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Synthesis, characterization, and controllable drug release of dendritic star-block copolymer by ring-opening polymerization and atom transfer radical polymerization

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Abstract

A series of well-defined dendritic star-block copolymers were successfully synthesized by combination of living ring-opening polymerization (ROP) and atom transfer radical polymerization (ATRP) with the hydroxyl-terminated dendrimer polyester. Dendritic star-shaped poly(L-lactide)s (PLLAs) were prepared by bulk polymerization of L-lactide (L-LA) with dendrimer polyester initiator and tin 2-ethylhexanoate catalyst. The number-average molecular weight of these polymers linearly increased with the molar ratio of L-LA to dendrimer initiator. Dendritic star-shaped PLLA was converted into a PLLABr macroinitiator with 2-bromopropionyl bromide. Dendritic star-block copolymers could be obtained via ATRP of 2-(*N*,*N*-dimethylamino)ethyl methacrylate (DMAEMA). The molecular weight distributions of these copolymers were narrow. The molecular weights of dendritic star-shaped polymers and star-block copolymers could be controlled by the molar ratios of monomer to initiator and monomer conversion. The thermal properties of these dendritic star-shaped polymers and star-block copolymers were investigated. The behavior of model drug chlorambucil release from the copolymer indicated that the rate of drug release could be effectively controlled by altering the pH values of the environment.

Keywords: Dendritic star-block copolymer; pH sensitivity; Controllable drug release

1. Introduction

More and more attention has been attracted toward star-shaped homopolymers and star-block copolymers due to their branched structures and unique physicochemical properties different from those of their linear polymeric counterparts [1–8]. Generally, two methods are employed to prepare these polymers. One is the so-called ''core first'' method in which a multifunctional initiator is used to initiate the polymerization of monomer to form multiarm star polymers [1,2]. The other is the so-called ''arm first'' strategy in which linear living polymer is synthesized initially, following by coupling reaction with a multifunctional coupling agent [8]. So far, the ''core first'' method has proven very efficient to prepare well-defined star polymers, including dendritic star polymers. Dendrimers are monodisperse molecules with well-defined and perfectly branched structure, and many terminal groups are located on the surface of molecule, which can provide unique properties such as high surface reactivity [9–22]. Therefore, dendrimers could be used as cores to synthesize dendritic star and star-block polymers.

Poly(L-lactide) (PLLA) possesses excellent biodegradability, biocompatibility and therefore has important applications in biomedical field. For instance, PLLA has been widely used as biodegradable sutures, implantable screws, drug delivery devices, and as temporary scaffolds for tissue [23–26].

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However, PLLA has suffered from the lack of controlled degradation due to its high degree of crystallinity and hydrophobicity [27–30]. Therefore, it is necessary to modify its structure and physical properties. Two main approaches, including introduction of branched structures [31,32] and hydrophilic units [33–35], have been used to improve the biodegradability and hydrophilicity of PLLA. Dendritic star-shaped PLLA is a class of well-defined and branched PLLA. Dendritic star-shaped PLLA can be synthesized via ring-opening polymerization (ROP) of L-lactide (LLA) with hydroxyl-terminated dendrimer initiator and tin 2-ethylhexanoate catalyst.

Much interest has been focused on poly(2-(*N*,*N*-dimethylamino)ethyl methacrylate) (PDMAEMA) owing to its excellent biocompatibility, hydrophilicity and pH sensitivities [36–43]. Therefore, it can be potentially used in drug and DNA delivery system [38]. A typical example is that Hu et al. successfully reported the controlled drug release from PDMAEMA with polyamidoamine (PAMAM) core [39]. Moreover, amphiphilic block copolymer can be obtained from the combination of PDMAEMA and PLLA. As a result, the hydrophilicity of PLLA can be improved obviously. In addition, this amphiphilic block copolymer makes the system more attractive as a drug delivery vehicle [40,43]. Recently, the preparation of PDMAEMA has been carried out by atom transfer radical polymerization (ATRP) and the process of polymerization can be well controlled with this living controllable polymerization [39–43].

Therefore, in this paper, novel and well-defined dendritic star-block poly(L-lactide)-*b*-poly(2-(*N*,*N*-dimethylamino)ethyl methacrylate) copolymers (PLLA-*b*-PDMAEMA) were prepared by the combination of ROP and ATRP of LLA and DMAEMA with hydroxyl-terminated dendrimer polyester initiator (Scheme 1). Namely, the dendrimer polyester with terminal hydroxyl groups was used as an initiator for the ROP of LLA to prepare a series of dendritic star-shaped PLLAs. Then, PLLABr was obtained by a reaction of PLLA and 2-bromopropionyl bromide. Star-block copolymer PLLA-*b*-PDMAEMA was synthesized by ATRP of DMAEMA with PLLABr macroinitiator. And the thermal properties of these dendritic star-shaped and star-block polymers were investigated. Finally, the behavior of controllable drug release from PLLA-*b*-PDMAEMA was investigated at buffer solutions with different pH values.

2. Experimental section

2.1. Materials

L-Lactide (Purac Biochem, The Netherlands) was purified by recrystallization from ethyl acetate twice and dried in a vacuum at room temperature. 2-(*N*,*N*-Dimethylamino)ethyl methacrylate (DMAEMA) (Acros Organic, USA) was dried over CaH_2 and distilled under reduced pressure. Tin 2-ethylhexanoate and 2-bromopropionyl bromide (Aldrich, USA) were distilled under reduced pressure before use. CuBr was purified by stirring in acetic acid and washing with ethanol and then dried in vacuum. Pentamethyldiethylenetriamine (PMDETA) (Acros Organic, USA) was stirred overnight over CaH_2 and distilled under reduced pressure. The dendrimer polyester (Perstorp Specialty Chemicals, Sweden) (M_n = 1747) was dried at 60 °C *in vacuo* for 24 h before use. Chlorambucil was purchased from Fluka Chemika (USA) and used directly. Methylene chloride, chloroform, triethylamine, hexane, and ethyl acetate were dried over CaH_2 and distilled. Tetrahydrofuran (THF) was distilled from CaH_2 under dry nitrogen purge.

