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Synthesis and characterization of poly(ethylene glycol)-*b*-poly(L-lactide)-*b*-poly(L-glutamic acid) triblock copolymer

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Abstract

A biodegradable amphiphilic triblock copolymer of poly(ethylene glycol)-*b*-poly(L-lactide)-*b*-poly(L-glutamic acid) (PEG-*b*-PLLA-*b*-PLGA) was obtained by catalytic hydrogenation of poly(ethylene glycol)-*b*-poly(L-lactide)-*b*-poly(γ-benzyl-L-glutamic acid) (PEG-*b*-PLLA-*b*-PBLGA) synthesized by the ring-opening polymerization (ROP) of *N*-carboxyanhydride of γ-benzyl-L-glutamate (BLG-NCA) with amino-terminated MPEG-*b*-PLLA-NH_2 as a macroinitiator. MPEG-*b*-PLLA-NH_2 converted from MPEG-*b*-PLLA-OH first reacted with *tert*-Butoxycarbonyl-L-phenylalanine (Phe-^{N}BOC) and dicyclohexylcarbodiimide (DCC) and then deprotected the *tert*-butoxycarbonyl group. MPEG-*b*-PLLA-OH was prepared by ROP of L-lactide with monomethoxy poly(ethylene glycol) in the presence of stannous octoate. The triblock copolymer and its diblock precursors were characterized by ^{1}H NMR, FTIR, GPC and DSA (drop shape analysis) measurements. The lengths of each block polymers could be tailored by molecular design and the ratios of feeding monomers. The triblock polymer PEG-*b*-PLLA-*b*-PLGA containing carboxyl groups showed obviously improved hydrophilic properties and could be a good potential candidate as a drug delivery carrier.

Keywords: Biodegradable polymer; Block copolymer; Ring-opening polymerization

1. Introduction

Hydrophobic aliphatic polyesters based on hydroxyalkanoic acids, such as polyglycolide (PGA), polylactide (PLA), poly(ε-caprolactone) (PCL), hydrophilic poly(ethylene glycol) (PEG), poly(α-amino acid)s and their amphiphilic copolymers are well known as very important synthetic biodegradable materials. Due to their low immunogenicity, good biocompatibility and excellent mechanical properties, they may be widely used in pharmaceutical and other medical applications [1,2], such as sutures, implants for bone fixation, carriers in drug delivery, and temporary matrices or scaffolds in tissue engineering [3–5].

Poly(ethylene glycol) (PEG) is provided with outstanding biological and physico-chemical properties, including hydrophilicity, solubility in water and organic solvents, lack of toxicity, and absence of antigenicity and immunogenicity, so as to be used in biomedical and pharmaceutical applications. Recently, many studies focused on the amphiphilic block copolymers of PEG-polyester in expectation of achieving unique properties and corresponding applications [6–8]. Inclusion of the functional side groups of –COOH in aspartic and glutamic acid and of –NH_2 in lysine in polylactide-type polymers can help to improve their affinity to proteins and cells, or to covalently or ionically combine with drugs, antibodies or DNA's, and thus may lead to breakthrough in the fields of targeting drug delivery and gene delivery [9,10].

Synthetic poly(α-amino acid)s can be rationally synthesized by means of ROP of α-amino acid *N*-carboxyanhydrides (NCA) initiated by primary amine [11,12] and their biodegradation in mammalian tissues can be well controlled by their chemical structure [13]. In addition, the presence of peptide bonds in the polymer backbone can modify

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degradation patterns of polymers, making them susceptible to peptidases. The polyester-*co*-PEG-*co*-poly(amino acid)-type triblock copolymer was synthesized by polyester-*co*-PEG-NH_2 initiated ROP of NCA [14,15].

In this paper, a novel structure of PEG-*b*-poly(L-lactide)-*b*-poly(γ-benzyl-L-glutamic acid) (PEG-*b*-PLLA-*b*-PBLG) triblock copolymer was synthesized with PEG-*b*-PLLA-NH_2 diblock copolymer as macroinitiators for the ROP of NCA by a convenient way. The protective group of the side carboxyl group could be easily removed by catalytic hydrogenation with Pd/C, which lead to the formation of a new polymer, PEG-*b*-poly(L-lactide)-*b*-poly(L-glutamic acid) (PEG-*b*-PLLA-*b*-PLGA). The triblock copolymer combined the characters of polyester, PEG and poly(amino acid). It would consist of hydrophilic/hydrophobic, soft/-hard chain segments and functional groups, which provided possibility and flexibility of adjusting the basic properties of each homopolymer. The structures and properties of its diblock copolymer precursors, protected and deprotected triblock polymers were all investigated in detail.

