Novel Amphiphilic Diblock Copolymer of Low Molecular Weight Poly(*N*-vinylpyrrolidone)-*block*-poly(D,L-lactide): Synthesis, Characterization, and Micellization

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ABSTRACT: Low molecular weight poly(*N*-vinylpyrrolidone) (PVP) with a hydroxyl group at one end was successfully synthesized by free radical polymerization of *N*-vinyl-2-pyrrolidone (NVP). Using isopropyl alcohol as solvent and 2-mercaptoethanol as chain transfer agent, a control over molecular weight (MW) profile of PVP was obtained, leading to average-number MW as low as 2500 Da and polydispersity indexes close to 1.5. MALDI−TOF mass spectrometry indicated that the insertion of hydroxyl group on one chain end was quantitative. Hydroxyl-terminated PVP was used as macroinitiator in ring-opening polymerization of D,L-lactide yielding amphiphilic poly(*N*-vinylpyrrolidone)-*block*-poly(D,L-lactide) (PVP-*b*-PDLLA) diblock copolymer with polydispersity indexes as low as 1.14. PDLLA contents could be tuned according to the feed ratio of DLLA, leading to molar percents up to 47%. The well-defined diblock copolymer self-assembles into micelles in aqueous solution. Polymeric micelles, composed of PVP-*b*-PDLLA with PVP M_n of 2500 and PDLLA molar content of 45%, displayed monodispersed size distribution of about 40 nm. The critical association concentration of micelles was determined to be around 6 mg/L.

1. Introduction

In the past decade, the use of various "living"/controlled polymerizations have resulted in well-defined copolymers, with different designs. For instance, nitroxide-mediated polymerization, dithio component-mediated reversible addition−fragmentation chain transfer, and atom transfer radical polymerization (ATRP) are different examples of "living"/controlled processes, which offer control over molecular weight (MW) and on the molecular architecture (e.g., diblock, grafted or tapered copolymers). However, a few monomers such as vinyl acetate and *N*-vinyl-2-pyrrolidinone (NVP) do not form radicals stabilized by resonance and inductive effects, and therefore, the polymerization of these monomers have not yet performed efficiently by controlled radical polymerizations. Matyjaszewski et al.[1,2] reported the homopolymerization of NVP using Me_4Cyclam as a ligand. This synthetic pathway showed some limitations, and chain end functionalities are difficult to obtain.

In this study, our interest in functionalized and well-defined poly(*N*-vinylpyrrolidone) (PVP) was essentially based on the replacement of poly(ethylene glycol) (PEG) in diverse drug delivery systems. PEG is widely used as hydrophilic arm on the surface of nanoparticles,[3] liposomes,[4] and polymeric micelles (PM).[5−7] The PEG-based outer shell can actually prevent the nanocarrier uptake by the mononuclear phagocytic system via steric effect.[5−7] This prevention substantially improves the circulation time of PM in the bloodstream. In cancer treatment, this prolonged time generally results in a selective accumulation in a solid tumor due to the enhanced permeability and retention (EPR) effect of the vascular endothelia at the tumor site.[8−12] However, aggregation of nanoparticles with PEG as corona occurs during lyophilization, it features some limitations. PVP has been proven to be biocompatible[13] and has been extensively used in pharmaceutical industry. Particularly, PVP can be used as a cryoprotectant[14] and a lyoprotectant.[15] Hence, replacing PEG with PVP might help to overcome some freeze-drying problems.

Torchillin et al.[16] pioneered the study of PVP as hydrophilic corona of liposomes. The design of PM with PVP outer shell have presented so far promising features for pharmaceutical uses. Thus, Benahmed et al.[17] reported the preparation of PVP-based micelles consisting of biodegradable diblock copolymers. In the previous work, PVP synthesis using 2-isopropoxyethanol as chain transfer agent was inspired from previous paper of Ranucci et al.[18,19] However, this synthetic procedure produced a lack of control over MW, and did not quantitatively provide hydroxyl-terminated PVP,[17] essential for polymerizing D,L-lactide (LA). Moreover, the removal of 2-isopropoxy-ethanol from the polymer turned out to be difficult because of its high boiling point (42−44 °C at 13 mmHg) and its binding to PVP via hydrogen bonding.[13] Alcohol entrapment into polymer might cause problems for subsequent reactions which require anhydrous and aprotic conditions such as the synthesis of poly(D,L-lactide). Recently, Sanner et al.[20] reported the synthesis of hydroxyl-terminated PVP oligomers via free radical polymerization in isopropyl alcohol (IPA), using cumene hydroperoxide as an initiator. ^{1}H NMR spectra have shown that there were 1.3 end groups of 2-hydroxyisopropyl per chain. It is suggested that significant termination by bimolecular combination occurred, be-