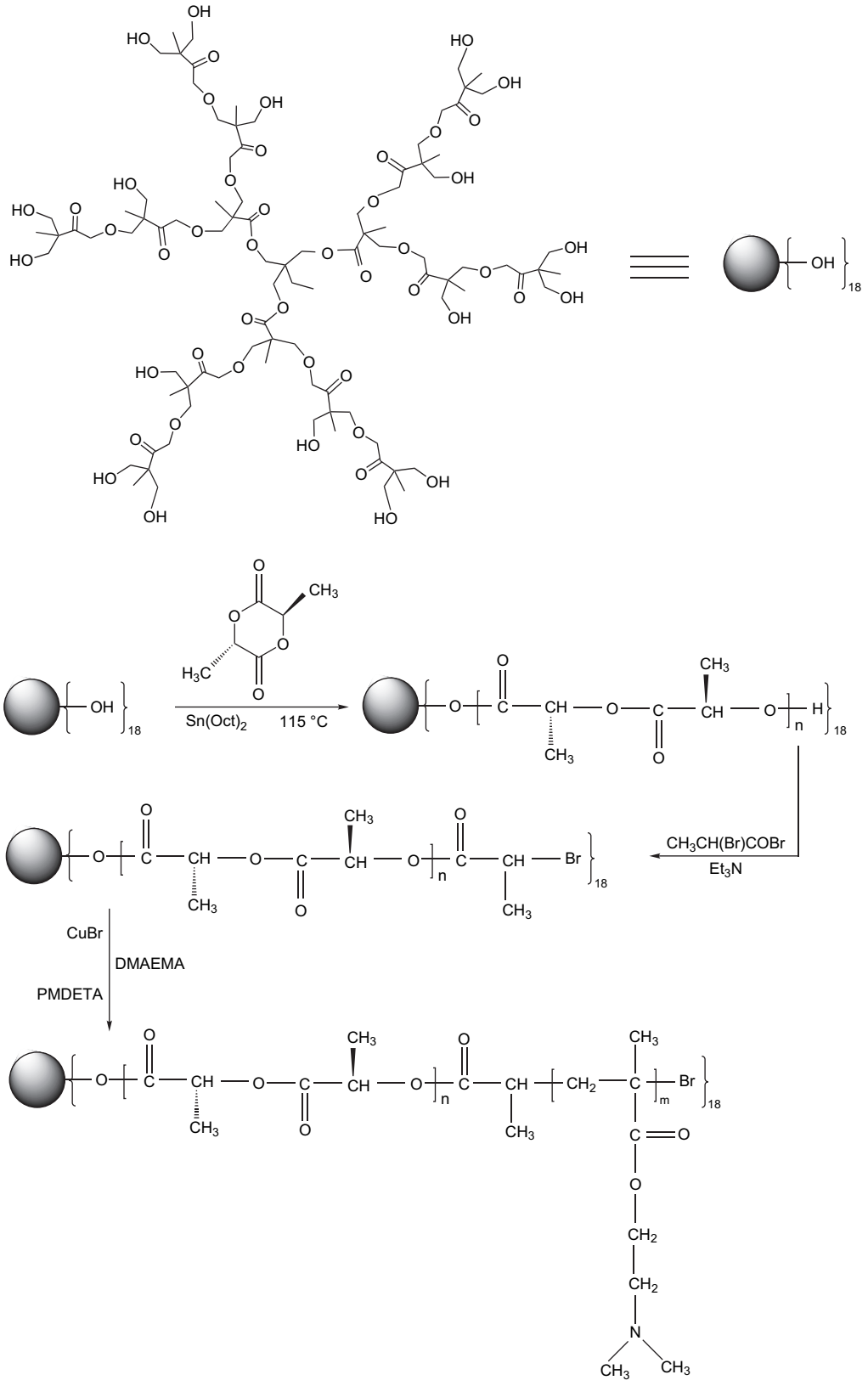
2.2. Measurements

Fourier transform infrared spectra (FT-IR) were recorded on an AVATAR 360 ESP FT-IR spectrometer (Nicolet, USA). ^{1}H NMR and ^{13}C NMR spectra were obtained from JOEL JNM-ECA300 NMR spectrometer with $CDCl_3$ as a solvent. The chemical shifts were relative to tetramethylsilane at $\delta = 0$ ppm for protons. The molecular weight and molecular weight distributions were measured on a Viscotek TDA 302 gel permeation chromatograph equipped with two columns (GMHHR-H, M Mixed Bed). THF was used as eluent at a flow rate of 1 mL/min at 30 °C and narrow-distributed polystyrene standards were used for calibrations. Differential scanning calorimetric (DSC) analysis was carried on a DSC 2910 thermal analysis system (TA Instruments Inc., USA) with a heating rate of 10 °C/min from 20 °C to 180 °C under nitrogen atmosphere. Thermogravimetric analysis (TGA) was carried on a TGA 2050 thermogravimetric analyzer (TA Instruments Inc., USA) with a heating rate of 20 °C/min from 30 °C to 500 °C under nitrogen atmosphere. Wide-angle X-ray diffraction (WAXD) patterns of powder samples were obtained at room temperature on a Cu Kα radiation source using a Bruker AXS D8 Advance X-ray diffractometer (Bruker, Germany). The supplied voltage and current were set to 40 kV and 120 mA. Samples were exposed at a scanning rate of $2\theta = 4°$/min between 2θ values from 1.5° to 60°. The mean sizes of micelles/aggregates were measured on a Zeta submicron size and potential analyzer (ZetaPALS) at 25 °C. UV spectra were performed on a UV 2100 UV–visible spectrophotometer (SHIMADZU, Japan).

2.3. Preparation of polymers

2.3.1. Synthesis of dendritic star-shaped PLLA

A typical polymerization procedure was as follows: LLA (6.19 g, 43 mmol), dendrimer polyester (0.208 g, 0.12 mmol), and a magnetic stirring bar were added into a flame-dried polymerization tube. The tube was then connected to a Schlenk-line, where an exhausting–refilling process was repeated three times. The tube was put into an oil bath at 120 °C with vigorous stirring for 5 min. Then catalytic amount of tin 2-ethylhexanoate catalyst in dry toluene was added to the melt mixture and the exhausting–refilling process was carried out again to remove the toluene. After being vacuumed and refilled with dried nitrogen for three times, the polymerization tube was sealed in nitrogen. Under stirring, the bulk polymerization was carried out at 115 °C for 24 h. The crude polymer was



Scheme 1. Synthesis of dendritic star-block copolymer by ring-opening polymerization and atom transfer radical polymerization.

dissolved in methylene chloride and precipitated in hexane for three times. The purified polymer was dried in a vacuum until constant weight to obtain white fine powders.

$M_{n,NMR} = 54\,600$, $M_{n,GPC} = 51\,950$, $M_w/M_n = 1.12$, IR (KBr, cm^{-1}): 3400–3680 (ν_{O-H}), 2993 (ν_{C-H}), 2948 (ν_{C-H}), 1756 ($\nu_{C=O}$), 1455 (ν_{C-H}). ^1H NMR ($CDCl_3$, δ, ppm): 5.16

(m, CH in PLLA), 4.35 (q, terminal CH in PLLA), 1.58 (m, CH_3 in PLLA), 1.21 (CH_3 in dendrimer). ^{13}C NMR ($CDCl_3$, δ, ppm): 16.6 (CH_3 in PLLA), 69.1 (CH in PLLA), 169.7 (C=O in PLLA).

