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Research Article

Synthesis of Poly(lactic acid)-block-poly(N,N-dimethylaminoethyl methacrylate) Copolymers with Controllable Block Structures via Reversible Addition Fragmentation Polymerization from Aminolyzed Poly(lactic acid)

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Poly(lactic acid)-*block*-poly(N,N-dimethylaminoethyl methacrylate) (PLA-PDMAEMA) copolymers were synthesized from aminolyzed PLA via reversible addition fragmentation (RAFT) polymerization. PLA undergoes aminolytic degradation with ethylenediamine (EDA). The kinetics of the aminolysis reaction of PLA at different temperatures and EDA concentrations was investigated in detail. The molar masses of products rapidly decreased in the initial stage at low aminolytic degree. Meanwhile, reactive $-NH_2$ and –OH groups were introduced to the end of shorter PLA chains and used as sites to further immobilize the RAFT agent. PLA-PDMAEMA block copolymers were synthesized. A pseudo-first-order reaction kinetics was observed for the RAFT polymerization of PDMAEMA at a low conversion. By controlling the aminolysis reaction of PLA and RAFT polymerization degree of DMAEMA, the length distributions of the PLA and PDMAEMA blocks can be controlled. This method can be extended to more systems to obtain block copolymers with controllable block structure.

1. Introduction

Poly(lactic acid) (PLA) is classified as an eco-friendly polyester not only because of its biodegradable but also its renewable resources (sugar beet, corn starch, among others.) [1]. It has been widely utilized in biomedical fields, as drug delivery carriers, scaffolds for tissue regeneration, matrices for prolonged drug delivery systems, and degradable surgical sutures due to its good biocompatibility and excellent processability [2, 3]. However, the serious challenge is associated with hydrophobic nature of PLA. As an example, in drug delivery, hydrophobic drug-loaded carriers may limit drug solubility in the blood stream, resulting in decreased in vivo drug efficiency [4]. In addition, the proteins and cells of the blood and tissue may be adsorbed and deposited on hydrophobic carriers via hydrophobic interaction, causing fatal injury to patients [5]. Therefore, PLA often requires modification to improve hydrophilicity before practical use as a drug carrier [6–8].

In recent years, PLA-based amphiphilic block copolymers are the most attractive nanocarriers (e.g., nanoparticles, micelles, and polymersomes) for drugs [9–13]. In the drug-loaded carriers, the hydrophobic PLA chains provide a loading space for hydrophobic drugs, and the hydrophilic polymer chains constitute a stable interface between the hydrophobic carriers and the aqueous medium [14, 15]. The carrier structure and functionality can be effectively controlled by the selection of polymer composition, architecture, molecular weight, and monomer chemistry [16–20]. In general, hydrophilic blocks include poly(meth)acrylates, poly(ethylene glycol) (PEG), polypeptides, polysaccharides, and polyurethanes. PLA-*b*-PEG copolymers are

the most popular and often synthesized by ring opening polymerization (ROP) of lactide [21–23]. The lack of functional groups in the resulting PEG-PLA block copolymers that can be used for further bioconjugation should be overcome. PLA-poly(meth)acrylates block copolymers, such as PLA-poly(hydroxyethyl methacrylate) (PLA-PHEMA) [17, 24], PLA-poly(N,N-dimethylaminoethyl methacrylate) (PLA-PDMAEMA) [11, 25], and PLA-poly (N-isopropylacrylamide) (PLA-PNIPAM) [19], are usually synthesized via ROP of lactide followed by atom transfer radical polymerization (ATRP) or reversible addition fragmentation chain transfer (RAFT) polymerization of various monomers.

The end-of-life scenario of poly(L-lactide) products is the degradation, which is often induced by oxidation [26], irradiation [27, 28], biological activity (i.e., enzymes [29] and microorganism [30–32]), thermal energy [33, 34], aqueous solutions, and so on. In numerous cases, a variety of chemical, physical, and biological processes are always coexistent and affect each other. Aminolysis is a chemical degradation process that was developed to modify polyester surfaces. Aminolysis between the bulk polyester material and amine solution is considered as nucleophilic substitution, conferring the polyester surface with amino ($–NH_2$) and hydroxyl (–OH) groups [35, 36]. The $–NH_2$ density and kinetics of aminolysis occurring on bulk surfaces have been studied. Furthermore, the $–NH_2$ groups on the surface can be used as sites to further immobilize bioactive molecules (such as peptides, proteins, and polysaccharides) on the aminolyzed PLA membrane surfaces to create highly bioactive materials [37, 38]. However, less attention has been focused on the basic knowledge on the aminolysis reaction of PLA in terms of reaction kinetics and the detailed structures of the aminolytic PLA chains.