2. Experimental section

2.1. Materials

Monomethoxy-poly(ethylene glycol) with a molecular weight of 750, 2000 (MPEG750, MPEG2000) was obtained from Aldrich. Prior to use, MPEG was dried by an azeotropic distillation in toluene. L-lactide (LLA) was purchased from PURAC Biochem bv Gorinchem and recrystallized from ethyl acetate for three times. *tert*-Butoxycarbonyl-L-phenylalanine (Phe-^{N}BOC) and dicyclohexylcarbodiimide (DCC) from Chengdu Tenglong Corporation in China were used as received. Pd/C (10%) was obtained from Suzhou Xukou Corporation in China and used without further purification. BLG-NCA was prepared according to Daly's method [16]. Hexane, methylene dichloride and chloroform were refluxed over CaH_2 and distilled under nitrogen. Tetrahydrofuran (THF) were dried and distilled from sodium immediately before use.

2.2. Measurements

FT-IR spectra were recorded on a Bio-Rad Win-IR instrument. ^{1}H NMR spectra were measured by a AV-400 NMR spectrometer at room temperature. Gel permeation chromatography (GPC) measurements were conducted with a Waters 410GPC with tetrahydrofuran (THF) as eluent (flow rate: 1 ml/min, at 35 °C). The molecular weights were calibrated against polystyrene (PS) standards. Water contact angle was measured by drop shape analysis (DSA 10, KRÜSS GmbH).

2.3. Synthesis of MPEG-PLLA-OH

Diblock copolymer of MPEG-PLLA was easily prepared by the ROP of L-lactide in the presence of MPEG and stannous octoate ($Sn(Oct)_2$). First, 8.0 g MPEG (M_n = 750), 30.0 g L-lactide, 40 ml toluene, and 30 mg $Sn(Oct)_2$ were added into a dried glass reactor already flame-dried and nitrogen-purged three times, and then the sealed reactor was maintained at 110 °C for 12 h. The product was dissolved in chloroform and precipitated with an excess of diethyl ether to give a white product. The product was washed with methanol several times. Yield: 34.2 g (90.1%). The Degree of Polymerization (DP) values of MPEG and PLLA were 17 and 23 (calculated from ^{1}H NMR), respectively. Diblock copolymers with different DP of PLLA could be obtained by adjusting the feed ratio of LLA to MPEG. The results were shown in Table 1.

2.4. Synthesis of MPEG-PLLA-Phe-^{N}BOC

The –OH end-group of the diblock copolymer MPEG-PLLA-OH was converted into -Phe-^{N}BOC as follows. A flask containing 10.0 g MPEG-PLLA-OH (DP_{MPEG} = 17, DP_{PLLA} = 23) and 4.0 g Phe-^{N}BOC dissolved in 80 ml CH_2Cl_2 was cooled to −10 °C and treated with a solution of 3.0 g DCC for 48 h at 0 °C, then, the dicyclohexylurea was removed by filtration. The filtrate was washed with 80 ml saturated aqueous $NaHCO_3$ and 2×80 ml H_2O. The copolymer in the CH_2Cl_2 solution was precipitated when poured into an excess of cold methanol. Yield 8.5 g (85%). The DP values of MPEG and PLLA were 17 and 23 (calculated from ^{1}H NMR), respectively.

2.5. Synthesis of MPEG-PLLA-NH_2

MPEG-PLLA-Phe-^{N}BOC (DP_{MPEG} = 17, DP_{PLLA} = 23) was dissolved in 30 ml CH_2Cl_2. The solution was cooled to 0 °C and treated with 15 ml trifluoroacetic acid (TFA) for 2 h. TFA was then removed in vacuum, the residue was dissolved in 40 ml chloroform and washed with 40 ml saturated aqueous $NaHCO_3$ and 2×40 ml H_2O. The polymer was precipitated when its chloroform solution was poured into an excess of diethyl ether. Yield 6.4 g (91.4%). The DP values of MPEG and PLLA were 17 and 23 (calculated from ^{1}H NMR), respectively.