2.3.2. Synthesis of dendritic star-shaped PLLABr macroinitiator

A typical example is given below. Dendritic star-shaped PLLA (4.06 g, 1.39 mmol of OH group) was dissolved in dry chloroform (50 mL) under stirring. To this solution was added triethylamine (0.141 g, 1.39 mmol) under nitrogen at room temperature. The mixture was stirred and cooled to 0 °C with ice bath. Then 2-bromopropionyl bromide (0.661 g, 3.06 mmol) in dry chloroform (20 mL) was added dropwise to the mixture within 40 min. The reaction mixture was stirred for 30 h at room temperature before it was washed with 1 M NaOH, 1 M HCl aqueous solution and deionized water and then the combined organic layer was dried overnight with $MgSO_4$. After evaporation of solvent, the resulting product was purified by precipitating from cold methanol.

$M_{n,NMR} = 57\,040$, $M_{n,GPC} = 54\,380$, $M_w/M_n = 1.12$, IR (KBr, cm^{-1}): 2990 (ν_{C-H}), 2941 (ν_{C-H}), 1758 ($\nu_{C=O}$), 1456 (ν_{C-H}). ^1H NMR ($CDCl_3$, δ, ppm): 5.16 (m, CH in PLLA), 4.40 (q, CHBr), 1.86 (d, CH_3Br), 1.58 (m, CH_3 in PLLA).

2.3.3. Synthesis of dendritic star-block PLLA-b-PDMAEMA copolymer

In a general procedure, dendritic star-shaped PLLABr macroinitiator (0.50 g, $M_{n,NMR} = 57\,040$, $M_w/M_n = 1.12$, containing 0.158 mmol of C–Br), CuBr (22.7 mg, 0.158 mmol), DMAEMA (1.49 g, 9.48 mmol), and THF (4 mL) were added into a dried flask with a magnetic stirring bar. The reaction system was degassed with three freeze–evacuate–thaw cycles and then deoxygenated PMDETA (33 μL, 0.158 mmol) was introduced into the flask by syringe under an argon atmosphere. Then the reaction was performed at 60 °C for 2 h. The crude product was dissolved in THF and passed through a neutral aluminum oxide column to remove the copper catalysts. The polymer was obtained by precipitation into cold hexane and dried *in vacuo*.

$M_{n,NMR} = 100\,500$, $M_{n,GPC} = 86\,400$, $M_w/M_n = 1.19$, IR (KBr, cm^{-1}): 3130–3680 (ν_{N-C}), 2993 (ν_{C-H}), 2941 (ν_{C-H}), 2830 (ν_{C-H}), 2764 (ν_{C-H}), 1763 ($\nu_{C=O}$), 1730 ($\nu_{C=O}$), 1455 (ν_{C-H}). ^1H NMR ($CDCl_3$, δ, ppm): 5.15 (m, CH in PLLA), 4.06 (m, OCH_2 in PDMAEMA), 2.56 (m, CH_2N in PDMAEMA), 2.27 (m, NCH_3 in PDMAEMA), 1.75–2.06 (m, CH_2 in PDMAEMA), 1.57 (m, CH_3 in PLLA), 0.88–1.04 (m, CH_3 in PDMAEMA).

2.4. PH sensitivities of dendritic star-block PLLA-b-PDMAEMA copolymer

PLLA-*b*-PDMAEMA (Sample 8) of 120 mg was dissolved in 24 mL DMF with stirring then 36 mL of distilled water was added slowly (1 mL/h) by microinfusion pump. The copolymer solution was left to stir overnight prior to dialysis against buffer solutions (pH = 2.0, 4.0, 6.0, 7.0, 9.0, 10.0) for 48 h using dialysis membrane and copolymer micelles were formed. The mean sizes of micelles in buffer solutions of different pH were determined by Zeta submicron size and potential analyzer at 25 °C. The copolymer concentration for the solutions analyzed was approximately 2 mg/mL.

2.5. Controllable drug release of dendritic star-block PLLA-b-PDMAEMA copolymer

Drug-loaded films of PLLA-*b*-PDMAEMA copolymer and model drug chlorambucil (5%, w/w) were cast from 6% THF solution (w/v). Residual solvent was removed *in vacuo* at room temperature for 2 days until a constant weight was obtained [44]. The film thickness was found to be about 0.2 mm. Films loading chlorambucil were sealed separately using dialysis membranes. The membranes were immersed into 40 mL of buffer solutions (pH = 2.0, 6.0, 7.0, 10.0) at 37 °C. In a certain time interval, 5.0 mL of buffer solution was withdrawn and replaced by 5.0 mL of fresh buffer solution. The chlorambucil release was measured by UV–visible spectrophotometer using 223.2 nm (pH = 2.0), 256.1 nm (pH = 6.0), 255.4 nm (pH = 7.0), and 256.0 nm (pH = 10.0) as characteristic bands. All solutions withdrawn were kept at 37 °C for 2 days prior to measurements. All release measurements were carried out three times for each sample and an average value was adopted. The cumulative release was calculated by using Eq. (1):

$$\text{Cumulative release}\ (\%) = \frac{40.0c_n + 5.0\sum c_{n-1}}{W_0} \times 100 \qquad (1)$$

where c_n (mg/mL) is the concentration of chlorambucil in buffer solution which was withdrawn for n times, c_{n-1} (mg/mL) is the concentration of chlorambucil in buffer solution which was withdrawn for $n-1$ times, and W_0 (mg) is the weight of chlorambucil in the copolymer.

3. Results and discussion

3.1. Synthesis and characterization of dendritic star-shaped PLLA

The dendritic star-shaped PLLA homopolymers were synthesized by the reaction of hydroxyl-terminated dendrimer polyester with LLA at 115 °C with bulk polymerization. IR spectrum of the PLLA is shown in Fig. 1(a). The wide absorption band at 3400–3680 cm^{-1} was attributed to the hydroxyl groups of polymer. The intensive absorption peak at 1756 cm^{-1} was assigned to the carbonyl band of PLLA. ^1H NMR spectrum of the dendritic star-shaped PLLA is shown in Fig. 2(a). The peak of the methine (b) protons was detected at 5.16 ppm. The peak of the protons of the terminal methine (b′) could be discovered at 4.35 ppm. The ^{13}C NMR spectrum of star-shaped PLLA was shown in Fig. 3. It can be seen that the typical signals of the main chain of the PLLA arms could be clearly detected at 16.6 ppm, 69.1 ppm, and 169.7 ppm. Various amounts of LLA were used to obtain PLLA with different