In the present work, in contrast to the known procedure for preparation of PLA-based block copolymers combining ROP of lactide and controllable radical polymerization, we synthesized PLA-PDMAEMA block copolymers via the aminolysis reaction of PLA chains and RAFT polymerization of DMAEMA for the first time. The synthesis strategy consisted of a three-step procedure: (a) controlled aminolysis reaction of PLA initiated by ethylenediamine (EDA), (b) conversion of the functional end-groups with RAFT agent, and (c) RAFT polymerization of DMAEMA. The aminolysis reaction of PLA was first investigated systematically. The reaction kinetics and chemical structures of the aminolytic PLA were analyzed as functions of temperature, reaction time, and diamine concentration. The molar masses of the copolymers were calculated via theoretical deduction and determined by gel permeation chromatography. Then chemical structures of the resultant PLA-PDMAEMA block copolymers and kinetic behaviors of the polymerization were characterized in detail. The results in this study provide valuable guidance for further synthesis of other PLA-poly(meth)acrylates block copolymers, which opens a new path to reuse PLA residues and reduce the consumption of lactide.

2. Experimental Section

2.1. Materials and Reagents. PLA (2002D) was supplied by Natural Works. Ethylenediamine (EDA), 4,6-dimethyl-2-pyridinamine (DMAP, 98%), and N,N′-dicyclohexyl carbodiimide (DCC, 99%) were purchased from Aladdin and used without further purification. 2-(Dimethylamino) ethyl methacrylate (DMAEMA) was bought from Aladdin and passed through a column filled with basic alumina to remove the polymerization inhibitors. Azobisisobutyronitrile (AIBN) was supplied by Shanghai Chemical Reagent Company and recrystallized twice with ethanol. RAFT agent of 4-cyano-4-(dodecylsulfanylthiocarbonyl)sulfanyl pentanoic acid (CDP) was synthesized according to the reported procedure in the literature [39]. All other reagents, such as 1,4-dioxane, N,N′-dimethylformamide (DMF), and tetrahydrofuran (THF) ethanol, were brought from Sinopharm Chemical Reagent Co., Ltd., China, and used directly.

2.2. Aminolysis of PLA. We followed the methods of Zhu et al. (2015) to synthesize PLA-based block copolymers via the aminolysis reaction of PLA chains and RAFT polymerization of DMAEMA [40]. In a typical aminolysis reaction of PLA with EDA, PLA (5 g) was dissolved in 1,4-dioxane (45 g) under stirring for 12 h. EDA at various concentrations (1, 0.5, and 0.1 mmol/g) was dropped into the above PLA solution under stirring. Immediately, the aminolysis of PLA was carried out at a given temperature (18, 30, and 40°C). After reaction for predetermined time, the polymer solution was precipitated in excessive water. The raw product was separated through filtration and thoroughly washed with water. The solid final product was obtained by freeze-drying for 24 h and named as PLA-EDA. The yield of the degraded PLAs after reprecipitation is 82~85%.

2.3. Synthesis of Macromolecular Chain Transfer Agent (PLA-CDP). In brief, the obtained PLA-EDA (5 g) was dissolved in THF (50 mL) under stirring at 25°C for 1 h. Then DCC (1.05 g, 5 mmol), DMAP (0.6 g, 5 mmol), and CDP (1.0 g, 2.5 mmol) were serially added to the mixture. Amide reaction and esterification between the $–NH_2$/–OH groups of PLA-EDA and the –COOH groups of CDP occurred. After 24 h, the mixture was precipitated and thoroughly washed in excessive ethanol for at least three times. The solid product of macromolecular chain transfer agent (PLA-CDP) was recovered through filtration and dried in vacuum oven at 40°C.

2.4. Synthesis of PLA-PDMAEMA Block Copolymers. PLA-based block copolymers were synthesized via RAFT polymerization. PLA-CDP and AIBN were used as macromolecular chain transfer agent and initiator, respectively. As an example, the synthesis procedures of PLA-PDMAEMA block copolymers via RAFT polymerization were briefly shown below. PLA-CDP (2 g) was dissolved in DMF (20 mL) under stirring at 20°C. After 1 h, DMAEMA (5 g, 32 mmol) and AIBN (5 mg, 0.03 mmol) were added and degassed with N_2 for an additional 1.5 h at 20°C. Then the mixture was transferred to an oil bath at 70°C under N_2 protection