2.6. Synthesis of triblock copolymer MPEG-b-PLLA-b-PBLG

In a dried flask, 1.0 g MPEG-PLLA-NH_2 (DP_{MPEG} = 17, DP_{PLLA} = 23) and 4.0 g BLG-NCA were dissolved in dried chloroform (60 ml) and the solution was stirred for 72 h at 30 °C. The product mixture was precipitated with an excess of a mixture of acetic acid and methanol (1:3, v/v) under vigorous stirring to give a white solid while the unreacted MPEG-PLLA was still dissolved in the mixture. Removal of

Table 1
Feed composition and molecular characteristics of triblock polymer

Polymer	Composition of feed (EO:L-LA:NCA)	Composition of the copolymer[a] (EO:LLA:NCA)	$M_n \times 10^{-3}$ (^{1}H NMR)
$MPEG_{750}$-$PLLA_{3400}$-$PBLG_{3000}$	17:20:10	17:23:14	7.1
$MPEG_{750}$-$PLLA_{3400}$-$PBLG_{13800}$	17:20:60	17:23:63	18.0
$MPEG_{2000}$-$PLLA_{2800}$-$PBLG_{10000}$	45:41:42	45:39:46	12.9

[a] Calculated from results of ^{1}H NMR spectroscopy.

the MPEG-PLLA solution, purified PEG-*b*-PLLA-*b*-PBLG was gained under vacuum at 40 °C for 24 h. Yield 3.8 g (87%). The DP value of PBLG was 63 (calculated from ^{1}HNMR). Triblock copolymers with different DP of PBLG could be obtained by adjusting the feed ratio of NCA to MPEG-PLLA-NH_2. The results were summarized in Table 1.

2.7. Deprotection of MPEG-b-PLLA-b-PBLG

MPEG-*b*-PLLA-*b*-PBLG ($DP_{MPEG}=17$, $DP_{PLLA}=23$, $DP_{PBLG}=63$) (0.5 g) was dissolved in 15 ml of THF. Then, 5 ml of methanol and a small amount of Pd/C (10%) were added to the solution. With vigorous stirring, hydrogen was bubbled through the suspension for 2 days. After removal of the Pd/C power, the solution was dropped into an excess of petroleum ether. The precipitate was dried in vacuum at 40 °C for 24 h.

3. Results and discussion

3.1. Synthesis of MPEG-PLLA-NH_2

Because the weak aliphatic ester bonds in MPEG-PLLA chain are easy to be broken down under strong reaction conditions such as strong acid or strong alkali, it is difficult to convert MPEG-PLLA-OH into MPEG-PLLA-NH_2 directly by the usual methods. Michael Gotsche [17] had successfully synthesized MPEG-PLA-NH_2 by endcapping PLA with *N-tert*-butoxycarbonylphenylalanine and deprotecting BOC group on the amino group. In the present experiment, the MPEG-PLLA-NH_2 copolymer prepared by endcapping method was used as a macromolecular initiator to carry out the ROP of BLG-NCA to get a triblock copolymer MPEG-*b*-PLLA-*b*-PBLG. Its synthetic route was outlined in Scheme 1. The more detailed synthetic steps were discussed as follows.