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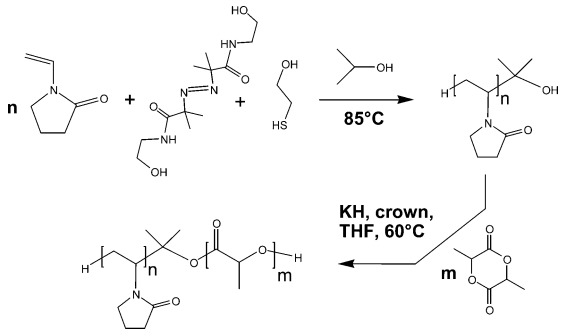
Scheme 1. Synthesis of PVPOH Homopolymer and PVP-*b*-PDLLA Diblock Copolymer



tween either a primary solvent radical and the propagating chain or two propagating chains.[20,21]

In this work, we have studied the synthesis of hydroxyl-terminated low molecular PVP using IPA and 2-mercaptoethanol as chain transfer agents. The molecular weight (MW), polydispersity index and functionality of PVP can be controlled. Then, such low MW PVP terminally bearing hydroxyl group were used as macroinitiator to synthesize PVP-*block*-poly(D,L-lactide) copolymers (PVP-*b*-PDLLA),via anionic polymerization of LA. The water molecules, which have strong binding with PVP chains were removed successfully prior to polymerization of LA. Self-assembly of PVP-*b*-PDLLA diblock copolymers have been extensively studied in aqueous media.

2. Experimental Section

2.1. Materials. *N*-vinyl-2-pyrrolidinone (NVP) and 2-mercaptoethanol (MCE) were purified by distillation. 3,6-Dimethyl-1,4-dioxane-2,5-dione, i.e., D,L-lactide (LA), was recrystallized twice in ethyl acetate. Tetrahydrofuran (THF) was distilled just before use over benzophenone/sodium couple as drying agent. 2,2′-Azobis(2-methyl-*N*-(2-hydroxyethyl)propionamide (AMPAHE) served as radical initiator and was used without further purification. Isopropyl alcohol (IPA), *N*,*N*-dimethylformamide (DMF), methylene chloride, diethyl ether, potassium hydride, *tert*-butyl alcohol (TBA, 99.5% pure), 18-crown-6. and AMPAHE were used as received. All the chemicals were purchased from Aldrich (Oakville, Ontario, Canada), except for AMPAHE that was purchased from Wako Chemicals (Richmond, VA).

2.2. Synthesis of Poly(*N*-vinylpyrrolidone) with a Hydroxyl-Bearing Chain End (PVPOH). As shown in Scheme 1, PVPOH was synthesized by free radical polymerization of NVP. A typical procedure is described as following. NVP (30 g, 270 mmol), AMPAHE (0.7783 g, 2.7 mmol), and MCE (0.844 g, 10.8 mmol) were dissolved in 540 mL of IPA. The solution was degassed with argon for 15 min. The polymerization was carried out at 85 °C for 24 h. Then, most of the IPA was removed under reduced pressure. Afterward, the polymer was precipitated in about 300 mL of diethyl ether. The polymer was dissolved in 60 mL of methylene chloride, and precipitated again in 300 mL of diethyl ether. Finally, the product (white powder) was transferred into a Whatman cellulose extraction thimble, and purified by diethyl ether Soxhlet extraction for 24 h. The polymer was dried at 80 °C under vacuum overnight.