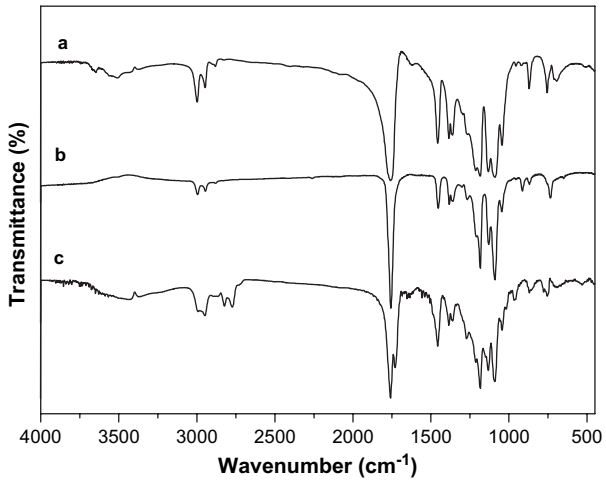


Fig. 1. IR spectra of dendritic star-shaped PLLA (a), PLLABr macroinitiator (b), and dendritic star-block copolymer PLLA-*b*-PDMAEMA (c).

molecular weight. The average degrees of polymerization for the PLLA arms were calculated from the integration ratio between the methine protons in the repeat units (b) and those in the terminal unit (b′) based on ^{1}H NMR spectrum. As shown in Table 1 and Fig. 4, the number-average molecular weight of the resulting polymer linearly increased with the molar ratio of monomer to initiator, which indicated that the hydroxyl-terminated dendrimer polyester could be used as effective propagation centers and all of the 18 hydroxyl groups of the dendrimer polyester molecule could initiate the ROP of LLA. In addition, the number-average molecular weight distributions of these polymers were narrow ($1.07 \leq M_w/M_n \leq 1.19$). The GPC trace of dendritic star-shaped PLLA (Sample 2) is shown in Fig. 5. It could be seen that the trace was comparatively symmetrical and monomodal, which indicated that the sample was pure star-shaped PLLA homopolymer. All these demonstrated that well-defined 18-arm star-shaped dendritic PLLA with narrow number-average molecular weight distributions could be successfully synthesized by ROP of LLA with hydroxyl-terminated dendrimer polyester initiator.

3.2. Synthesis and characterization of dendritic star-shaped PLLABr macroinitiator and star-block PLLA-b-PDMAEMA copolymers

The dendritic star-shaped PLLABr macroinitiator of ATRP was obtained by the reaction of PLLA with 2-bromopropionyl bromide. The molecular weight of PLLABr increased slightly and the molecular weight distribution was similar to that of PLLA. In IR spectrum (Fig. 1(b)), the absorption band 3400–3680 cm^{-1} corresponding to hydroxyl groups was absent. ^{1}H NMR spectrum was shown in Fig. 2(b). The signal at 4.35 ppm disappeared, while novel signals corresponding to methyl protons (d) and methine proton (c) of 2-bromopropionates appeared at 1.86 ppm and 4.40 ppm (the integral ratio between d and c was 3.06), indicating that all the terminal hydroxyl groups have been reacted completely.

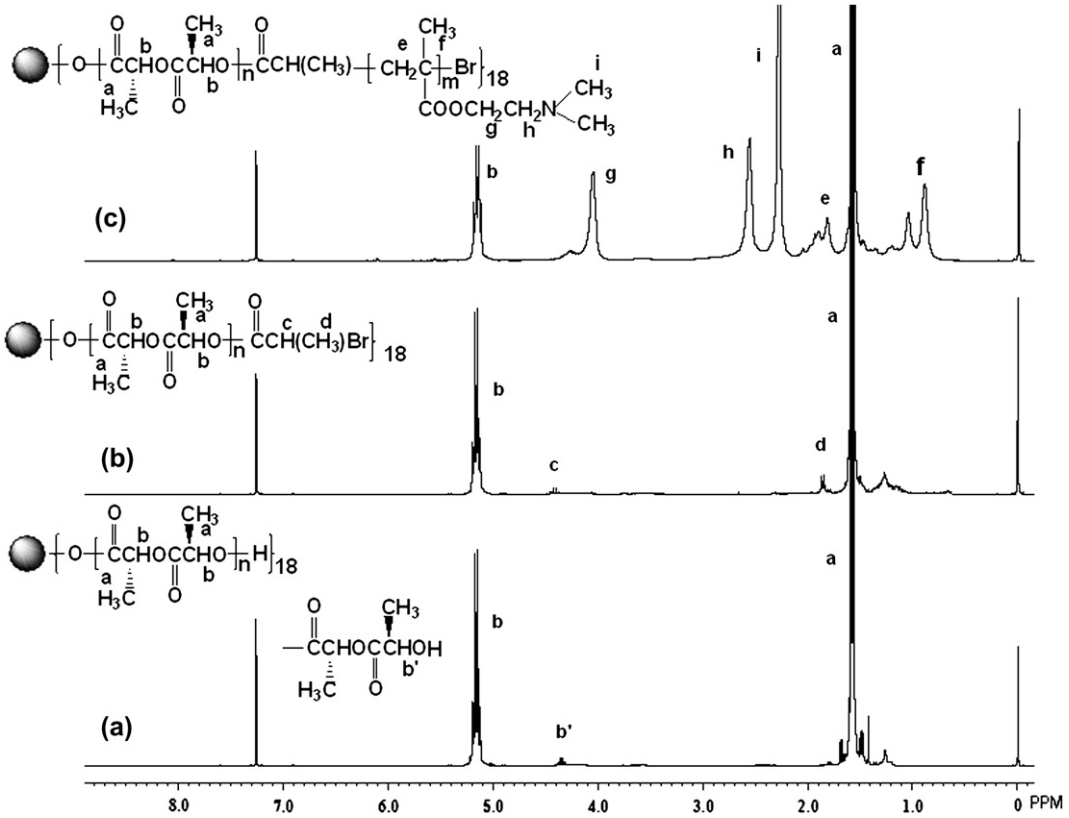


Fig. 2. ^{1}H NMR spectra of dendritic star-shaped PLLA (a), PLLABr macroinitiator (b), and dendritic star-block copolymer PLLA-*b*-PDMAEMA (c).