3.2. Synthesis of MPEG-PLLA-OH

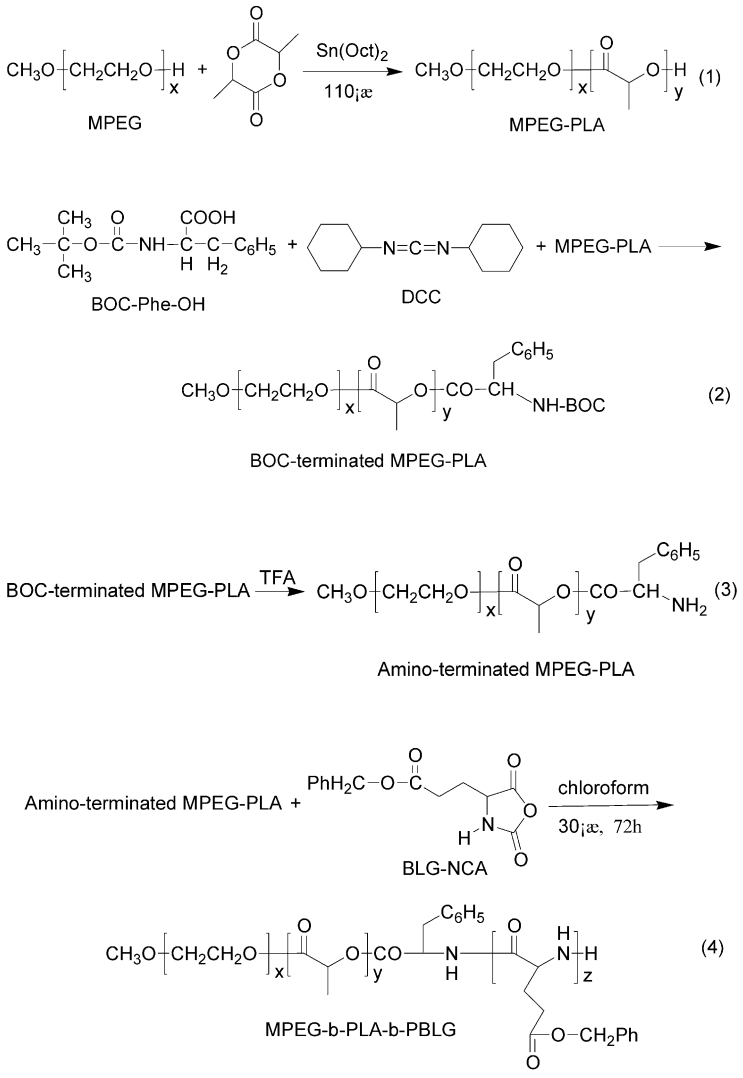
The MPEG-PLLA-OH was synthesized with high conversion directly from the ROP of L-lactide (LLA) in the presence of MPEG and stannous octoate in toluene solution. The block lengths of MPEG and PLLA could be designed and adjusted by using a desired molecular weight of MPEG and molar ratio of the LLA to MPEG (Table 1). A typical ^{1}H NMR spectrum of MPEG-PLLA-OH was displayed in Fig. 1(A). The peaks marked with letters from *a* to *d* could be assigned to the characteristic signals of hydrogen in PEG-PLLA repeat-units, such as *a* at 3.38 ppm (singlet, CH_3O–), *b* at 3.65 ppm (singlet, –OCH_2CH_2O–), *c* at 5.17 ppm (quadruplet, –C(O)C*H*(CH_3)O–), and *d* at 1.38 ppm (doublet, –C(O)CH(CH_3)O–). DP_{PLLA} in the copolymer was obtained from the integral ratio of CH_3O– (*a* at 3.38 ppm) to –C(O)C*H*(CH_3)O–C(O)C*H*(CH_3)O– (*c* at 5.17 ppm) in the ^{1}H NMR spectrum of MPEG-PLLA-OH, as shown in the following formula, $DP_{PLLA}=3c/2a$. Thus, the value of DP_{PLLA} was 23. The GPC curve of MPEG-PLLA-OH ($DP_{MPEG}=17$, $DP_{PLLA}=23$) presented a single and sharp peak as shown in Fig. 2(A), with polydispersity of 1.04 and Mn of 5700, further indicating that the MPEG750 had almost reacted with LLA, and no homopolymerization of LLA occurred in the reaction system.

3.3. Synthesis of BOC-terminated MPEG-PLLA

BOC-terminated MPEG-PLLA was obtained by the reaction of *tert*-butoxycarbonyl-protected phenylalanine with MPEG-PLLA-OH using the carbodiimide method [18]. The ^{1}H NMR spectrum of BOC-terminated MPEG-PLLA ($DP_{MPEG}=17$, $DP_{PLLA}=23$) were shown in Fig. 1(B), two new peaks distinctly appeared at 1.38 ppm (*f*, singlet, $(CH_3)_3C$–) and at 7.30 ppm (*e*, singlet, C_6H_5–), revealing the presence of *tert*-butoxycarbonyl and phenyl in Phe-^{N}BOC. Based on the intensity ratio of tert-butoxycarbonyl to unchangeable terminal groups (CH_3O– for MPEG-PLLA-Boc), the efficiencies of the end-group functionalization were close to 100%. Its GPC curve (Fig. 2(B)) shows similar shape and same position of retention time as that of MPEG-PLLA-OH ($DP_{MPEG}=17$, $DP_{PLLA}=23$) (Fig. 1(A)), indicating that the polymeric backbone was kept unchanged. As a result, the end-group had been successfully converted.