2.3. Synthesis of Diblock Copolymer Poly(*N*-vinylpyrrolidone)-*block*-poly(D,L-lactide) (PVP-*b*-PDLLA). As illustrated in Scheme 1, PVP-*b*-PDLLA was synthesized by anionic polymerization of LA using PVPOH as macroinitiator. PVPOH (M_n: 2500) (15 g, 6 mmol) was dissolved in 250 mL of toluene. Using a Dean−Stark trap, the polymer was dried with toluene as azeotropic solvent. Toluene was then removed by distillation under reduced pressure. The polymer was dried under vacuum over P_2O_5 at 150 °C for 4 h. After the reaction was cooled to room temperature, potassium hydride (KH, 278.4 mg, 6.96 mmol) in mineral oil was added into the flask under argon atmosphere. The flask was placed under vacuum again for 30 min. A volume of 75 mL of freshly distilled and anhydrous THF was added to dissolve the mixture. After the polymer was dissolved, the solution was stirred for 10 min. LA (30 g, 20.8 mmol) and 18-crown-6 (1.84 g, 6.96 mmol), both previously dried under vacuum at 80 °C for 4 h, were placed in a flask and then dissolved with a volume of 150 mL of anhydrous THF. The solution was transferred into the alcoholate solution under argon atmosphere, and stirred. The polymerization was carried out at 60 °C for 18 h. PVP-*b*-PDLLA was precipitated in 1.2 L of cold diethyl ether. The polymer was collected and dried under vacuum at room temperature. PVP-*b*-PDLLA (20 g) was dissolved in 100 mL of DMF. Then 100 mL of deionized water was added to the polymer solution for micellization. The micelle solution was placed in dialysis bag (Spectrum, MW cutoff: 3500) and dialyzed against water (8 L) at 4 °C for 24 h. Water was changed at least four times over that period. The aqueous solution was centrifuged at 11600*g* at 4 °C for 30 min, and then filtered through a 0.2 μm filter. The filtered solution was collected and freeze-dried during 48 h. The diblock copolymer was stored at −80 °C to avoid degradation.

2.4. Size-Exclusion Chromatography (SEC). The SEC analysis was carried out on a Breeze Waters system using refractometer Waters 2410 (Milford, MA) and light-scattering (LS) detector Precision detectors PD2000 (Bellingham, MA). LS data were collected at 15 and 90°. SEC was performed in DMF containing 10 mM LiBr. 200 μL of solution (about 3%w/v) was injected through a series of three columns, Styragel Waters HT2, HT3, and HT4, at a flow rate of 1.0 mL/min, to separate MW ranging from 10^2 to 10^6. The temperature of columns (separation) was maintained at 40 °C, while the temperature of refractometer/LS detectors was set at 35 °C. The instrument was calibrated with monodisperse polystyrene standards.

2.5. Nuclear Magnetic Resonance (^{1}H NMR). ^{1}H NMR spectra were recorded on Varian 300 and Bruker AMX 600 spectrometers (Milton, Ontario, Canada) in $CDCl_3$ at 25 °C. The PDLLA content (% mol) was determined using eq 1.

$$\text{PDLLA (\% mol)} = \frac{I_{5.2\text{ppm}}}{\left[\frac{(I_{4.5-0.8\text{ppm}}) - 3I_{5.2\text{ppm}}}{9_{\text{H}}}\right] + I_{5.2\text{ppm}}} \times 100 \quad (1)$$

where $I_{5.2\ \text{ppm}}$ represents signal intensity at 5.2 ppm, and corresponds to the tertiary proton (α-position of carbonyl group). This signal was normalized to 1. ^{1}H NMR was also performed in deuterated water (D_2O) at 25 °C to prove the presence of self-assembled micelle.

2.6. Elementary Analysis (EA). EA was carried out in an oxidative atmosphere at 1021 °C. Using a thermal conductivity probe, the amount of nitrogen oxide, carbonic acid, sulfur oxide (NO_2, SO_2, and CO_2) and water were quantified and provided the amount of nitrogen (N), carbon (C), hydrogen (H) and sulfur (S) atoms into the sample. The block compositions of PVP and PDLLA correspond to the repeating unit of C_6H_9NO and $C_3H_4O_2$, respectively. The PDLLA content (% mol) was determined using eq 2 and based on the content of C and N atoms.

$$\text{PDLLA (\% mol)} = \frac{7\text{C} - 36\text{N}}{7\text{C} - 18\text{N}} \times 100 \quad (2)$$

2.7. MALDI—TOF Spectrometry for Analysis of PVP. MALDI−TOF mass spectra were obtained with a Micromass TofSpec-2E mass spectrometer (Manchester, U.K.). The instrument was operated in positive ion reflectron mode with an accelerating potential of +20 kV. Spectra were acquired by averaging at least 100 laser shots. Dithranol was used as matrix and chloroform as solvent. Sodium iodide was dissolved in methanol and used as the ionizing agent. Samples were

prepared by mixing 20 μL of polymer solution (6−8 mg/mL) with 20 μL of matrix solution (10 mg/mL) and 10 μL of a solution of ionizing agent (2 mg/mL). Then 1 mL of these mixtures was deposited on a target plate, and the solvent was removed in a stream of nitrogen. An external multipoint calibration was performed by using bradykinin (1060.2 g/mol), angiotensin (1265.5 g/mol), substance P (1347.6 g/mol), renin substrate tetradecapeptide (1759.0 g/mol), and insulin (5733.5 g/mol) as standards.