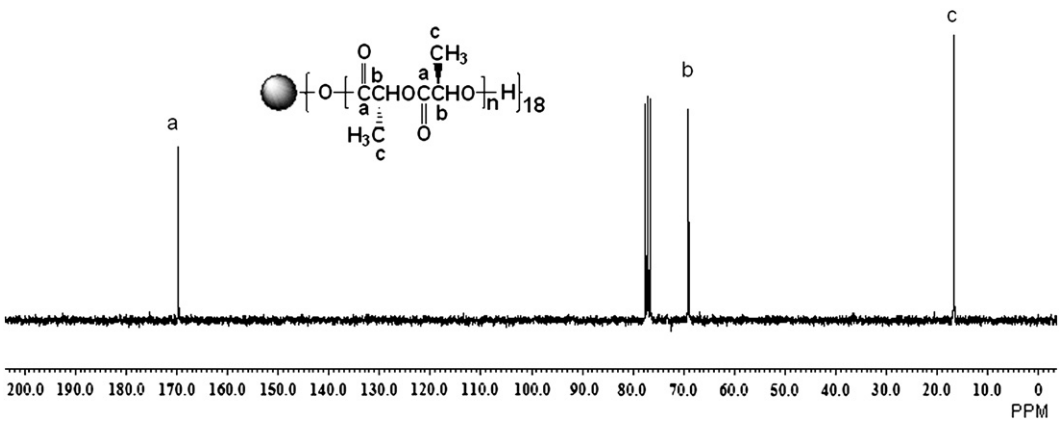


Fig. 3. ^{13}C NMR spectrum of dendritic star-shaped PLLA.

Table 1
Results of the polymerization of dendrimer polyester with various amounts of L-lactide (LLA) in bulk at 115 °C and [LLA]/[Sn(Oct)$_2$] = 1000, polymerization time = 24 h

Sample	[LLA]/[OH]	$M_{n,th}$ [b]	$M_{n,NMR}$ [c]	$M_{n,GPC}$ [d]	M_w/M_n [d]	Conversion (%)
LPLLA[a]		29 480	30 160	28 500	1.28	95.2
1	10	27 300	28 840	26 200	1.07	98.4
2	20	52 600	54 600	51 950	1.12	98.0
3	40	101 160	106 200	94 750	1.15	95.8
4	80	193 300	201 300	180 200	1.19	92.3

[a] Denotes the linear PLLA.
[b] $M_{n,th} = [LLA]/[OH] \times 18 \times M_{LLA} \times$ conversion (%) $+ M_{initiator}$; $M_{n,th}$ denotes the number-average molecular weight of dendritic star-shaped PLLA.
[c] Determined by ^{1}H NMR spectroscopy of linear and dendritic star-shaped PLLA.
[d] Determined by GPC analysis with polystyrene standards. THF was used as eluent.

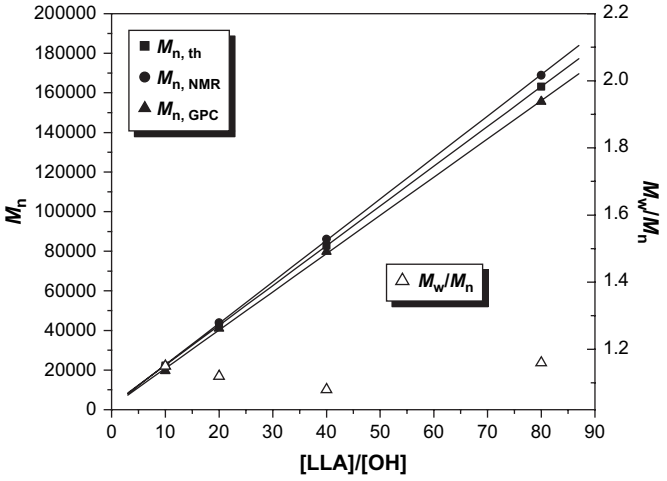


Fig. 4. Dependence of M_n on the molar ratio of [LLA]/[OH] with dendrimer polyester initiator and tin 2-ethylhexanoate catalyst in bulk at 115 °C.

Dendritic star-block PLLA-*b*-PDMAEMA copolymer was prepared from PLLABr macroinitiator and DMAEMA via ATRP at 60 °C. According to the IR spectrum shown in Fig. 1(c), the wide band at 3130–3680 cm^{-1} was the absorption band of methylamino groups. In addition, carbonyl

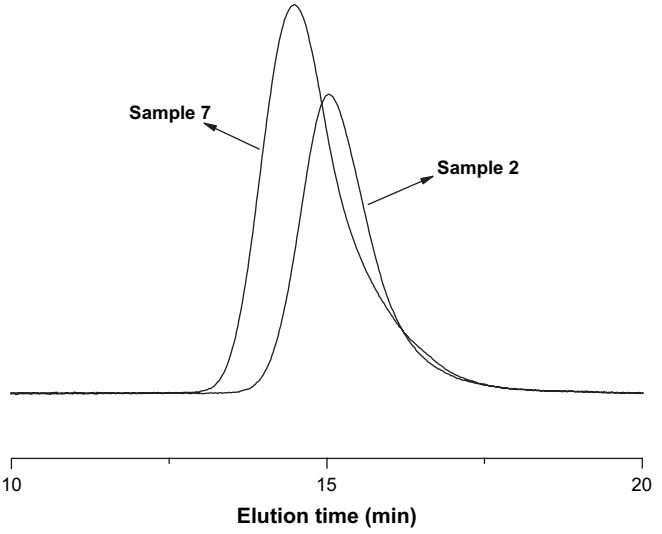


Fig. 5. GPC traces of dendritic star-shaped PLLA (Sample 2) and dendritic star-block copolymer PLLA-*b*-PDMAEMA (Sample 7).

absorption band became wide obviously and split into two peaks. The peak at 1763 cm^{-1} corresponded to the carbonyl absorption of PLLA units, while the peak at 1730 cm^{-1} was assigned to the carbonyl absorption of PDMAEMA units. ^{1}H NMR spectrum of the copolymer is shown in Fig. 2(c). All the protons signals of the copolymer could be detected. The degree of polymerization of the DMAEMA block was obtained from the integration of the proton signals at 5.15 ppm (b in PLLA block) and 2.56 ppm (h in PDMAEMA block). The GPC trace of the amphiphilic copolymer is shown in Fig. 3 (Sample 7). It could be seen that the trace was monomodal but showed a small tailing toward the low molecular weight. Furthermore, according to the data given in Table 2, the molecular weights determined by GPC ($M_{n,GPC}$) were much lower than those determined by ^{1}H NMR ($M_{n,NMR}$) and theoretic values ($M_{n,th}$). All these could be attributed to the absorption of PDMAEMA onto the GPC column which resulted in an increase of retention time and led to the tailing phenomenon of GPC trace and lower molecular weight detected by GPC [32,33]. The kinetic plot of dendritic star-block

Table 2
Results for ATRP of DMAEMA with dendritic star-shaped PLLABr macroinitiator

Sample	Time (h)	$M_{n,th}$[a]	$M_{n,NMR}$[b]	$M_{n,GPC}$[c]	M_w/M_n[c]	Conversion[d] (%)
5	0.5	66 060	68 770	60 510	1.16	6.5
6	1	73 530	76 050	66 220	1.14	10.9
7	2	95 950	100 500	86 400	1.19	24.1
8	3	110 380	114 410	94 860	1.18	32.6
9	4	122 600	126 700	104 300	1.23	39.8

[a] $M_{n,th} = M_{monomer} \times ([monomer]/[C-Br]) \times 18 \times conversion\,(\%) + M_{macro\text{-}initiator}$, $[monomer]/[C-Br] = 60$.
[b] Determined by ^{1}H NMR spectroscopy of dendritic star-block copolymer.
[c] Determined by GPC analysis with polystyrene standards. THF used as eluent.
[d] Calculated from: $[W_p/(W_i + W_m)] \times 100\%$, where W_p, W_i, and W_m were the weight of the block copolymer produced and the initial weights of the related macroinitiator and monomer, respectively.

