether and dried under vacuum for 24 h.

2.3 Synthesis of PCL-Br

PCL-OH (0.5 mmol) and TEA (0.4 mL, 3.1 mmol) were dissolved in 100 mL of anhydrous THF at 0 °C. Then, 2-bromopropionyl bromide (0.2 mL 1.6 mmol) was drop wised for 15 min. The solution was stirred for 24 h. After desire time, salt was removed by filtration and solvent was evaporated. Product was precipitated in diethyl ether and dried under vacuum for 24 h.

2.4 Synthesis of PCL-CTA

PCL-Br (0.4 mmol) and potassium ethyl xanthogenate (0.7 g, 4.3 mmol) was dissolved in 150 mL of THF at room temperature and stirred for 48 h. THF was removed by evaporation and the product was precipitated in methanol/water for 3 times and dried under vacuum for 24 h. The degree of reaction of PCL-Br was determined by $^1\text{H-NMR}$.

2.5 Polymerization of PCL-*b*-PVP

PCL-CTA (0.04 mmol) and V-70 (2.1 mg, 0.01 mmol) were dissolved in 1 mL of anisole, and

degassed VP (0.55 mL, 5.2 mmol) was added under a N₂ atmosphere. The mixture was stirred at 30 °C for 24 h. The product was precipitated in diethyl ether and dried under vacuum for 24 h. The monomer conversion was determined by gravimetric method.

2.6 Preparation of PVP-*b*-PCL Micelles

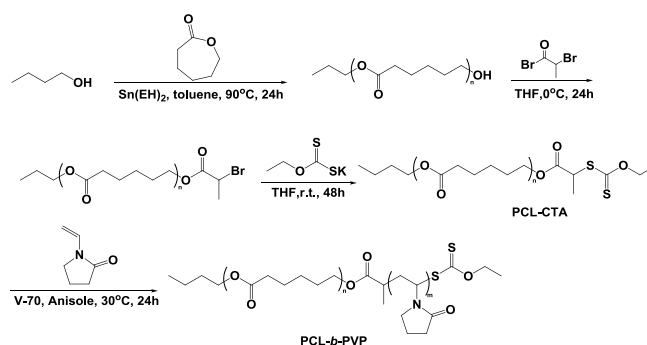
A micelle solution of PVP-*b*-PCL was prepared by adding 10 mL of deionized water dropwise to 1 mL of a PVP-*b*-PCL solution in DMF (2 mg/mL). The solution was dialyzed (cut-off 3500 Da) against distilled water at 4 °C for 1 day.

2.7 Characterization

Molecular weight and molecular weight distribution of the polymers produced were determined using gel permeation chromatography. The measurement was conducted with a Young Lin SP930D solvent delivery pump and RI750F differential refractometer using two columns (GPC KD-G and KF-806, Shodex) columns with DMF as the eluent (40 °C, flow rate of 1 mL/min). Linear polystyrene standards were used for calibration. A 400 MHz Varian VXR-Unity NMR spectrometer was used for ¹H-NMR analysis. The micellar size and size distribution were determined by dynamic light scattering (DLS) using a BI-200SM particle size analyzer. Each analysis lasted 360s and was performed at room temperature with a detection angle of 90°. The concentration of the polymer solution was 0.2 mg/mL. The morphology of the copolymer micelles was investigated using a JEM-2100F transmission electron microscope operating at an accelerating voltage of 120 kV. For these measurements, a drop of aqueous PVP-*b*-PCL solution (0.2 mg/mL) was deposited onto a 200 mesh copper grid that had been coated with carbon.

3 Results and Discussion

In order to prepare PCL-*b*-PVP, PCL-OHs were first synthesized by ROP at different feed ratios of CL/butanol at 100 °C, and then modified to PCL-CTA (Scheme 1).

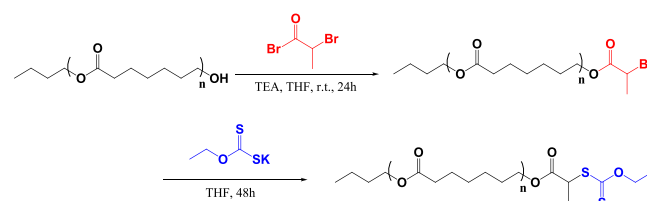


Scheme 1. Synthesis route for PCL-*b*-PVP.