2.8. Viscosity-Average Molecular Weight (M_v) Determination of PVP. The limiting viscosity number "*K* value" (or Fikentscher *K* value) of homopolymer PVPOH was determined in accordance with BASF protocol (US Pharmacopeia) using Ubbelohde viscometer Type 1a. With the *K* value, M_v is directly obtained from the following equation:

$$M_v = 22.22(K + 0.075K^2)^{1.69} \quad (3)$$

2.9. Critical Association Concentration (CAC). CAC was measured by the steady-state pyrene fluorescence method.[17] The procedure is described briefly as follows. Several polymeric solutions in water containing 10^{-7} M of pyrene were prepared and stirred overnight in the dark at 4 °C. Steady-state fluorescent spectra were measured ($\lambda_{ex} = 390$ nm) after 5 min under stirring at 20 °C using a Series 2 Aminco Bowman fluorimeter (Spectronic Instruments Inc., Rochester, NY). Experiments were run in duplicate.

2.10. Dynamic Light Scattering (DLS). DLS was used for the determination of particle size in water. For this analysis, a series of aqueous solutions of PVP-*b*-PLA with concentrations of 0.5, 1, and 2 mg/mL was prepared by dissolving the polymer directly in water. The solutions were analyzed with a Malvern instrument Autosizer 4700 (Mississauga, Ontario, Canada). Each measurement was carried out in triplicata at 25 °C at an angle of 90 °C. The size distribution of particles and the intensity mean size were recorded.

2.11. Thermogravimetry Analysis (TGA). TGA measurements were collected on a TA Instrument Hi-Res TGA 2950 Thermogravimetric analyzer (New Castle, DE). About 1 mg of polymer was used for the experiments. Temperature ramp was 20 °C/min between room temperature and 700 °C. The residual amount of water was quantified after freeze-drying. PDLLA and PVP contents (% w/w) in diblock copolymer were also analyzed.

2.12. Differential Scanning Calometry (DCS). DSC measurements were carried out on a DSC Q1000 from TA instruments (New Castle, DE). It is equipped with a refrigerated cooling system (RCS) and interfaced with a PC running Q series explorer. The data were analyzed with the software TA Universal Analysis 2000, version 3.6c. The following method was used for all the runs: (a) equilibrate at −20 °C, (b) hold isothermal for 1 min, (c) ramp 10 °C/min until 150 °C, (d) hold isothermal for 5 min, (e) ramp 10 °C/min until 20 °C, (f) hold isothermal for 5 min, and (g) ramp 10 °C/min until 150 °C.

All samples were run in the T4P heat flow mode, which provides the best quality of results. It also takes into account the cell resistances and capacitances, as well as the effect of the pans. Calibration was made using, in terms of enthalpy, zero-temperature and temperature ramp.

3. Results and Discussion

3.1. Synthesis of Hydroxyl-Terminated PVP Oligomers (PVPOH). Mercapto compounds are good chain transfer agents (CTA),[18,19,22] capable of functionalizing chain ends and controlling indirectly polymer MW. Hydroxyl group can be introduced at the end of polymer chains by using MCE as CTA in free radical polymerization of vinyl monomers. However, it was reported that when NVP was radically polymerized in the presence of mercapto derivatives, only a small fraction of functionalized short oligomers was obtained. Moreover, a large amount of high MW polymers without

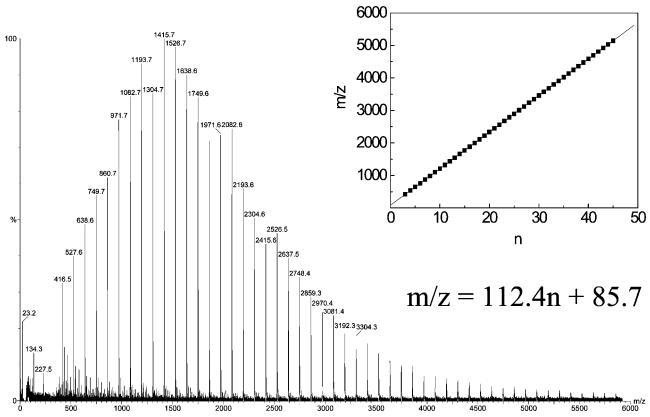


Figure 1. MALDI−TOF spectrum of PVPOH-2500.

terminal functionality was found in the product. This was due to the high transfer constant of thiol to NVP.[18,19] As we discussed in the Introduction, in the free radical polymerization of NVP, radicals can transfer to solvent and possibly to a monomer. Hence, functionalized PVP have been synthesized using particular solvents (i.e., isopropoxyethanol[18]). However, the functionality of PVP was not under control quantitatively.[18,19] To obtain quantitative hydroxyl-terminated PVP homopolymers and also to control their MW profile, IPA, MCE, and a hydroxyl-bearing azo initiator (AMPAHE) have been all combined in the present work for the radical polymerization of NVP (Scheme 1).