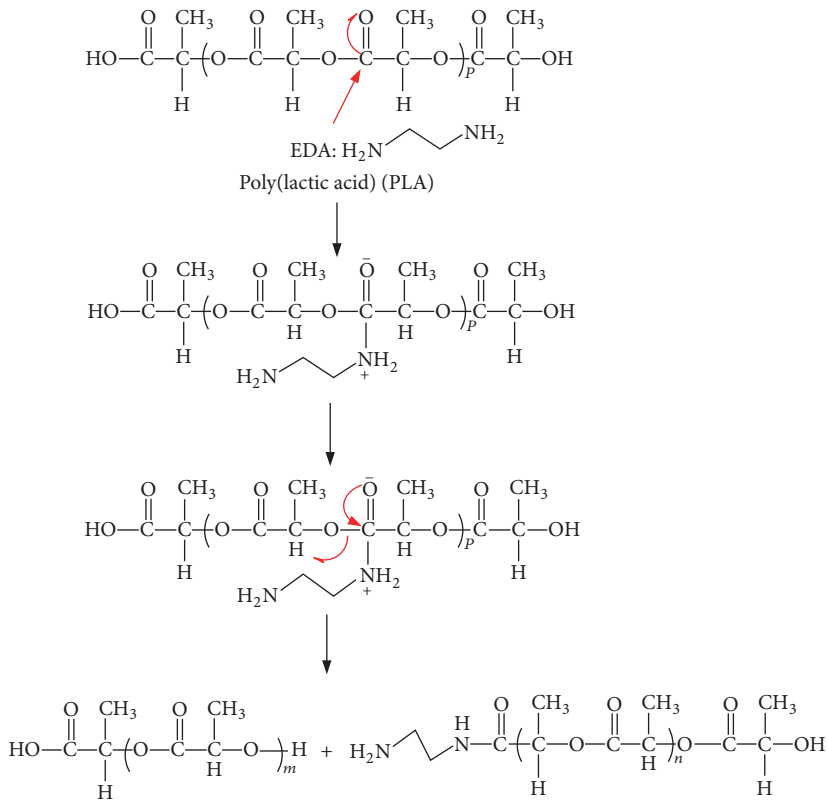

Figure 1: Aminolysis mechanism of PLA with EDA.

and stirring. After a predetermined time, the reaction was terminated by quenching in ice water, and the polymer solution was precipitated and washed in excessive water. The solid PLA-PDMAEMA block copolymers were obtained through filtration and freeze dried.

2.5. Characterization. ^{1}H NMR spectra were performed with a Bruker Advance III spectrometer at room temperature in $CDCl_3$ or DMSO-d_6 with $Si(CH_3)_4$ as an internal standard. Gel permeation chromatography (GPC) was conducted using a Waters 510 HPLC pump, Waters Styragel columns, and a Waters 410 differential refractometer (Millipore Corp., Bedford, MA) at 40°C in THF with a flow rate of 1 mL/min. PMMA was used as a calibration standard. The chemical compositions of the synthesized block copolymers were characterized by Fourier transform infrared spectrometer (FTIR, Thermo-Nicolet 6700, US) and X-ray photoelectron spectrometer (XPS, Shimadzu Axis UltraDLD, Japan) with Mg Kα excitation radiation at a take-off angle of 45°.

3. Results and Discussion

3.1. Structure and Characterization of the Aminolyzed PLA with EDA

3.1.1. Chemical Structure. Similar to the reaction with polyethylene terephthalate (PET) [41], amine acts as a nucleophile to attack PLA at the electron deficient center –C=O. A new active group is introduced to the end units. The reaction of PLA with EDA was studied carefully in this work. The aminolysis mechanism is shown in Figure 1. Figure 2 shows the structures of raw PLA and PLA-EDA as characterized by ^{1}H NMR. Several signals can be distinguished as follows. Signals in the 1.59~1.57 (A) and 5.19~5.14 ppm range (B) belong to the $-CH_3$ and –CH protons of the PLA main chain units. Compared to raw PLA, PLA-EDA exhibits the new peaks in the 1.48~1.50 (a) and 4.33~4.39 ppm ranges (b), which are attributed to the $-CH_3$ and –CH protons of the hydroxylated lactyl end units. The peaks at 5.23 and 1.61 ppm ((d) and (c)) are assigned to the –CH and $-CH_3$ protons connecting with EDA groups. The peaks of the C_2H_4 protons from residual EDA are presented at 3.75~3.21 ppm range (e). In addition, the signals at 5.25 and 1.54 ppm ((g) and (f)) belong to the –CH and $-CH_3$ protons of the carboxylated lactyl end units. The ^{1}H NMR results confirmed the proposed aminolysis mechanism illustrated in Figure 1.

3.1.2. Aminolysis Degree. Aminolysis degree (AD, %) was introduced to evaluate the extent of aminolysis reaction and calculated from the ^{1}H NMR spectra according to

$$\mathrm{AD} = \frac{S_b}{S_{\mathrm{all}}} \times 100\%, \quad (1)$$

where S_b and S_{all} are the integral areas of peak b as shown in Figure 2 and all peaks of the –CH protons, respectively.

The AD of PLA with EDA is dependent on EDA concentration, reaction time, and temperature as shown in Figure 3.