3.4. Synthesis of amino-terminated MPEG-PLLA

The reduction of BOC-terminated MPEG-PLLA into MPEG-PLLA-NH_2 was carried out by removing the protecting *tert*-butoxycarbonyl group from the amino group with trifluoroacetic acid under anhydrous conditions. After the reaction, the ^{1}H NMR peak *f* at 1.38 ppm of BOC (Fig. 1(B)) disappeared completely in Fig. 1(C), demonstrating the elimination of *tert*-butoxycarbonyl group. The



Scheme 1. Synthesis of triblock copolymer MPEG-*b*-PLLA-*b*-PBLG.

GPC trace of MPEG-PLLA-NH_2 (DP_{MPEG} = 17, DP_{PLLA} = 23) in Fig. 2(C) looked similar to those in Fig. 2(A) and (B). The molecular weight characteristics of the three intermediate diblock polymers were determined by comparing the GPC results with that of ^{1}H NMR (Table 2). The molecular weights and their distribution did not change very

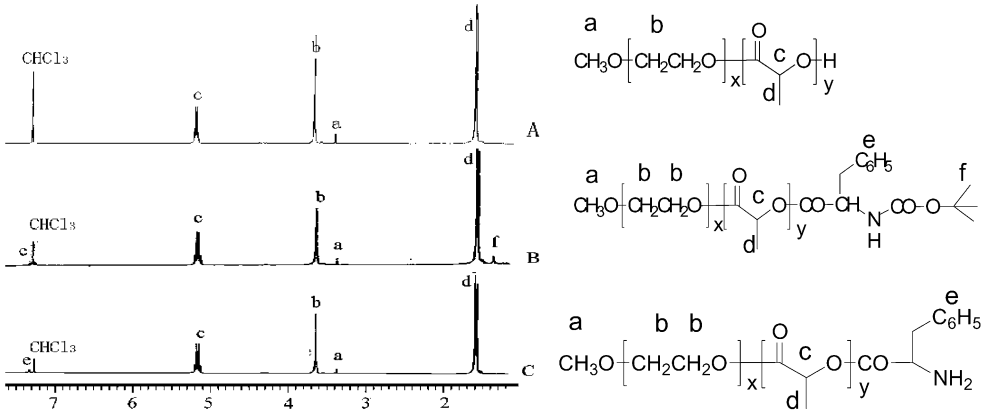


Fig. 1. The ^{1}H NMR spectra and their assignments of (A) MPEG-PLLA-OH (DP_{MPEG} = 17, DP_{PLLA} = 23), (B) MPEG-PLLA-BOC (DP_{MPEG} = 17, DP_{PLLA} = 23), (C) MPEG-PLLA-NH_2 (DP_{MPEG} = 17, DP_{PLLA} = 23) in $CDCl_3$.

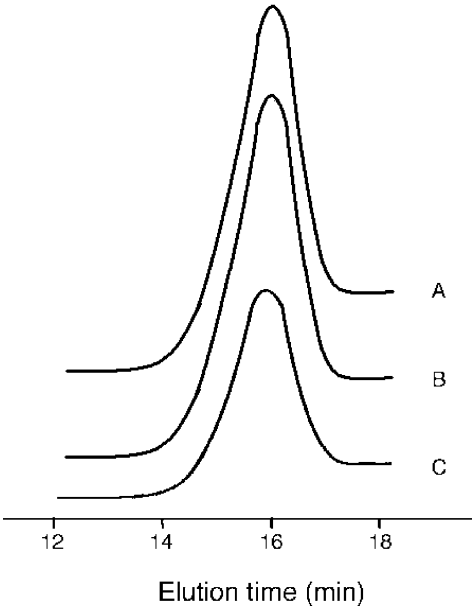


Fig. 2. The GPC traces of (A) MPEG-PLLA-OH ($DP_{MPEG}=17$, $DP_{PLLA}=23$), (B) MPEG-PLLA-BOC ($DP_{MPEG}=17$, $DP_{PLLA}=23$), (C) MPEG-PLLA-NH_2 ($DP_{MPEG}=17$, $DP_{PLLA}=23$).

much, so that the polymeric main chains were kept unchanged. Therefore, the designed MPEG-PLLA-NH_2 with high purity and desired structure was successfully synthesized.

3.5. Synthesis of the triblock copolymer MPEG-b-PLLA-b-PBLG

It is well known that primary amines can be used as initiators for the ROP of NCA to prepare poly(α-amino acid)s, undergoing a nucleophilic addition to the C-5 carbonyl group of the NCA [11]. Therefore, the MPEG-PLLA-NH_2 was used as a macromolecular initiator to synthesize triblock copolymer MPEG-*b*-PLLA-*b*-PBLG according to Scheme 1. The results were summarized in Table 1.