As shown in Figure 1, MALDI−TOF spectrometry showed that the majority of PVP chains (>95%) bore a hydroxyl group at one chain end of PVP. Most chains featured a 2-hydroxyisopropyl group at the end, meaning that the solvent was the main species initiating polymer growth. These results are consistent with previous studies.[13,17−21] Using diluted conditions of polymerization, MALDI−TOF data suggests that no significant termination by bimolecular combination occurred during the reaction, because the mass of chain end was only that of IPA plus the sodium ion ($59_{IPA} + 23_{Na^+} = 82$, at *n* equals 0 in the linear equation). Two other distributions were also observed, which were attributed to PVP bearing MCE and NVP as chain end, respectively. These distributions were only significant at low values of *m*/*z* (<1000 g mol^{-1}) and represented less than 5% of the spectrum, related to MCE- and NVP-terminated chains. Since MCE is more efficient as CTA than IPA, all the MCE were consumed early in the reaction. Previous syntheses of PVP in THF (instead of IPA) using MCE have shown that radicals may also transfer directly to monomers.[18,19] In consequence, by combining MCE and IPA as CTA, the synthesis of low MW PVP could be achieved with the quantitative insertion of hydroxyl group on one chain end.

The molecular weights of PVPOH were determined by SEC and viscometry (Table 1). Polydispersity indexes (PI) of about 1.5 indicated that radical transfers prevailed over bimolecular combination, being consistent with MALDI−TOF data. Results from SEC and viscometry were in good agreement. M_v might be slightly overestimated because the viscosity analysis has been carried out in water and there is a high degree of association between PVPOH and water.[13] Furthermore, the SEC characterization was done in DMF/LiBr where the extent of association is negligible. Analysis of PVPOH by EA revealed that the weight ratios of N/C

Table 1. Characterization of Hydroxyl-Terminated PVP Homopolymers

polymers	M_n SEC[a] (g mol^{-1})	M_w SEC[a] (g mol^{-1})	M_w/M_n SEC[a]	M_v viscometry[b] (g mol^{-1})	N/C EA
PVPOH-2300	2300	3600	1.56	5400	0.192
PVPOH-2500	2500	4000	1.60	5500	0.190
PVPOH-4000	4000	7400	1.85	9000	0.193
PVPOH-6100	6100	9600	1.57	11 100	0.197

[a] SEC analysis was performed in DMF containing 10 mM LiBr. [b] Viscometry analysis was performed in M.-Q. water.

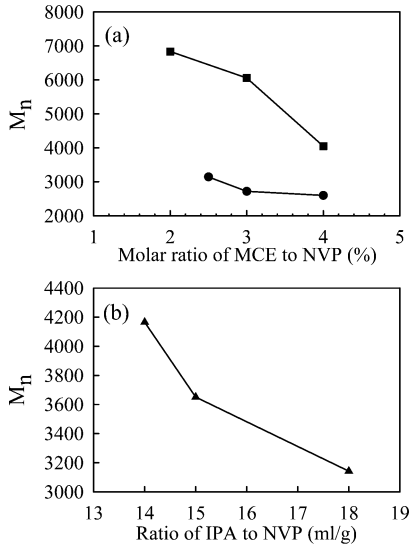


Figure 2. Influence of the ratios of (a) MCE and (b) IPA to NVP on the M_n of PVPOH: (a) ratios of IPA/NVP fixed at (●) 18 mL/g and (■) 12 mL/g; (b) ratio of MCE/NVP fixed at (▲) 2.5%.

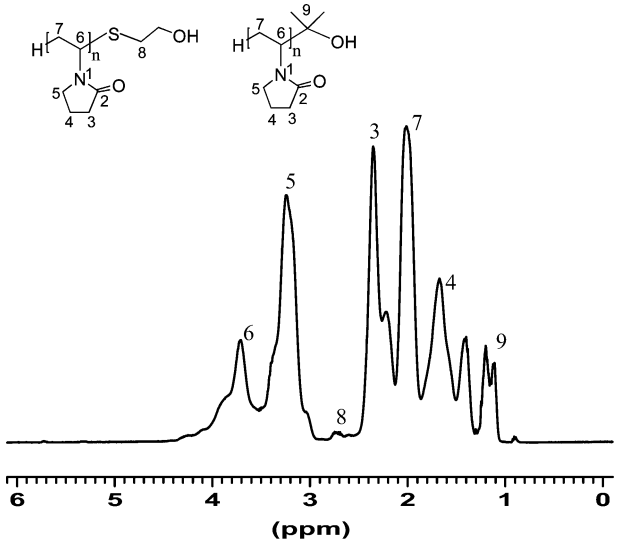


Figure 3. ^{1}H NMR spectrum of PVPOH-2500 in $CDCl_3$.

atoms in all PVPOH were similar to the theoretical number (0.194).