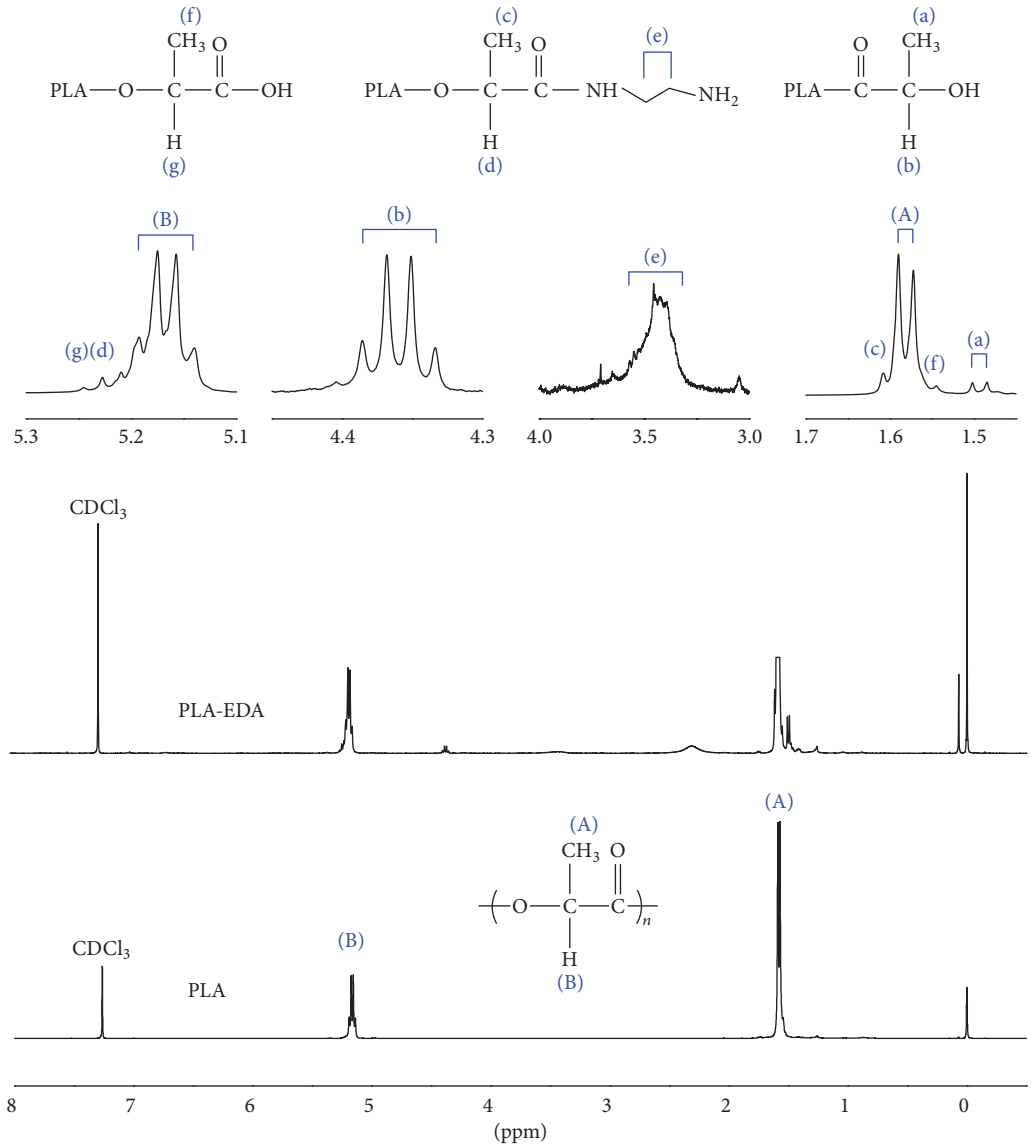

FIGURE 2: ^{1}H NMR spectra of raw PLA and PLA-EDA in $CDCl_3$. Aminolysis condition of PLA with EDA: 30°C, 30 min, [EDA] = 1.0 mmol/g.

The AD of PLA increases with the prolongation of reaction time. In detail, AD is rapidly increased in the initial 10 min of aminolysis and slows down from 10 to 60 min. After 60 min, AD data becomes difficult to obtain because the solid products cannot be separated from the precipitation solution. Figure 3(a) shows a faster growth of AD with increasing EDA concentration. Furthermore, the aminolysis reaction was also accelerated at higher temperature when the EDA concentration was 0.5 mmol/g (Figure 3(b)). At the EDA concentration of 1.0 mmol/g, the AD is as high as 10.3% after reacting at 40°C for 60 min.

3.1.3. Molar Mass Analysis. According to the aminolysis mechanism of PLA, chain scission results in decreased molar mass. The products were subjected to GPC analyses, and the results are shown in Figure 4. The GPC traces (Figure 4(a)) indicated that the molar mass distribution of the measured PLA-EDA remained unimodal, suggesting statistically random scission of the polymer chains. Furthermore, with increasing reaction time, the GPC traces shift toward low molar mass. The number average molecular weight determined by GPC ($Mn_{,GPC}$) is exhibited in Figure 4(b). The $Mn_{,GPC}$ decreased rapidly in the low AD range, and the decline rate slowed down with increasing AD. The aminolysis reaction is considered as the reverse of polycondensation [42]. Lower AD is roughly equivalent to higher polycondensation extent. For the polymer synthesized via polycondensation, $Mn_{,GPC}$ increases gradually in the initial polymerization; under high polymerization degree, $Mn_{,GPC}$ significantly increases due to a small increase in the polymerization degree [42]. As a result, the changing trend of Mn for the aminolyzed PLA is similar to that of polycondensation polymer. Moreover, similar to the change in polydispersity index ($Đ$) in polycondensation, the $Đ$ of PLA-EDA became narrower with the increase of AD (Figure 4(b)). Lower polycondensation extent indicates less