PLLA copolymer formation is shown in Fig. 6. The conversion of DMAEMA reached 39.8% in 4 h in THF. The plot of $\ln([M_0]/[M])$ against polymerization time seemed linear and crossed the zero point. This result demonstrated that the first-order kinetics could be maintained until relative high conversion, suggesting the concentration of active species remained constant throughout the course of polymerization of DMAEMA. It could be seen from Fig. 7 that $M_{n,NMR}$ values were close to $M_{n,th}$, increased linearly with conversion, indicating that the molecular weight of the copolymer could be manipulated by the control of monomer conversion. Moreover, the molecular weight distributions of the copolymers were narrow ($M_w/M_n \leq 1.23$). Obviously, the dendritic star-shaped PLLABr could be used as an efficient macroinitiator for living polymerization of DMAEMA to form amphiphilic dendritic star-block copolymer PLLA-*b*-PDMAEMA.

3.3. Thermal properties of dendritic star-shaped PLLA and dendritic star-block PLLA-b-PDMAEMA copolymers

The thermal properties of dendritic star-shaped PLLA and dendritic star-block PLLA-*b*-PDMAEMA are presented in Table 3 and Figs. 8 and 9. According to the DSC data and curves, the melting point (T_m) and the degree of crystallinity (X_c) of dendritic star-shaped PLLA were lower than those of linear PLLA and increased with the length of the PLLA arms, which could be ascribed to the crystalline imperfection due to the branched structure and the short chain length of the PLLA arms. In dendritic star-shaped PLLA, the chain movements of PLLA were hindered and their crystallizability was weakened, whereas no such steric hindrance existed in linear PLLA. For example, the T_m and X_c of the linear PLLA (LPLLA) were 170.9 °C and 35.8%, whereas those of dendritic star-shaped PLLA (Sample 2) were 149.9 °C and 22.6%, respectively. Similarly, the glass transition temperature (T_g) of the dendritic star-shaped PLLA was lower than that of linear

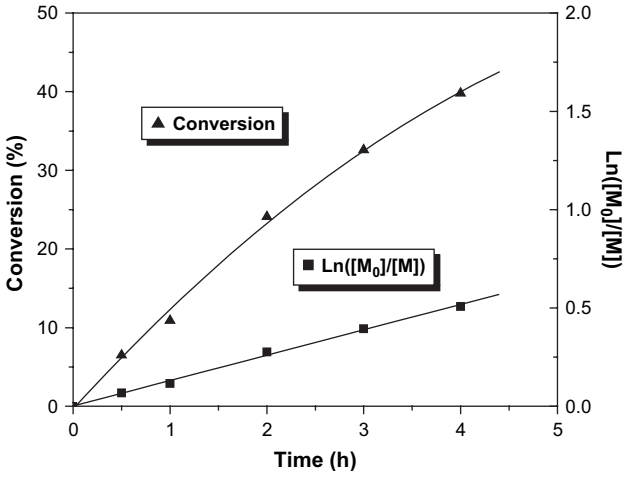


Fig. 6. Kinetic plot for ATRP of DMAEMA with dendritic star-shaped PLLABr initiator. [DMAEMA]:[C−Br]:[CuBr]:[PMDETA] = 60:1:1:1 in THF at 60 °C.

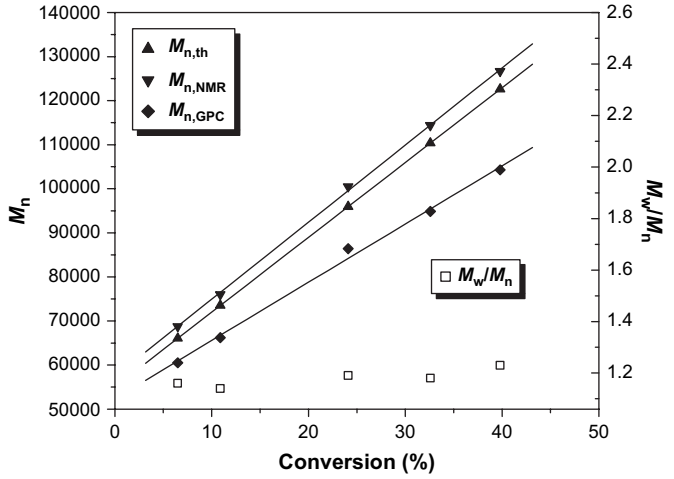


Fig. 7. Evolution of M_n and M_w/M_n of dendritic star-block copolymer PLLA-*b*-PDMAEMA with conversion for ATRP of DMAEMA. See Fig. 6 for reaction conditions.

Table 3
Thermal properties of linear PLLA, dendritic star-shaped PLLA, and dendritic star-block PLLA-*b*-PDMAEMA

Sample[a]	T_g[b] (°C)	T_m[c] (°C)	ΔH[d] (J/g)	X_c[e] (%)	T_{onset}[f] (°C)	T_{max}[g] (°C)
LPLLA	57.7	170.9	33.5	35.8	269.1	302.1
1	46.9	131.5	16.8	17.9	222.7	268.7
2	48.6	149.9	21.2	22.6	235.9	275.6
3	54.0	156.6	24.9	26.6	239.8	279.9
4	55.9	163.7	26.5	28.3	257.8	283.2
5	48.8	148.8	12.7	13.6	227.8	406.1
6	49.1	147.2	9.6	10.3	226.4	418.2
7	48.5	143.9	7.8	8.3	222.1	429.8
8	48.3	143.5	6.9	7.4	218.9	437.6
9	47.9	141.9	5.1	5.4	220.2	439.8

[a] Samples are the same as in Table 1 and Table 2.
[b] The glass transition temperature of PLLA segments in linear PLLA, dendritic star-shaped PLLA, and dendritic star-block PLLA-*b*-PDMAEMA.
[c] The melting point of PLLA segments in linear PLLA, dendritic star-shaped PLLA, and dendritic star-block PLLA-*b*-PDMAEMA.
[d] Heat of melting of crystalline PLLA segments.
[e] The degree of crystallinity of PLLA segments in linear PLLA, dendritic star-shaped PLLA, and PLLA-*b*-PDMAEMA. Calculated from the heat of melting using the melting of 93.6 J/g of 100% crystalline PLLA.
[f] Onset decomposition temperature.
[g] Temperature corresponding to the maximum rate of weight loss.