Molecular weight profile of PVPOH was controlled by changing ratios of both MCE (CTA) and IPA, to NVP monomer. As expected, the molecular weights of PVPOH decreased when either CTA/NVP or IPA/NVP ratios increased (Figure 2).

The ^{1}H NMR spectrum of PVPOH-2500 in $CDCl_3$ is shown in Figure 3. The chemical shifts of the methylene groups of MCE are 2.7 and 3.8 ppm. When MCE was introduced at the end of the PVPOH chains by forming S−C bond instead of S−H bond, the peaks of one methylene group appear at 2.7 and 2.75 ppm instead of 2.7 ppm, and the signal located around 3.8 ppm is overlapped with the peaks of PVPOH in the spectrum. Signals between 1.1 and 1.3 ppm are assigned to the methyl protons of the 2-hydroxyisopropyl group (IPA fragment). These results suggest that PVP radicals transferred to both MCE and IPA, and this is in agreement with the results obtained from MALDI−TOF spectrometry.

3.2. Synthesis of PVP-*b*-PDLLA Copolymers. Potassium hydroxylate derivatives are widely used for anionic ring-opening polymerization of LA.[23−25] In this work, the reaction between the OH group at the chain end of PVPOH and potassium hydride produced potassium PVP−hydroxylate as macroinitiator for the polymerization of LA. Water and alcohol molecules in the reaction system may initiate the formation of free PLA homopolymer. Since there are strong hydrogen bonds between PVP and water as well as alcohol, residues of these protic solvents, which interact with the polymer are difficult to remove.[13] In the present case, low MW PVPOH's were synthesized in IPA. Therefore, traces of IPA and water molecules might be contained in the polymer. Two drying steps were required for solvent removal. Briefly, at first, PVPOH was dissolved in toluene and then, an azeotropic distillation was made. Then, the polymer was dried under vacuum at 150 °C over P_2O_5 for 4 h. The polymer was actually molten under these conditions and resulted in a highly dried material.

MWs and PI of PVP-*b*-PDLLA were determined by SEC using light-scattering and a differential refractometer as detectors (Table 2). As expected, PVP-*b*-PDLLA MWs were larger than that of corresponding PVPOH, while PI decreased. Anionic polymerization leads to very small PI.[23−25] Therefore, the second polymerization step might decrease the PI of the diblock copolymer, suggesting that resulting materials were diblock copolymers and not a mixture of homopolymers. Another plausible explanation of lower PI was that PVP-*b*-PDLLA having shortest PVP chains were removed by the precipitation in diethyl ether.

The PDLLA contents (% mol) in the diblock copolymers was determined by ^{1}H NMR, EA, and SEC. A ^{1}H NMR spectrum of PVP-*b*-PDLLA copolymer in $CDCl_3$ is shown in Figure 4a. The peak at 5.2 ppm corresponds to the −CH− group of PDLLA. Signals from 0.8 to 4.5 ppm were assigned to all protons associated with the PVP segment, which overlap the peak of the PDLLA methyl group (1.4 ppm). PDLLA content was calculated using eq 1, and results are presented in Table 2. Since traces of water in PVP-*b*-PDLLA copolymers slightly overestimated the integration of PVP signals, EA was performed, and the amount of nitrogen and carbon atoms were used for the calculation of PLA content using eq 2. As shown in eq 2, hydrogen atoms of moisture, even from the polymer, are not taken in account into the calculation of PLA content by EA. Contrary to ^{1}H NMR analysis, EA results were quite constant and reproducible regardless of the moisture content EA analysis turned out to be suitable for the quantification of PDLLA content into PVP-*b*-PDLLA. Actually, PDLLA content from NMR data was usually 6−8% less than that determined by EA. Although SEC resulted in higher PDLLA contents (about 5%) than EA,

