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Controlled synthesis of AB_2 amphiphilic triarm star-shaped block copolymers by ring-opening polymerization

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ABSTRACT

This paper describes the synthesis of a novel amphiphilic AB_2 triarm star-shaped copolymer with A = non-toxic and biocompatible hydrophilic poly(ethylene oxide) (PEO) and B = biodegradable and hydrophobic poly(ε-caprolactone) (PCL). A series of AB_2 triarm star-shaped copolymers with different molecular-weights for the PCL block were successfully synthesized by a three-step procedure. α-Methoxy-ω-epoxy-poly(ethylene oxide) (PEO-epoxide) was first synthesized by the nucleophilic substitution of α-methoxy-ω-hydroxy-poly(ethylene oxide) (MPEO) on epichlorohydrin. In a second step, the α-methoxy-ω,ω'-dihydroxy-poly(ethylene oxide) ($PEO(OH)_2$) macroinitiator was prepared by the selective hydrolysis of the ω-epoxy end-group of the PEO-epoxide chain. Finally, $PEO(OH)_2$ was used as a macroinitiator for the ring-opening polymerization (ROP) of ε-caprolactone (εCL) catalyzed by tin octoaote ($Sn(Oct)_2$). PEO-epoxide, $PEO(OH)_2$ and the AB_2 triarm star-shaped copolymers were assessed by ^{1}H NMR spectroscopy, size exclusion chromatography (SEC) and MALDI-TOF. The behavior of the AB_2 triarm star-shaped copolymer in aqueous solution was studied by dynamic light scattering (DLS) and transmission electron microscopy (TEM).

Keywords*:* Aliphatic polyesters Poly(ethylene oxide) Star-shaped copolymers Micelles

1. Introduction

Over the last few years, most of the research has been focused on the synthesis of linear block copolymers by various polymerization methods. Nonlinear block copolymers have also attracted the interest of polymer scientists to determine the effect of the macromolecular architecture of block copolymers on their properties [1]. Nonlinear block copolymers, such as branched polymers, exhibit significantly different physicochemical properties as compared to their linear counterparts with a similar molar mass [2-4]. Recently, some investigators have paid attention to the synthesis and properties of the star-shaped block copolymers, which are representative of branched polymers [5-11]. A typical example of a star-shaped block copolymer is the AB_2 copolymer composed of one arm of the polymer A and two arms of the polymer B. The synthesis of AB_2 star-shaped copolymers is largely described in the literature, generally by the combination of different polymerization techniques [12].

Two methods are typically used for the synthesis of star-shaped polymers, namely the "core-first" and "arm-first" methods. The "core-first" method involves a polymerization using a multifunctional initiator while in the "arm-first" method, linear polymer arms are coupled to a multifunctional coupling agent [13]. Various strategies have been proposed to prepare block copolymers with linear and nonlinear architectures, comprising PEO segments and biodegradable PCL blocks [9,14-16]. These copolymers received a great interest for their environmental, biomedical and pharmaceutical applications [17-19]. Indeed, PEO is widely used for biomedical applications due to its biocompatibility, low immunogenicity, high flexibility, hydrophilicity and lack of protein fouling [20]. On the other hand, PCL has been extensively used as an important biomaterial for a wide variety of drug delivery carriers and biomedical devices due to its biodegradability, versatile mechanical properties and proven biocompatibility [21,22].

Amphiphilic block copolymers have attracted a significant attention due to their useful properties stemming from their rich phase separation behavior and resulting in a variety of morphologies, both in the solid state and in selective solvents [23]. Polymer composition and structural architecture are known to affect the behavior and the morphology of micelles such as the size, shape and aggregation number [24]. Moreover, amphiphilic star-shaped block copolymers exhibit significant differences in comparison with linear copolymers of the same molecular weight and composition, such as a smaller hydrodynamic radius, lower solution and melt viscosities [25]. Several amphiphilic star-shaped block copolymers comprising hydrophobic biodegradable and hydrophilic

biocompatible segments have been synthesized with a particular interest especially for biomedical applications [26-30]. For example, Meier et al. synthesized star-shaped amphiphilic copolymers, whose each arm is a block copolymer based on PEO and PCL [31]. Later on, Kim et al. investigated micellar properties of similar block copolymers as a function of the number of arms [32]. Recently, other polymers based on PEO and aliphatic polyesters with more complex architectures have also been made available [33-41]. That leads to our motivation to apply a novel synthetic route for the synthesis of amphiphilic triarm star-shaped block copolymers based on PEO and PCL. The "arm-first" method has been used in this work to prepare an AB_2 star-shaped copolymer, whose the three arms are biocompatible and biodegradable or bioeliminable. Poly(ethylene oxide monomethyl ether) end-capped by two hydroxyl groups has been designed as a macroinitiator for the polymerization of εCL (Scheme 1). DLS and TEM analysis of the new biocompatible star copolymers synthesized in this work have confirmed the micellization of these amphiphilic materials in water.