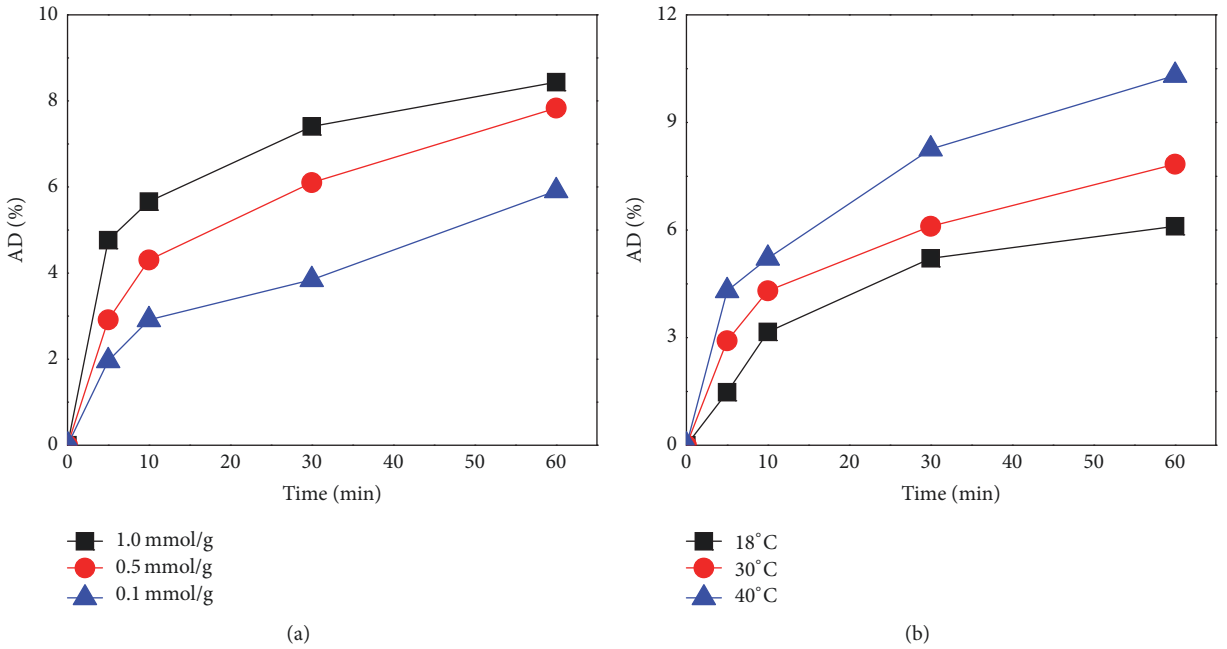

Figure 3: AD as a function of reaction time with different EDA concentrations at 30°C (a) and different reaction temperatures at an EDA concentration of 0.5 mmol/g.

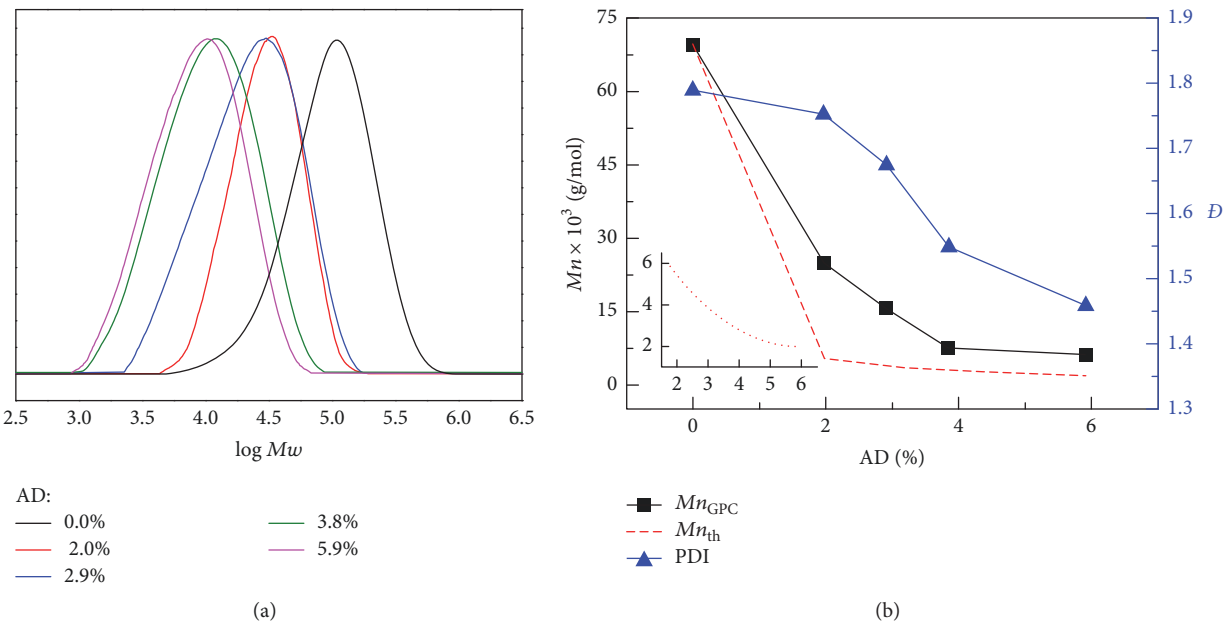

Figure 4: Evolution of GPC traces (a) and number average molecular weight (Mn) and molecular weight polydispersity ($Đ = Mw/Mn$) (b) of the PLA-PEA with aminolysis degree (AD).