Table 2. Characterization of PVP-*b*-PDLLA Diblock Copolymers

PVP-*b*-PDLLA[a]	PVPOH used	M_n SEC (g mol^{-1})	M_w SEC (g mol^{-1})	M_w/M_n SEC	PDLLA (% mol) NMR[b]	EA[c]	SEC[d]
diblock-47	PVPOH-2500	4380	5000	1.14	38	47	54
diblock-35	PVPOH-2500	3840	5030	1.30	27	35	45
diblock-37	PVPOH-6100	8290	10 360	1.39	32	37	36
diblock-39	PVPOH-4000	6070	8960	1.48	34	39	44
diblock-45	PVPOH-2300	3770	4860	1.29	37	45	50

[a] Labeling based on PDLLA content into PVP-*b*-PDLLA diblock copolymers, obtained from EA. [b] From eq 1. [c] From eq 2. [d] From the DM_n of PVPOH and its corresponding PVP-*b*-PDLLA.

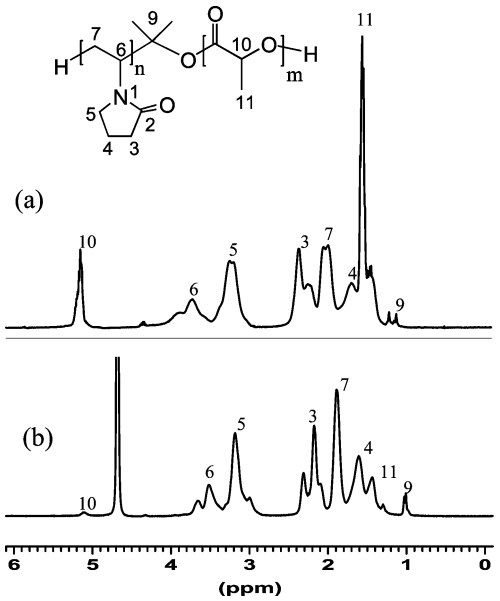


Figure 4. ^{1}H NMR spectrum of PVP-*b*-PDLLA (diblock-47) in (a) $CDCl_3$ and (b) D_2O.

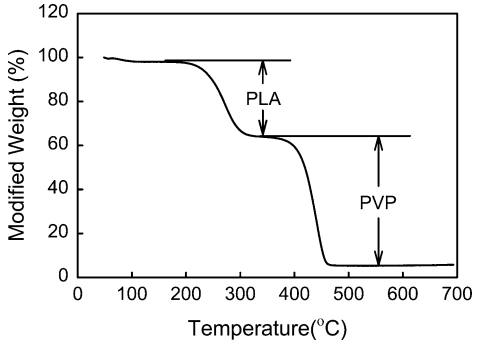


Figure 5. Thermogravimetric profile of PVP-*b*-PDLLA diblock copolymer (diblock-47).

the consistence between EA, SEC, and NMR were quite good (Table 2).

Thermogravimetry (TGA) was also a good method for characterizing the diblock copolymer.[26] As shown in Figure 5, the trace of solvents (less than 4%) in the diblock polymer was removed below 100 °C. PDLLA in the diblock copolymer was then degraded between 200 and 350 °C, followed by the degradation of PVP from 350 to 480 °C. Hence, the PDLLA content could also be determined by TGA. For instance, TGA of diblock-45 revealed a PDLLA content of 48% mol, which was in good agreement with EA results.

3.3. Micellization of PVP-*b*-PLA. Because of their amphiphilic properties, the well-defined PVP-*b*-PDLLA diblock copolymers can self-assemble in aqueous solution to form micelles. The size of micelles was measured by DLS at different concentrations. As shown in Figure 6, micelles composed of PVP-*b*-PDLLA (diblock-47) in water at a concentration of 2 mg/mL feature a single narrow size distribution of about 40 nm. Upon dilution to 0.5 mg/mL, no change in the size of micelles was observed. The results indicate that there is no micelle aggregation in the solutions. In contrast, Benahmed et al.[17] reported bimodal size distributions for PVP-*b*-PDLLA micelles. It has been suggested that the larger population reflects the aggregation of small individual micelles, governed by a secondary order of aggregation. The plausible explanation of the difference is that the molecular weights, PDLLA contents and polydispersity indices reported in Benahmed et al.[17] were higher than the polymers described in the present paper.

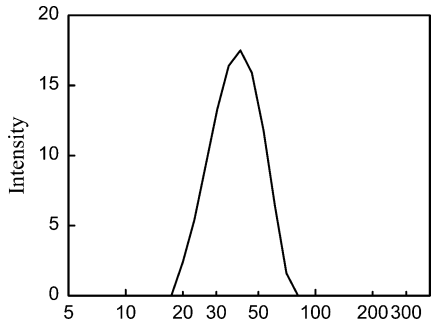


Figure 6. Size distribution of micelles composed of PVP-*b*-PDLLA (diblock-47) in water measured by DLS.