2. Experimental

2.1. Materials

ε-Caprolactone (εCL) (Adrich, 99%) was dried over calcium hydride under stirring at room temperature for 48 h and distilled under reduced pressure before use. Poly(ethylene oxide monomethyl ether) (MPEO M_n ~ 2000 g/mol) was purchased from Fluka. NaH (dry, 95%, Aldrich) was used without further purification. Epichlorohydrin (99%, Janssen Chemical) was purified by distillation from calcium hydride under reduced pressure. Tin (II) bis(2-ethyl-hexanoate) ($Sn(Oct)_2$, 95%, Aldrich, 0.06 M solution in toluene) and sodium hydroxide (NaOH) were used as received. Toluene (Chem-lab) was dried by refluxing from Na/benzophenone for 48 h and distilled under nitrogen. All other chemicals were used as received.

2.2. Synthesis of α-methoxy-ω-epoxy-poly(ethylene oxide) (2)

PEO-epoxide was synthesized according to the literature [42]. Briefly, 10 g (5 mmol) of MPEO was dried by three azeotropic distillations with toluene. The MPEO was dissolved in 50 mL of dried toluene before to add 0.18 g (7.5 mmol) of sodium hydride. The solution was stirred at 30 °C for 2 h. About 2 mL (2.5 mmol) of epichlorohydrin was then added to the solution and the mixture was stirred at 40 °C for 6 h. The PEO-epoxide was precipitated in cool diethyl ether, filtered off, washed with diethyl ether and dried under vacuum before to be dissolved in dichloromethane (200 mL). The CH_2C1_2 solution was washed twice with distillated water, followed by drying over anhydrous magnesium sulfate. After filtration, PEO-epoxide was collected by elimination of dichloromethane under reduce pressure (Yield = 97%).

^{1}H NMR, δ (TMS, ppm): 3.65 (m, 4H, $OC\underline{H}_2C\underline{H}_2$), 3.37 (t, 3H, $OC\underline{H}_3$), 3.11 (m, 1H, $C\underline{H}OCH_2$), 2.78 (t, 1H, $CH\underline{H}$'-OCH), 2.55 (m, 1H, $C\underline{H}$H'OCH), M_n (NMR) = 2100 g/mol:

M_n(CES) = 1900 g/mol, M_w/M_n(CES) = 1.05.

2.3. Synthesis of α-methoxy-ω,ω'-dihydroxy-poly(ethylene oxide) macroinitiator (3)

Typically, 5 g (2.6 mmol) of PEO-epoxide 2 were poured into 20 mL of a 1 M NaOH aqueous solution. The reaction mixture was stirred at 50 °C for 17 h. The solution was cooled to room temperature and then lyophilized overnight. The crude polymer was dissolved in dry toluene (30 mL) and the insoluble salt (NaOH) was filtrated off. $PEO(OH)_2$ was recovered by precipitation in cool diethyl ether, filtered and dried in vacuo at 40 °C overnight (Yield 97%).

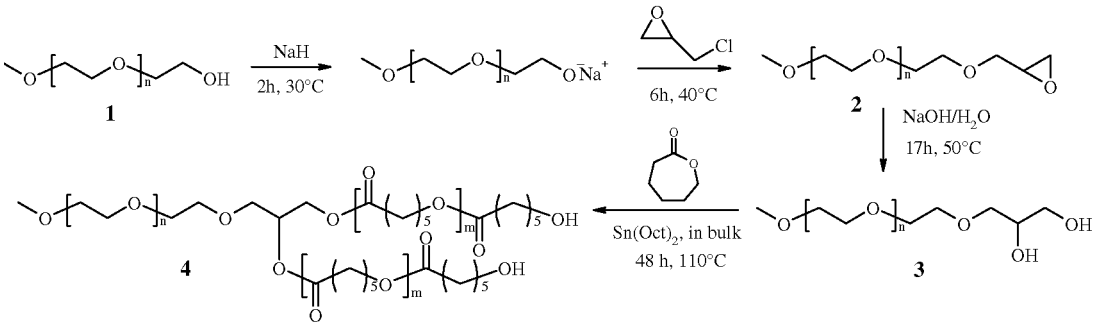
^{1}H NMR, δ (TMS, ppm): 3.65 (m, 4H, $OC\underline{H}_2C\underline{H}_2$ + 2 $C\underline{H}_2OH$), 3.38 (t, 3H, $OC\underline{H}3$), M_n (NMR) = 1800 g/mol:

M_n(CES) = 2000 g/mol, M_w/M_n (CES) = 1.10.