$Đ$. The $Đ$ decreases with the increasing AD of PLA with EDA. Except for $Mn_{,\mathrm{GPC}}$, the theoretical Mn ($Mn_{,\mathrm{th}}$) of PLA-EDA was calculated by (2) as shown in Figure 4(b). The $Mn_{,\mathrm{th}}$ value is slightly less than the GPC obtained value due to the different flexibilities of the polymer chains between PLA-EDA and the GPC calibrating standards (PMMA). However, the tendency of $Mn_{,\mathrm{th}}$ is in accordance with $Mn_{,\mathrm{GPC}}$.

$$Mn_{,\mathrm{th}} = \frac{Mn_{,\mathrm{PLA}} + \mathrm{AD} \times M_{\mathrm{EDA}} \times Mn_{,\mathrm{PLA}}/M_{\mathrm{PLA}}}{1 + \mathrm{AD} \times Mn_{,\mathrm{PLA}}/M_{\mathrm{PLA}}}, \quad (2)$$

where $Mn_{,\mathrm{PLA}}$ and M_{PLA} are the number average molar masses of PLA and PLA repeating units, respectively. M_{EDA} and AD are the molar mass of EDA and degree of aminolysis, respectively.

3.2. Structure and Characterization of the Synthesized PLA-Based Block Copolymers

3.2.1. Chemical Structure. Despite being an eco-friendly bioplastic with excellent biocompatibility and processability,

Table 1: Molar weight (Mn), polydispersity ($Đ$) of the synthesized PLA-PDMAEMA block copolymers, and mass ratio of PDMAEMA blocks ($f_{PDMAEMA}$) in the copolymers.

ID	Time (min)	$Mn_{,GPC}$ (g/mol)	$Đ_{,GPC}$	$f_{PDMAEMA,NMR}$ (wt%)
PLA_{345}-$PDMAEMA_0$	0	24900	1.75	/
PLA_{345}-$PDMAEMA_9$	1	26300	1.36	5.1
PLA_{345}-$PDMAEMA_{60}$	3	34400	1.23	32.6
PLA_{345}-$PDMAEMA_{213}$	10	58400	1.32	66.7
PLA_{217}-$PDMAEMA_0$	0	10200	1.67	/
PLA_{217}-$PDMAEMA_{47}$	2	17600	1.75	21.8
PLA_{217}-$PDMAEMA_{63}$	3	20100	1.71	37.9
PLA_{217}-$PDMAEMA_{79}$	4	22700	1.67	63.4
PLA_{103}-$PDMAEMA_0$	0	7280	1.56	/
PLA_{103}-$PDMAEMA_{40}$	2	13600	1.62	47.9
PLA_{103}-$PDMAEMA_{57}$	4	16300	1.78	75.3

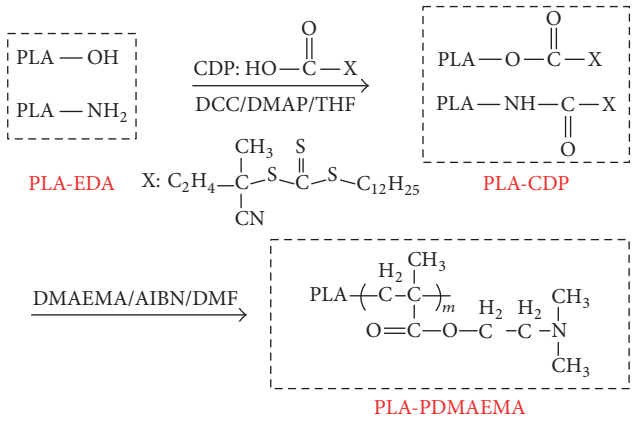

Figure 5: Schematic illustration for the preparation of PLA-PDMAEMA block copolymers via RAFT polymerization.

PLA is chemically inert without reactive sidechain groups, thereby making its modifications a challenging task [43]. After the aminolysis reaction of PLA with EDA, the reactive $-NH_2$ and $-OH$ groups can be introduced to the ends of the PLA chains, providing opportunity to further modify PLA. In the present work, PLA-PDMAEMA block copolymers were synthesized from PLA segments after aminolysis reaction via RAFT polymerization; Figure 5 shows the fabrication processes. First, RAFT agent CDP was immobilized on the reactive groups of PLA-EDA via the amide reaction/esterification under the catalysis of DCC/DMAP in THF. Then the obtained PLA-CDP was used as the chain transfer agent to regulate RAFT polymerization of monomers to produce PLA-based block copolymers. In the present work, a serial of PLA-PDMAEMA block copolymers were synthesized. The molar weight (Mn), polydispersity ($Đ$), and mass ratio of PDMAEMA blocks ($f_{PDMAEMA}$) in the copolymers are listed in Table 1.