Steady-state fluorescence, using pyrene as hydrophobic fluorescence probe, is well used as technique to show the formation of micelles.[27−29] The polarity of the surrounding environment of the probe molecules affects some vibrational bands in the fluorescence emission spectrum. The changes in the relative intensity of the first and the third vibrational bands (I_{338}/I_{333}), which is due to the shift of the (0,0) band from 333 to 338 nm in the emission spectrum have been suggested to examine the polarity of the microenvironment. The CAC of micelles can be determined by this method. After micellar formation, pyrene partitions into the micellar phase and the water phase. Since the core of the micelle is hydrophobic, the intensity ratio of I_{338}/I_{333} is changed. The extrapolation of tangent of the major change in the slope of the fluorescence intensity ratio leads to CAC. As illustrated in Figure 7, PVP-*b*-PDLLA copolymers exhibited a CAC of about 6 mg/L.

The micellization of PVP-*b*-PDLLA also can be assessed by ^{1}H NMR in D_2O.[17,30,31] As shown in Figure 4b, the peaks of the methyl protons (−CH_3) and the methine proton (−CH−) of PDLLA are highly suppressed while the peaks of PVP still appear in the spectrum, providing evidences of the formation of core−shell structures. The mobility of PDLLA chains in the core is highly restricted, resulting in masking of the PDLLA signals. On the other hand, PVP chains are still

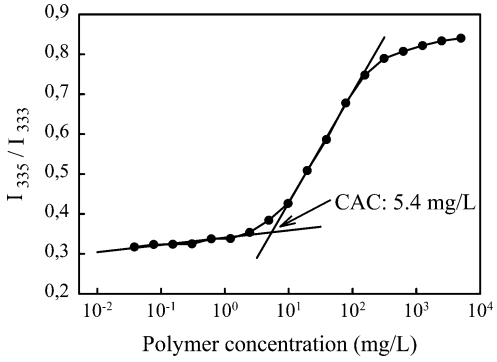


Figure 7. Determination of CAC of PVP-*b*-PDLLA (diblock-47) in water at 25 °C.

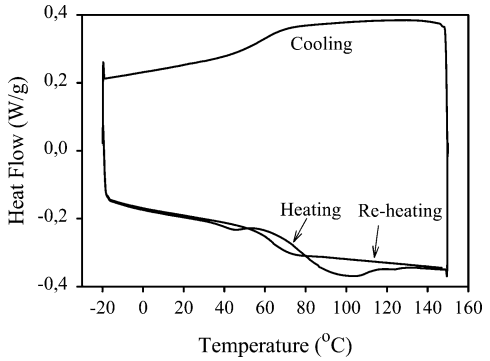


Figure 8. DSC profile of PVP-*b*-PDLLA diblock copolymer (diblock-47).

observed by ^{1}H NMR because of their high mobility as outer shell of micelles

Thermal analysis of PVP-*b*-PDLLA block copolymer micelles by DSC has been performed by using heating, cooling, and reheating scans. T_g of PDLLA and PVP in micelles prepared from diblock-45 copolymer were observed at 42 and 80 °C, respectively, during the first heating scan. T_g value of PDLLA is similar to the T_g value of PDLLD in PEG-*b*-PDLLA micelle as reported by Yamamoto et al.[30] During the second heating scan, only one value of T_g was observed at 68 °C. These results suggest that there is phase separation from PDLLA domain to PVP domain in PVP-*b*-PDLLA block copolymer micelles. After first heating scan, the micelle structure is destroyed. PVP and PDLLA are mixed.

4. Conclusion

By combining MCE and IPA as chain transfer agents, PVP bearing one terminal hydroxyl group on one extremity was successfully synthesized. PVP MWs were efficiently controlled by changing ratios of either MCE or IPA, to NVP. Terminally functionalized low MW PVP were used to efficiently synthesize the PVP-*b*-PDLLA diblock copolymer by anionic ring-opening polymerization of D,L-lactide. PVP-*b*-PDLLA self-assembled into micelles in water. These micelle-forming copolymers presented very low CAC of a few milligrams/liter, leading to the formation of 40 nm PM. These polymeric self-assemblies based on low molecular weight PVP blocks are presently in development as drug carriers for parenteral administration.

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Supporting Information Available: Size-exclusion chromatography profiles of PVPOH (PVPOH-2500) and PVP-*b*-PLA (diblock-47) (Figures S1 and S2). This material is available free of charge via the Internet at http://pubs.acs.org.

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