2.4. Typical synthesis of AB_2 star-shaped copolymers (4)

About 0.5 g (2.5 mmol) of $PEO(OH)_2$ was dried by three azeotropic distillations with anhydrous toluene. 0.6 mL (5 mmol) of freshly distilled εCL was then added. The solution was heated to 110 °C before to inject rapidly, through a septum, 0.1 mL of 0.06 M $Sn(Oct)_2$ solution. After 48 h of polymerization at 110 °C, the reactor was cooled to room temperature and the reaction mixture was dissolved in toluene. The copolymer was collected by precipitation in cool diethyl ether, filtration and drying at 40 °C under vacuo overnight.

Scheme 1. *Synthesis of AB_2 star-shaped copolymers.*



2.5. Characterization techniques

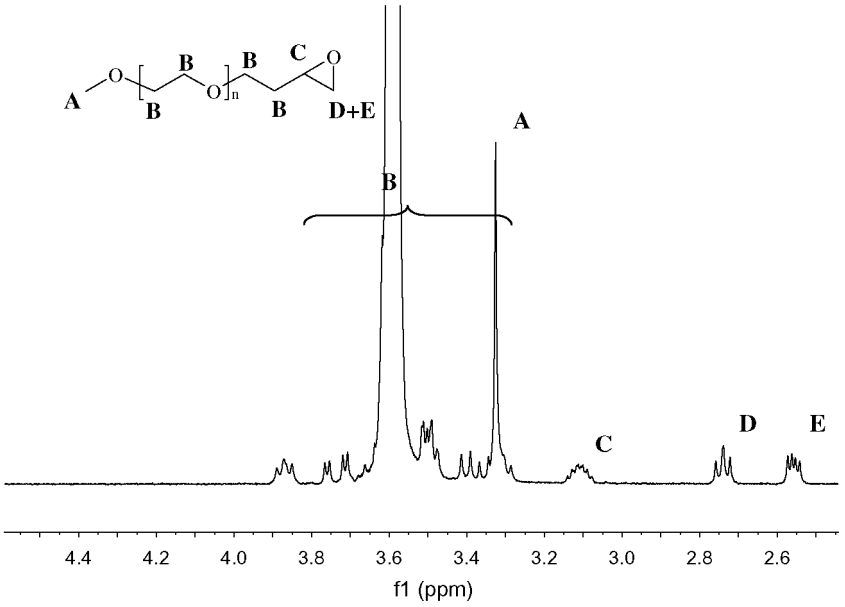
^{1}H NMR (400 MHz) spectra were recorded in $CDCl_3$ with Bruker AM 400 apparatus at 25 °C. Size exclusion chromatography (SEC) was carried out in THF at 45 °C at a flow rate of 1 mL/min using an SFD S5200 autosampler liquid chromatograph equipped with a SFD refractometer index detector 2000. Columns (HP PL gel 5 µm 10^5Å, 10^4Å, 10^3Å, 100 Å) were calibrated with polystyrene standards and PEO standards, respectively. MALDI-TOF spectra were recorded with a PerSeptive Biosystem Voyager-DE STR MALDI-TOF spectrometer equipped with 2 m linear and 3 m reflector flight tubes and a 337 nm nitrogen laser (3 ns pulse). Mass spectra were recorded at an accelerating potential of 20 kV in positive ion linear or reflectron mode. The data were processed with the Polymerix software. To generate the isotopic distributions, the isotope calculator tool of Data Explorer (software supplied by Applied Biosystems) was used. Dithranol (20 mg/mL THF) was used as a matrix and no cationating agent was added. Polymer was dissolved in THF (1 mg/mL THF). A PEG standard with a molecular weight of 1900 (1 mg/mL THF) was used for calibration, with dithranol as a matrix (20 mg/mL THF) and without additional cation. The samples for DLS analysis were prepared by dissolution of 50 mg of the copolymer in 5 mL of DMF to obtain a solution of 1 wt.% in polymer. This solution was then rapidly poured into 20 mL of MilliQ. water under vigorous stirring. The agitation was maintained for 2 h. The solutions were transferred into porous membrane (porosity: 1000 or 3500 Da depending of the molecular weight of the AB_2 copolymer) and dialyzed against MilliQ water overnight. The sample solutions were purified by passing through a 0.2 µm acrodisc filter aimed to remove aggregates and dirt before analysis. Dynamic light scattering measurements were performed using a Viscotek 802 DLS apparatus and data were treated by Omnisize 3.0 software. All the measurements were carried out at 25 °C at a measurement angle of 90°. Samples for transmission electron microscopy (TEM) were prepared by slow evaporation of the DLS solution on a formvar-coated copper grid. The excess of solution was removed with a filter paper. The samples were analyzed with a Philips CM100 microscope equipped with a Gatan 673 CCD camera and transferred to a computer equipped with the Kontron KS100 system.