The IR spectra of MPEG, MPEG-PLLA and MPEG-*b*-PLLA-*b*-PBLG were shown in Fig. 3. The absorption peak at 3292 cm^{-1} was assigned to ν_{NH} stretch vibration and the peaks at 1653 cm^{-1} (ν_{CO}) and 1548 cm^{-1} (ν_{CO-NH}) were attributed to the amide group, indicating the formation of

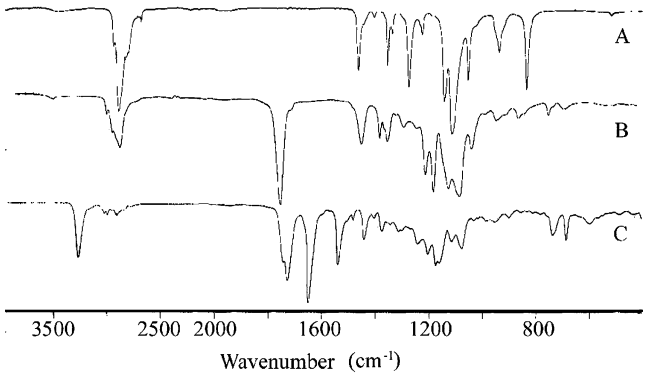


Fig. 3. The IR spectra of (A) MPEG ($DP_{MPEG}=17$), (B) MPEG-PLLA ($DP_{MPEG}=17$, $DP_{PLLA}=23$), (C) MPEG-*b*-PLLA-*b*-PBLG ($DP_{MPEG}=17$, $DP_{PLLA}=23$, $DP_{PBLG}=63$).

the polypeptide block. The peak at 1734 cm^{-1} (ν_{CO}) was characteristic of the PLLA block. The absorptions at 697 and 749 cm^{-1} from the phenyl group were characteristic of the PBLG block carrying protection groups. The peak at 1127 and 1454 cm^{-1} (ν_{C-O-C}) belonged to the MPEG block. The peak at 1087 cm^{-1} (ν_{C-O-C}) was corresponding to PLLA block.

The structure of the triblock copolymer (MPEG750-*b*-PLLA3400-*b*-PBLG13800) was also comfirmed by the ^1H NMR spectra (Fig. 4). As the mixture solvent of $CDCl_3$ and TFA-d was selected, the chemical shifts of every copolymer unit had little differences compared with those in $CDCl_3$. The peak *i* at 7.35 ppm was attributed to the benzene ring of the protecting group. The peaks at 5.13, 4.67, 2.50, 2.18 and 1.98 ppm were assigned to protons of the PBLG block. The peaks at 3.86 and 3.58 ppm were assigned to protons of the MPEG block. The peaks at 5.32 and 1.65 ppm were assigned to protons of the PLLA block. DP_{PBLG} in the triblock copolymer was obtained from the integral ratio of CH_3O– (*a* at 3.38 ppm) to $-C_6H_5CH_2OCOCH_2-$ (*g* at 2.50 ppm) in the ^1H NMR spectrum of MPEG-*b*-PLLA-*b*-PBLG, as shown in the following formula, $DP_{PBLG}=3\,g/2a$. Thus, the value of DP_{PBLG} was calculated to be 63.

The GPC (Fig. 5(D)) trace of the triblock copolymer showed a unimodal shape. (polydispersity $M_n/M_w=1.35$, $M_n=13{,}400$ in Table 2). This further indicated that the copolymerization was completed successfully and there was no homopolymer in the copolymer.

Table 2
Molecular weight data of di- and tri-block copolymers

Polymer	$M_n\times10^{-3}$ (^1H NMR)	$M_n\times10^{-3}$ (GPC)	$M_w\times10^{-3}$ (GPC)	M_w/M_n
$MPEG_{750}$-$PLLA_{3400}$-OH	4.1	5.7	6.0	1.04
$MPEG_{750}$-$PLLA_{3400}$-BOC	4.1	5.8	6.1	1.04
$MPEG_{750}$-$PLLA_{3400}$-NH_2	4.1	6.1	6.4	1.04
$MPEG_{750}$-$PLLA_{3400}$-$PBLG_{13800}$	18.0	13.4	18.2	1.35
$MPEG_{750}$-$PLLA_{3400}$ -$PLGA_{7900}$	12.0	9.3	10.4	1.12