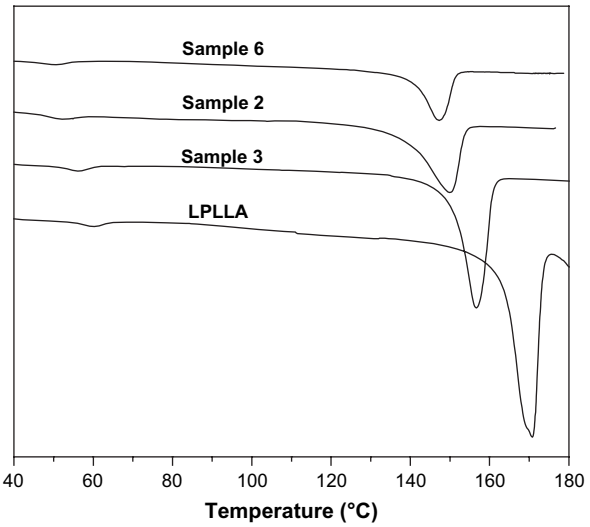


Fig. 8. DSC curves of linear PLLA (LPLLA), dendritic star-shaped PLLA (Samples 2 and 3), and dendritic star-block PLLA-*b*-PDMAEMA (Sample 6).

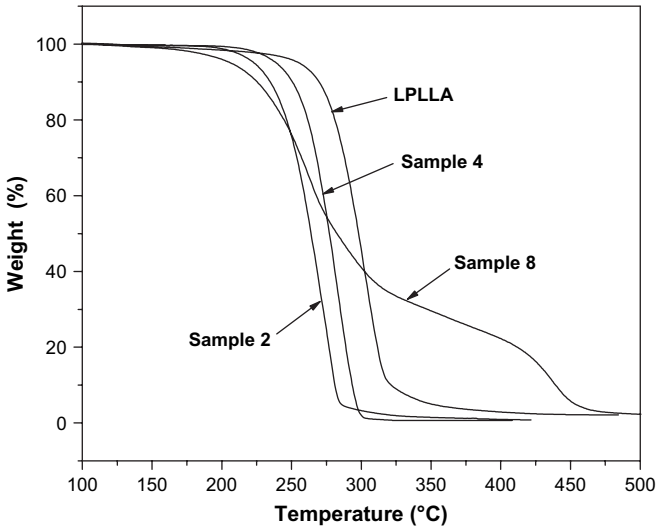


Fig. 9. TGA thermograms of linear PLLA (LPLLA), dendritic star-shaped PLLA (Samples 2 and 4), and dendritic star-block PLLA-*b*-PDMAEMA (Sample 8).

one and increased with the length of the PLLA arms. For instance, the T_g of LPLLA was 57.7 °C, while that of Sample 2 was 48.6 °C. In dendritic star-block PLLA-*b*-PDMAEMA, such as Sample 6, the T_m and X_c of PLLA block decreased to 147.2 °C and 10.3%, respectively. These could be attributed to the presence of amorphous PDMAEMA segments in the dendritic star-block copolymer. Therefore, the crystallinity of PLLA segments was seriously hindered by amorphous PDMAEMA segments. The branched structure of the dendritic star-block copolymer and the presence of PDMAEMA segments together led to the crystallinity imperfection which resulted in the decrease of T_m and X_c of the block copolymer. With the increase of the PDMAEMA block length in copolymer, the decrease of the degree of crystallinity occurred. According to the TGA data and thermograms, the onset decomposition (T_{onset}) and the maximum decomposition (T_{max}) of linear PLLA were higher than those of dendritic star-shaped PLLA, which could be attributed to the increase of thermally unstable hydroxyl groups in dendritic star-shaped PLLA. For instance, the T_{onset} and T_{max} of the linear PLLA (LPLLA) were 269.1 °C and 302.1 °C, while those of the dendritic star-shaped PLLA (Sample 2) were 235.9 °C and 275.6 °C, respectively. PLLA-*b*-PDMAEMA copolymer possessed lower T_{onset} and higher T_{max} than the dendritic star-shaped PLLA. As shown in Fig. 9, the behavior of thermal decomposition temperature of PLLA-*b*-PDMAEMA copolymer was different from that of the dendritic star-shaped PLLA. The decomposition process included two stages. The first stage should be ascribed to the decomposition of PLLA segments ($T_{onset} = 218.9$ °C, Sample 8) while the second one should be attributed to the decomposition of PDMAEMA segments ($T_{max} = 437.6$ °C, Sample 8), which could further confirm the presence of two blocks in the copolymer.

3.4. Wide-angle X-ray scattering analysis

The results from wide-angle X-ray diffraction (WAXD) analysis of the linear PLLA (LPLLA), dendritic star-shaped PLLA (Sample 2), and dendritic star-block PLLA-*b*-PDMAEMA copolymer (Sample 8) are shown in Fig. 10. It could be seen that the linear PLLA and dendritic star-shaped PLLA showed intense peaks at 16.8° (due to diffraction from (200) and/or (110) planes) and 19.2° (owing to diffraction from (203) and/or (113) planes of α crystalline form of PLLA). These results were in good agreement with previous reports on linear PLLA [45]. This suggested that the dendritic star-shaped PLLA had the same crystalline structure as the linear PLLA. However, the intensity of peak of dendritic star-block copolymer became weaker and the width of peak became wider than those of linear and star-shaped PLLA. This could be attributed to the presence of amorphous PDMAEMA

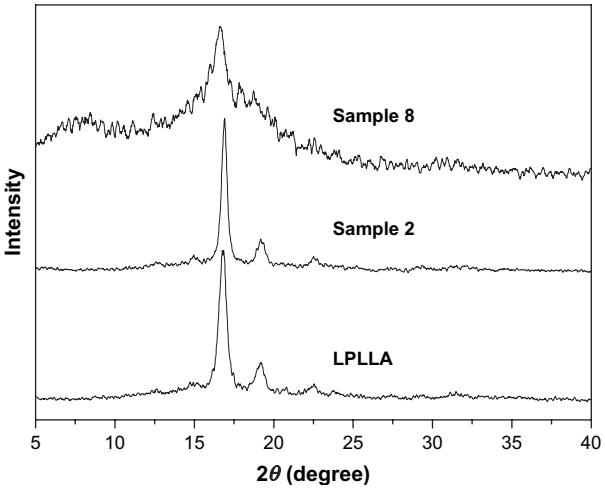


Fig. 10. WAXD patterns of linear PLLA (LPLLA), dendritic star-shaped PLLA (Sample 2), and dendritic star-block copolymer PLLA-*b*-PDMAEMA (Sample 8).

block in copolymer which seriously hindered the crystalline condition of PLLA block.