Table 1 lists the polymerization results of PCL-OH. The molecular weights of PCL-OH were very close to theoretical molecular weights, and they exhibited very narrow molecular weight distributions.

Table1. ROP of CL using butanol as an initiator

Entry	CL/butanol molar ratio	Conv. (%)	M _n (NMR) (g/mol)	M _w /M _n
1	50	98	5100	1.21
2	100	98	11600	1.20
3	150	93	16000	1.16



Scheme 2. Synthetic route of PCL-Br and PCL-CTA.

PCL-OH was modified to PCL-CTA.(Scheme 2) Fig. 2 shows the typical ¹H-NMR spectra of the PCL-OH, PCL-Br, and PCL-CTA. PCL-OH showed the specific methyl peak at 3.6 ppm (-CH₂-OH) and methane peak at 0.9 ppm (-CH₃) of butanol. Modification to PCL-Br was confirmed from the appearance of methylene protons (-CH-) at 4.3 ppm and disappearance of methyl group at 3.6 ppm of PCL-OH. The conversion of bromo end-group into the corresponding xanthate end-group was confirmed by the appearance of the new characteristic peak at 4.6 ppm attributed to the methylene proton of the xanthate end group.

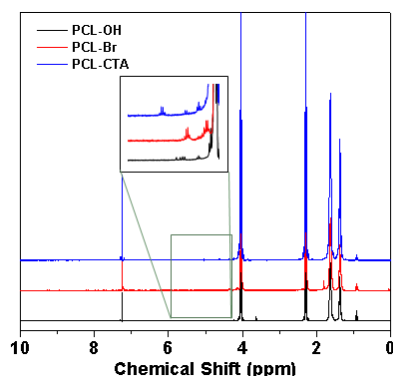


Fig. 1. ^1H -NMR of PCL-OH, PCL-Br, and PCL-CTA.

PCL-*b*-PVP block copolymers were synthesized by RAFT polymerization at 30 °C at different feed ratios of VP/PCL-CTA. Table 2 lists the polymerization results of PCL-*b*-PVP block copolymers.

Table 2. RAFT polymerization of PCL-*b*-PVP

	Mn of PCL-CTA	Feed ratio of VP/ PCL-CTA	Conv. (%)	$M_{n,theo}$ (g/mol)	$M_{n,GPC}$ (g/mol)	M_w/M_n
1	5100	100/1	94.5	15600	46100	1.28
2	5100	200/1	79.5	22800	50700	1.28
3	5100	300/1	54.0	23100	47900	1.27
4	5100	400/1	91.1	46700	96400	1.36
5	11600	100/1	42.0	16300	32200	1.25
6	11600	200/1	52.5	23300	40500	1.28
7	11600	300/1	66.6	33800	45300	1.24
8	11600	400/1	68.2	41900	53000	1.24
9	16000	100/1	49.5	21500	41400	1.15
10	16000	200/1	58.5	29000	52330	1.19
11	16000	300/1	52.1	33400	49000	1.24
12	16000	400/1	73.3	48600	66500	1.22

All of the PCL-*b*-PVP block copolymers had very narrow molecular weight distributions. Figs. 2 and 3 show the GPC traces of PCL-CTA and the resulting PCL-*b*-PVP block copolymers.

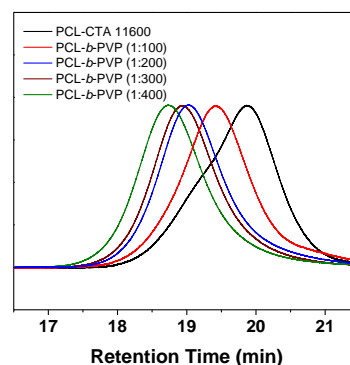


Fig. 2. GPC traces of PCL-CTA ($M_n=11,600$ g/mol) and the resulting PCL-*b*-PVP block copolymers.