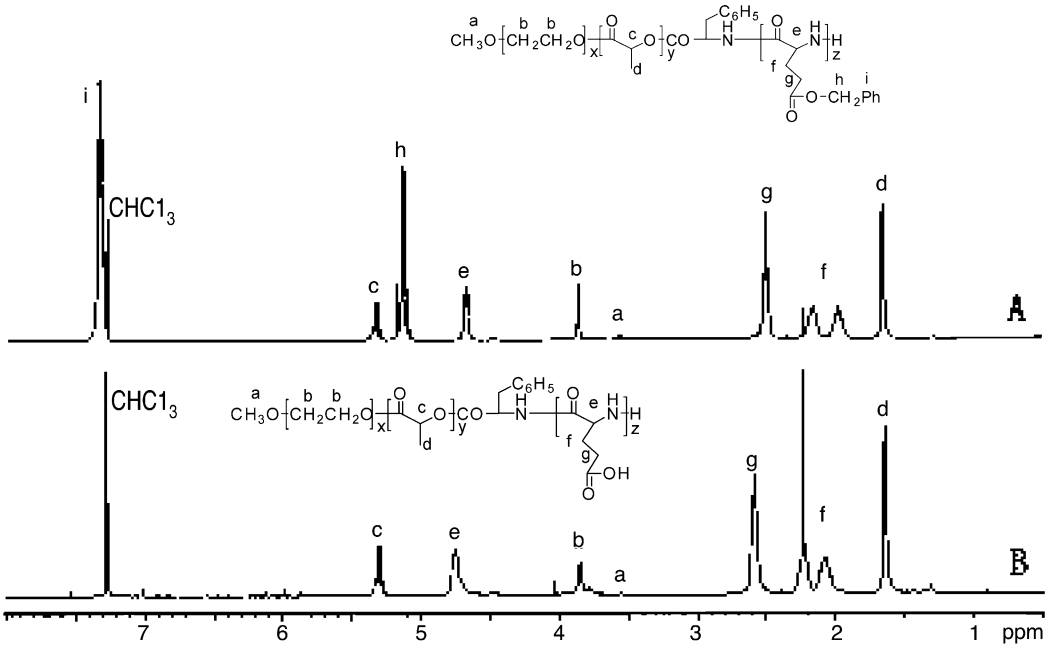


Fig. 4. The ^{1}H NMR spectra of (A) MPEG-*b*-PLLA-*b*-PBLG ($DP_{MPEG}=17$, $DP_{PLLA}=23$, $DP_{PBLG}=63$), (B) MPEG-*b*-PLLA-*b*-PLGA ($DP_{MPEG}=17$, $DP_{PLLA}=23$, $DP_{PLGA}=61$) in $CDCl_3$ and TFA-d (1:1, v/v).

3.6. Deprotection

It is well known that the benzyl protective group of the polymer can be removed by catalytic hydrogenation with the use of Pd/C as a catalyst [19–20]. The deprotection of MPEG-*b*-PLLA-*b*-PBLG ($DP_{MPEG}=17$, $DP_{PLLA}=23$, $DP_{PBLG}=63$) was confirmed with ^{1}HNMR and FTIR as show in Figs. 4 and 5, respectively. In the ^{1}H NMR spectrum, the disappearance of the benzyl peaks at 5.13, 7.35 ppm (Fig. 4) indicated that the protective group in the polymers was removed completely. In the FTIR spectrum, the δ_{CH} vibration of the benzyl at 749 and 697 cm^{-1} disappeared and the vibration of OH in the carboxyl group at 3440 cm^{-1} was strengthened greatly after hydrogenation (Fig. 5). The result also clearly confirmed that the benzyl groups had been removed completely. The GPC data of the deprotected polymer (Table 2, Fig. 6) suggested that main-chain cleavage in the polymers did not occur during the deprotection reaction.