To detect the chemical compositions of the synthesized PLA-CDP, XPS was employed. The XPS wide scan and the elemental mole percentages are shown in Figure 6(a). The peak of S 2p is observed. Figure 6(b) shows the ^{1}H NMR spectrum of PLA-CDP. The peaks in 4.25~4.13 ppm range are attributed to the C_2H_4 protons connected with amide group. The peaks of the CH_3 protons at (a) and (c) in Figure 2 disappeared. These results confirm that PLA-CDP was synthesized successfully. It can be used as the chain transfer agent to regulate RAFT polymerization of DMAEMA.

PLA_{345}-$PDMAEMA_{60}$ block copolymers were characterized by ^{1}H NMR in $CDCl_3$, and the obtained ^{1}H NMR spectrum is shown in Figure 7(a). The signals in the 5.19~5.14 (A) and 1.59~1.57 ppm range (B) belong to –CH and $-CH_3$ protons of the main chain PLA units. The peaks in the 1.82 (C) and 0.91~1.06 ppm range (D) are attributed to the $-CH_2$ and $-CH_3$ protons of the main chain PDMAEMA units. The signals at 4.09 (E) and 2.63 ppm (F) correspond to the $-CH_2$ protons connected to the ester and tertiary amine groups of PDMAEMA, respectively. The peaks in 2.38~2.34 ppm range (G) are attributed to $-CH_3$ protons connected to the tertiary amine groups. In addition, FT-IR spectrum of PLA_{345}-$PDMAEMA_{213}$ block copolymers is shown in Figure 7(b). The peak at around 1758 cm^{-1} is the stretching vibration of C=O in ester groups of PLA blocks. The adsorption peaks at about 2823~2722 and 1730 cm^{-1} are ascribed to $-N(CH_3)_2$ and O–C=O groups of PDMAEMA chains, respectively. Furthermore, the GPC traces of PLA_{345}-PDMAEMA block copolymers with different polymerization times are shown in Figure 7(c). The GPC traces of PLA_{345}-DMAEMA block copolymers exhibit one monomodal distribution. The Mn of PLA_{345}-PDMAEMA increases from 26300 to 58400 g/mol with the increase of polymerization time from 1 to 10 h as shown in Table 1. All data indicate that the PLA_{345}-PDMAEMA block copolymers were successfully synthesized via RAFT polymerization based on aminolyzed PLA with EDA.

3.2.2. Kinetic Behavior of the RAFT Polymerization. The RAFT polymerization kinetic behavior of PLA_{345}-PDMAEMA block copolymers was investigated. Conversion and kinetics plots for the RAFT polymerization of the block copolymers with increasing polymerization time (1, 2, 3, 4, 7, and 10 h) are shown in Figure 8. Figure 8(a) further shows that the conversion of DMAEMA linearly increases with RAFT

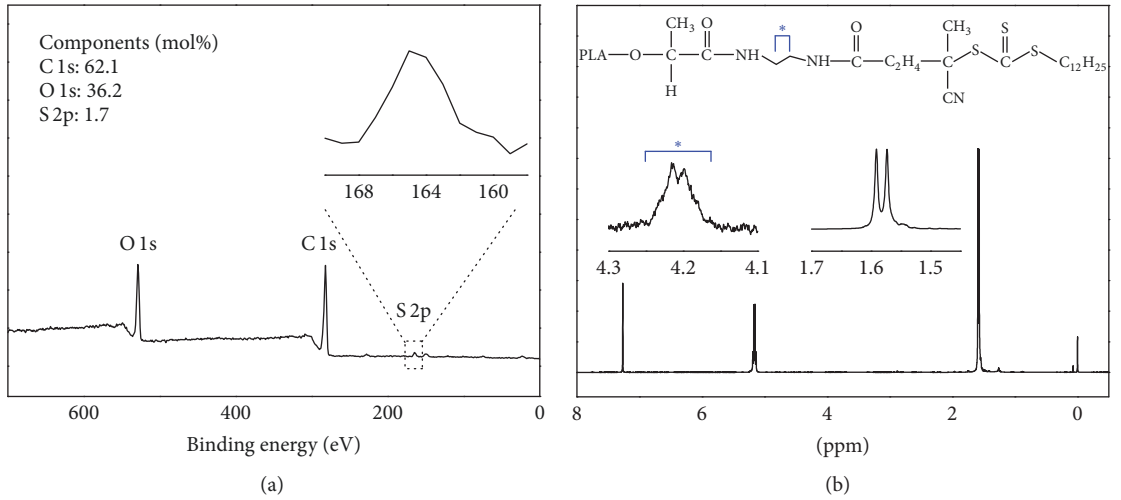

Figure 6: (a) XPS wide scan and elemental mole percentages and (b) ^{1}H NMR spectrum in $CDCl_3$ of PLA_{345}-CDP.