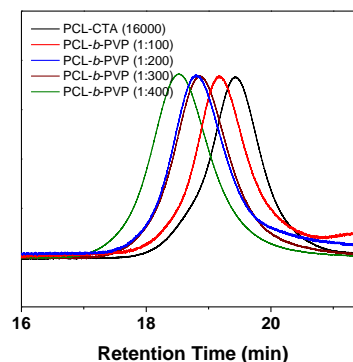


Fig. 3. GPC traces of PCL-CTA ($M_n=16,000$ g/mol) and the resulting PCL-*b*-PVP block copolymers.

GPC traces of PCL-*b*-PVP were monomodal without any tailing caused by residual PCL-CTA, indicating that the initiation efficiency was very high, and the RAFT polymerization was well-controlled.

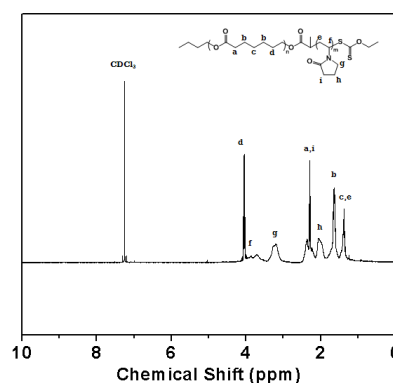


Fig. 4. ^1H -NMR spectrum of PCL-*b*-PVP in CDCl_3 .

Fig. 4 shows the ^1H -NMR spectrum of PVP-*b*-PCL ($M_n=49,000$, $\text{PDI}=1.24$). The peaks in the spectrum are attributed to both the PVP and PCL units. The chemical composition of the PVP-*b*-PCL was evaluated from the relative intensities of the ^1H -NMR peaks at 3.19 and 4.05 ppm, which are attributed to the PVP ring methylene group in the α -position to the nitrogen atom and to the PCL methylene in the α -position to the ester oxygen, respectively. The molar ratio of the PCL and PVP units was 1/1.06.

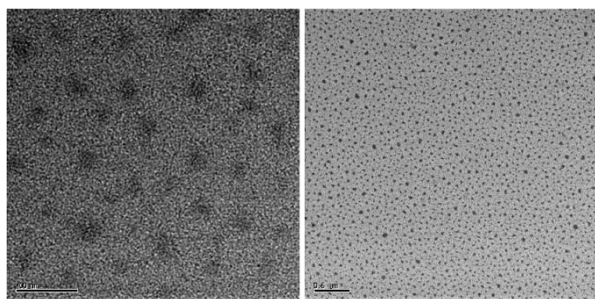


Fig. 5. TEM images of the PCL-*b*-PVP micelles.

The micellar characteristics of PVP-*b*-PCL in aqueous solution were investigated using DLS, and TEM. TEM was used to confirm the formation of the micelles and their sizes. Fig. 5 shows the TEM images of the PCL-*b*-PVP micelles. The micelle solution of the PCL-*b*-PVP was prepared by adding deionized water dropwise to the PVP-*b*-PCL solution in DMF (2 mg/mL). It can be seen that the micelles are spherical in shape.

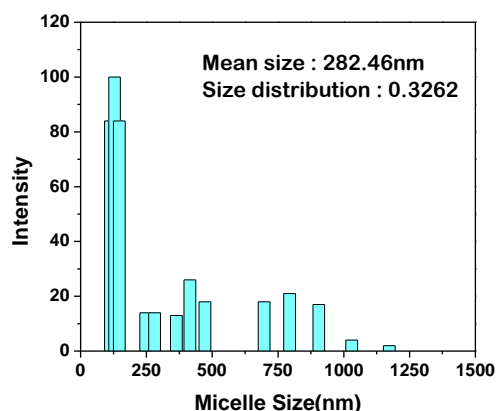


Fig. 6. Particle size distribution of the PCL-*b*-PVP micelles

The particle size and size distribution of the micelles were investigated further by DLS (Fig. 6). The micelles have an average diameter of 282.46 nm and a size distribution value of 0.3262.

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