3.5. PH sensitivities of dendritic star-block PLLA-b-PDMAEMA copolymer

The pH sensitivities of dendritic star-block PLLA-*b*-PDMAEMA copolymer were investigated by measuring the sizes of micelles/aggregates of copolymer. The micelles/aggregates were obtained by dialysis of copolymer–DMF solution against buffer solution with different pHs because the copolymer was amphiphilic and did not dissolve in water directly. The effect of pH on the mean radius (R_m) of micelles of PLLA-*b*-PDMAEMA copolymer is plotted in Fig. 11. At pH $\leq$ 7.0, micelles/aggregates were observed with R_m in the 210–228 nm range. But at pH $>$ 7.0, the R_m of the micelles/aggregates was decreased dramatically. Namely, the copolymer presented larger sizes in acidic and neutral solutions than in basic solutions, which should be attributed to the protonation/deprotonation of *N*,*N*- dimethylaminoethyl groups in PDMAEMA segment. Under acidic and neutral conditions, the *N*,*N*-dimethylaminoethyl groups were protonated and the PDMAEMA block was quasi-completely charged. The aggregates were thought to be micelles with a hydrophobic PLLA core and a protonated PDMAEMA corona. Under basic conditions, the charge density of the PDMAEMA block decreased dramatically as the pH increased. The PDMAEMA block was almost deprotonated and micelles with a hydrophobic PLLA core and an essentially uncharged PDMAEMA corona formed.

3.6. Controllable drug release of dendritic star-block PLLA-b-PDMAEMA copolymer

Considering the pH sensitivities of dendritic star-block PLLA-*b*-PDMAEMA, the copolymer could be expected to become an intelligent carrier in controllable drug release system. Chlorambucil (Fig. 12) was a kind of alkylating anticancer agent and used as a model drug to investigate the controllable release properties of the copolymer. All release experiments were carried out under the conditions of pH 2.0, 6.0, 7.0, and 10.0 at 37 °C. The cumulative release of chlorambucil from loading Sample 8 is presented in Fig. 13. As shown in figure, the release rate for chlorambucil from the copolymer was the fastest at pH 2.0, then pH 6.0 and 7.0. The least release rate was at pH 10.0. The results should be ascribed to the conformational transition of PDMAEMA block from an expanding shape to a compact coil in accordance with the variation of the surrounding pH values [39]. As a result, the release rate of chlorambucil should be changed according to the change of conformation of PDMAEMA block. In acidic and neutral solutions, PDMAEMA block presented expanding conformation and chlorambucil could diffuse out from the copolymer. In basic solutions, PDMAEMA block showed compact conformation and chlorambucil was prevented releasing from the copolymer. All these demonstrated that the surrounding pH values could effectively control the release rate from the dendritic star-block PLLA-*b*-PDMAEMA copolymer. The investigation of model drug chlorambucil release indicted that the release rate of the drug could be effectively controlled by altering the pH values of buffer solutions.

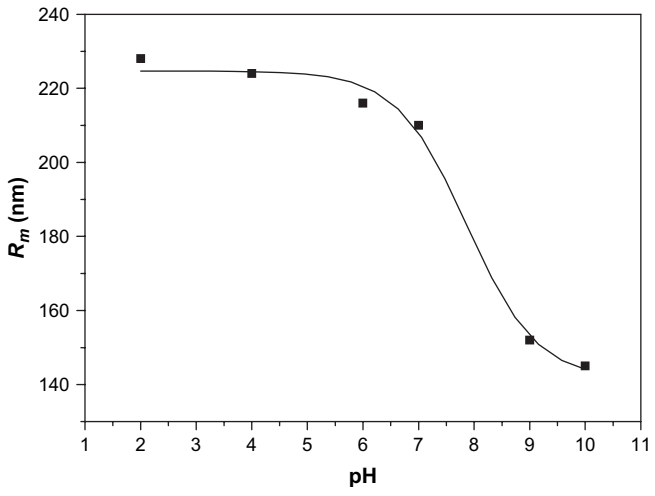


Fig. 11. Effect of pH on the mean radius (R_m) of micelles/aggregates of PLLA-*b*-PDMAEMA (Sample 8).

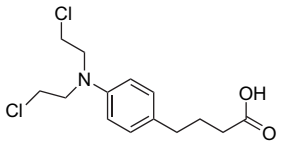


Fig. 12. Chemical structure of chlorambucil.

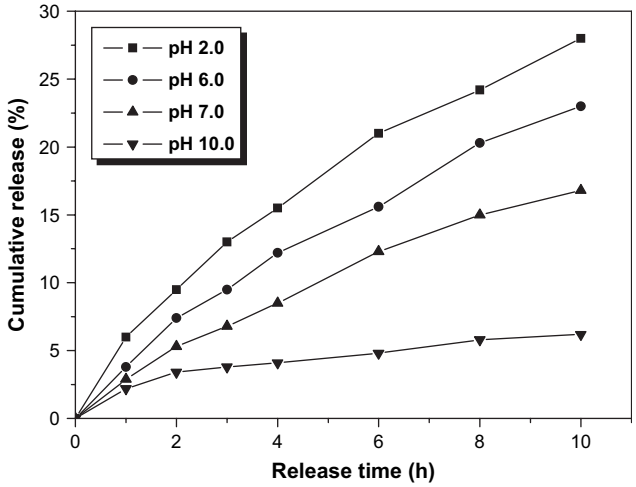


Fig. 13. Release profiles of chlorambucil from dendritic star-shaped PLLA-*b*-PDMAEMA copolymer under the conditions of pH 2.0, 6.0, 7.0, and 10.0 at 37 °C.

4. Conclusion

The novel dendritic star-shaped PLLAs and amphiphilic dendritic star-block PLLA-*b*-PDMAEMAs were successfully synthesized. Dendritic star-shaped PLLAs with narrow weight distribution were synthesized by living ROP of LLA with

hydroxyl-terminated dendrimer polyester initiator. Then, dendritic star-shaped PLLA was converted into a macroinitiator for the preparation of amphiphilic dendritic star-block PLLA-*b*-PDMAEMA copolymers via ATRP. The thermal properties of dendritic star-shaped PLLA and dendritic star-block PLLA-*b*-PDMAEMA were investigated. The investigation of model drug chlorambucil release indicated that the release rate of the drug could be effectively controlled by altering the pH values of the environment.

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