3. Results and discussion

3.1. Synthesis of α-methoxy-ω-epoxypoly(ethylene oxide) (2)

In the first step, MPEO (M_π ~ 2000 g/mol) was end-capped by an epoxy group at the ω-position in agreement with a previously reported work [43]. For this purpose, the ω-hydroxyl end-group of commercially available MPEO was converted into sodium alkoxide by the reaction with an excess of sodium hydride before to be reacted with epichlorohydrin according to a nucleophile substitution mechanism. Toluene was used as a reaction medium in order to precipitate sodium chloride as a byproduct and to shift the equilibrium towards the expected α-methoxy-ω-epoxy-poly(ethylene oxide) [31]. After purification, the ^{1}H NMR spectrum of PEO-epoxyde was recorded and the assignments of the different signals was realized (Fig. 1).

***Fig. 1**. [1]H NMR spectrum of PEO-epoxide.*



The broad peak labeled as B at 3.65 ppm is a well-known characteristic of the methylene protons of a PEO chain, whereas the peak marked as A at 3.37 ppm, is distinctive of the methyl protons from the methoxy end-group. Furthermore, the ^{1}H NMR spectrum shows peaks, which are labeled as C, D and E at 3.15, 2.78 and 2.55 ppm, respectively. These signals are attributed to protons of the epoxide end-group in agreement with the expected structure. The epoxy functionality was determined by the ^{1}H NMR spectrum and is equal to 97% by the estimation from the integral value of the peak areas of A (protons of the methoxy end-group at 3.37 ppm) and D (protons of the epoxide end-group at 2.78 ppm) (Table 1). The molecular weight of PEO-epoxide was calculated by the Eq. (1):

$$M_{n(NMR)} = [(I/B/4)/I_D] \times 44 + 31 + 57 \qquad (1)$$

where I_B and I_D stand for the integral values of the peaks at 3.65 ppm ($C\underline{H}_2$-O of PEO repeating unit) and at 2.78 ppm (epoxide end-group), respectively. About 31 and 57 being the molecular weight of the two functional groups at the chain-end (CH_3O- and -CH_2-epoxide), respectively. The Fig. 2 shows the SEC curves of MPEO before and after epoxidation.

Low molecular weight distributions (M_w/M_n), 1.05 for MPEO and 1.05 for PEO-epoxide, respectively, were observed (Table 1). Moreover, the average molecular weight, purity and chain-end functionalization of the obtained PEO-epoxide were assessed in detail by MALDI-TOF. Indeed, MALDI-TOF is a valuable tool for determining the absolute molecular values and structureof polymers. The Fig. 3 shows the MALDI-TOF spectrum of PEO-epoxide in the 1200-2800 *m/z* mass range, revealing the expected 44 Da repeat unit spacing of ethylene oxide. Moreover, the MALDI-TOF spectrum confirms the presence of the epoxide group at the ω chain-end. The number of the average molecular weight (M_n) displays a good agreement with the MALDI-TOF results (Table 1). The theoretical molecular weight M_n of the PEO-epoxide was calculated according to the Eq. (2):