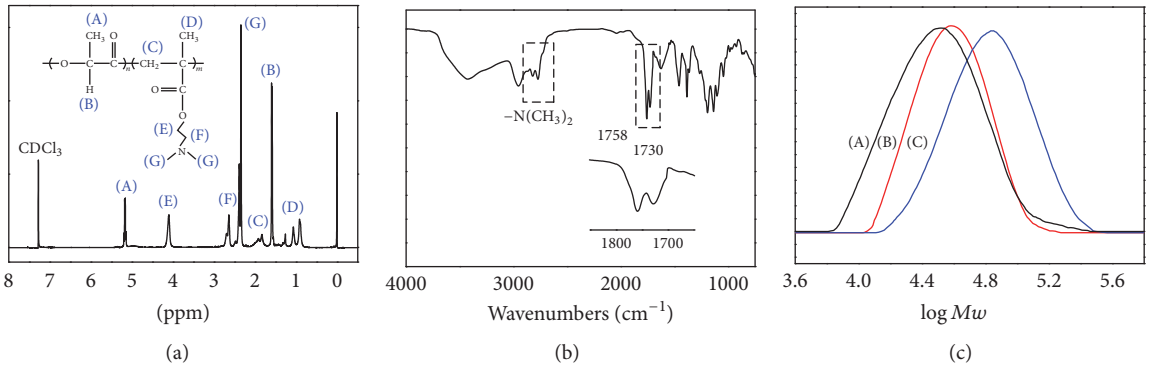

Figure 7: (a) ^{1}H NMR spectrum in $CDCl_3$ and (b) FTIR spectrum of PLA_{345}-$PDMAEMA_{213}$ block copolymers. (c) Evolution of GPC traces of the synthesized PLA_{345}-PDMAEMA block copolymers with polymerization time of 1 (A), 3 (B), and 10 h (C).

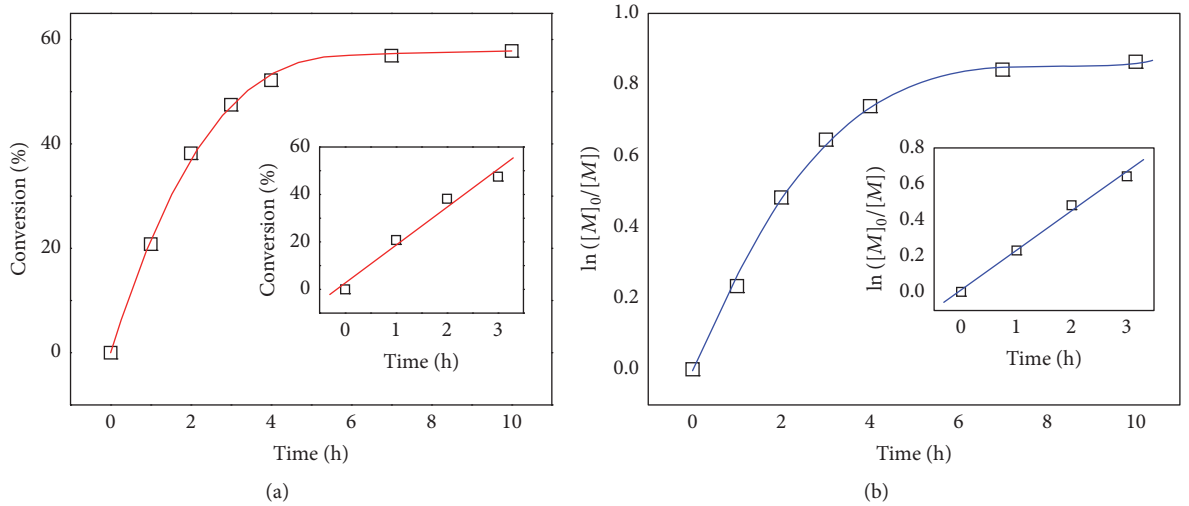

Figure 8: (a) Conversion and (b) kinetics plots for the RAFT polymerization of PLA-PDMAEMA block copolymers with increasing polymerization time (1, 2, 3, 4, 7, and 10 h).

polymerization time in the initial 3 h. A pseudo-first-order kinetics for the RAFT polymerization of PDMAEMA was depicted at a low conversion (Figure 8(b)). However, the rate of conversion decreases from 3 to 7 h and remains almost unchanged when the polymerization time increases from 7 to 10 h. These phenomena were mainly attributed to the increasing viscosity of the reaction solution with the increase of conversion. At higher viscosity, the motion of polymer chains becomes more difficult. As a result, termination occurred and the reaction rate decreased.

4. Conclusions

PLA undergoes aminolytic degradation with EDA. The aminolysis reaction accelerated at increased EDA concentration and reaction temperature. The AD of PLA was rapidly increased in the initial stage and then reached a plateau. Thus, the molar masses of products rapidly decreased in the early reaction stage. Furthermore, $-NH_2$ and –OH groups were introduced to the ends of the produced short PLA chains. Then, the RAFT agent was immobilized onto the aminolyzed PLA chains, and PLA-PDMAEMA block copolymers were synthesized via RAFT polymerization. Conversion and kinetics plots for the RAFT polymerization of the block copolymers with increasing polymerization time were studied. The results suggested a pseudo-first-order kinetics of the RAFT polymerization of PDMAEMA at a low conversion. The length distributions of the PLA and PDMAEMA blocks can be controlled by controlling the aminolytic reaction and RAFT polymerization degrees in the process.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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