Variation of the water contact angles of MPEG-PLLA-PLGA from MPEG-*b*-PLLA-*b*-PBLG was summarized in Table 3. The water contact angle of MPEG-PLLA-PLGA changed to 13.45° from 78.45° of MPEG-*b*-PLLA-*b*-PBLG ($DP_{MPEG}=17$, $DP_{PLLA}=23$, $DP_{PBLG}=63$) due to the

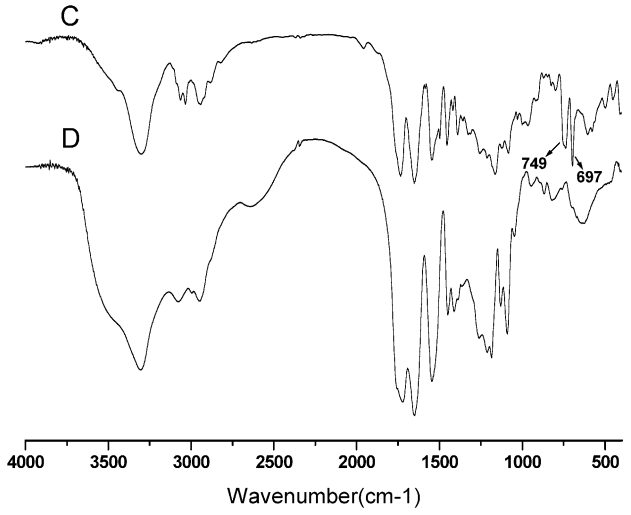


Fig. 5. The IR spectra of (C) MPEG-*b*-PLLA-*b*-PBLG ($DP_{MPEG}=17$, $DP_{PLLA}=23$, $DP_{PBLG}=63$). (D) MPEG-*b*-PLLA-*b*-PLGA ($DP_{MPEG}=17$, $DP_{PLLA}=23$, $DP_{PLGA}=61$).

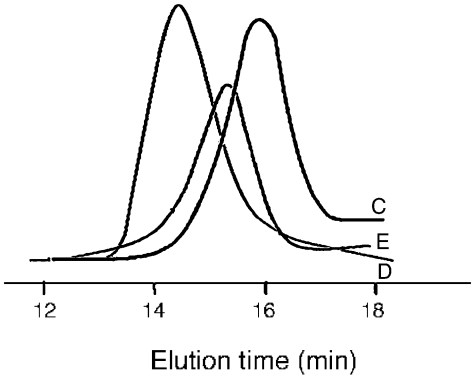


Fig. 6. The GPC traces of (C) MPEG-PLLA-NH_2 ($DP_{MPEG}=17$, $DP_{PLLA}=23$) (D) MPEG-*b*-PLLA-*b*-PBLG ($DP_{MPEG}=17$, $DP_{PLLA}=23$, $DP_{PBLG}=63$). (E) MPEG-*b*-PLLA-*b*-PLGA($DP_{MPEG}=17$, $DP_{PLLA}=23$, $DP_{PLGA}=61$).

Table 3
Water contact angles of MPEG-PLLA-PBLG and MPEG-PLLA-PLGA

Polymer	Water contact angle (degree)	
	Protected copolymer	Deprotected copolymer
$MPEG_{750}$-$PLLA_{3400}$-$PBLG_{3000}$	70.59°	44.90°
$MPEG_{750}$-$PLLA_{3400}$-$PBLG_{13800}$	78.45°	13.45°
$MPEG_{2000}$-$PLLA_{2800}$-$PBLG_{10000}$	77.70°	12.29°

reduction of γ-benzyl-L-glutamic acid groups into carboxyl groups after deprotection. These data clearly demonstrated the promising hydrophilicity of MPEG-PLLA-PLGA (the deprotected polymer) compared with that of the protected polymer. The hydrophilicity of MPEG-PLLA-PLGA increased with glutamic acid content in the copolymer.

4. Conclusion

Starting from MPEG, a triblock copolymer MPEG-*b*-PLLA-*b*-PLGA was obtained by catalytic hydrogenation of MPEG-*b*-PLLA-*b*-PBLGA that was synthesized from the ROP of BLG-NCA with amino-terminated MPEG-*b*-PLLA-NH_2 as a macroinitiator. The MPEG-*b*-PLLA-NH_2 was converted from MPEG-*b*-PLLA-OH that was prepared by the polymerization of L-lactide in the presence of MPEG and stannous octoate. ^{1}H NMR, FTIR, GPC and DSA analysis manifested that the intermediate and final products were successfully synthesized. Because the length of each block could be controlled and the structure of NCA could be selected at will, MPEG-*b*-PLLA-*b*-PLGA provided possibility and flexibility of adjusting its physical and chemical properties, such as solubility, hydrophilicity/hydrophobicity, processability, etc. The carboxyl groups of MPEG-*b*-PLLA-*b*-PLGA can be used to connect peptides, antibodies, and even DNA's. Therefore, it is a promising biomedical triblock copolymer.

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