$$M_{n(MALDI\text{-}TOF)} = p \times A + X + Y \qquad (2)$$

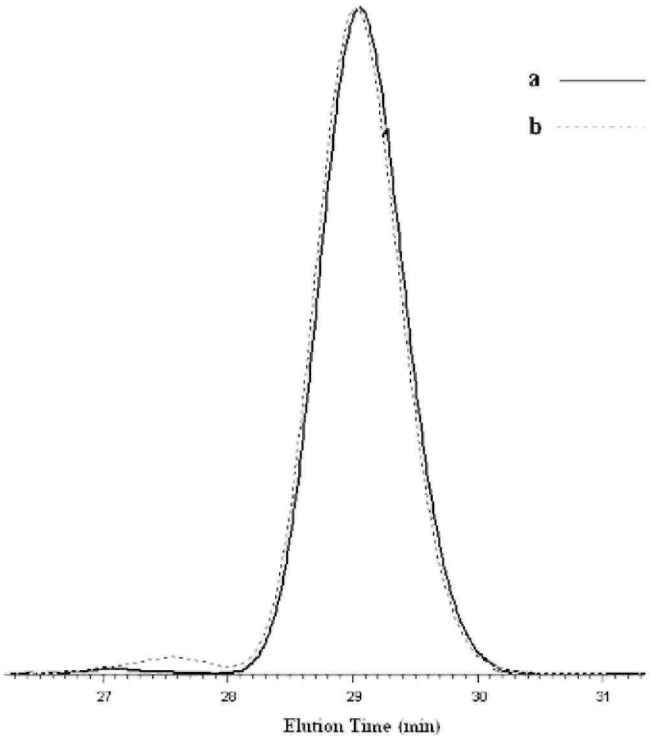
in which *A* is the mass of the repeating unit (ethylene oxide), *p* is the number of repeating units, *X* and *Y* are the mass of the end-groups (methoxy and methylene oxirane, respectively).

Table 1 *Macromolecular characteristitics of functional PEO.*

N°	Sample	Conversion[a]. (%)	M_n[b], (NMR)	M_n[c], MALDI-TOF	M_n[d], (SEC)	M_W/M_N[E] (SEC)
1a	MPEO	-	2000	n.d.	1800	1.05
1b	PEO-epoxide	97	2100	2000	1900	1.05
1c	$PEO(diOH)_2$	97	1800	2000	2000	1.10

[a] Conversion was calculated by ^{1}H NMR spectroscopy (Fig. 1). [b] M_n was calculated by ^{1}H NMR spectroscopy according to Eq. (1). [c] M_n was determined by MALDI-TOF. [d] M_n were determined by SEC calibrated with PEO standards. [e] M_w/M_n were determined by SEC calibrated with PEO standards.

Fig*. 2. Size exclusion chromatography curves of (a) MPEO (la, in Table 1), (b) PEO-epoxide (lb, in Table 1).*



3.2. Synthesis of a-methoxy-ω,ω'-dihydroxypoly(ethylene oxide) macroinitiator (3)

In a second step, $PEO(OH)_2$ was prepared by the hydrolysis with NaOH of the epoxy ring of PEO-epoxide. After purification, $PEO(OH)_2$ was analyzed by ^{1}H NMR, SEC and MALDI-TOF spectroscopy. The ^{1}H NMR spectrum of $PEO(OH)_2$ after treatment with an aqueous solution of NaOH (Fig. 4) is significantly different from the ^{1}H NMR spectrum of PEO-epoxide (Fig. 1). The ^{1}H NMR spectrum confirms the completeness of the ring-opening of the epoxide by the complete disappearance of the signal of the epoxide protons labeled as C, D and E at 3.15, 2.78 and 2.55 ppm, respectively, in the Fig. 1. Nevertheless, the signals of the two CH_2-OH formed after the epoxide ring-opening were not detectable as they were hidden by the peak of the CH_2O units of PEO repeating unit at 3.65 ppm. The number-average molecular weight of $PEO(OH)_2$ was determined by ^{1}H NMR from the ratio of the integrals of the signal at 3.65 ppm (CH_2-O from PEO) and the signal at 3.37 ppm (O-CH_3), by SEC with PEO standards and by MALDI-TOF, respectively (Table 1).

The SEC analysis of PEO-epoxide before and after the alkaline hydrolysis with NaOH shows that M_n remains unchanged with a slight shift towards higher M_n and a slight increase in M_w/M_n (Table 1, Fig. 5).

Nevertheless, a second peak appeared at a lower elution time. This second population of PEO-chains is certainly due to an unavoidable epoxide ring-opening by $PEO(OH)_2$ during the hydrolysis. The Fig. 6 shows the MALDI-TOF spectrum of the $PEO(OH)_2$ macroinitiator in the 1400-2600 *m/z* mass range. Moreover, the MALDI-TOF analysis shows only one population at $M_{n\ MALDI}$ = 2044 g/mol (Table 1). The MALDI-TOFMS spectrum also

showed an increase of the M_n of 18 Da (Eq. (2)), which confirmed the successful hydrolysis of the epoxy ring by NaOH of PEO-epoxide.

Fig. 3. *MALDI-TOF spectrum (linear mode) for PEO-epoxide (lb, in Table 1).*

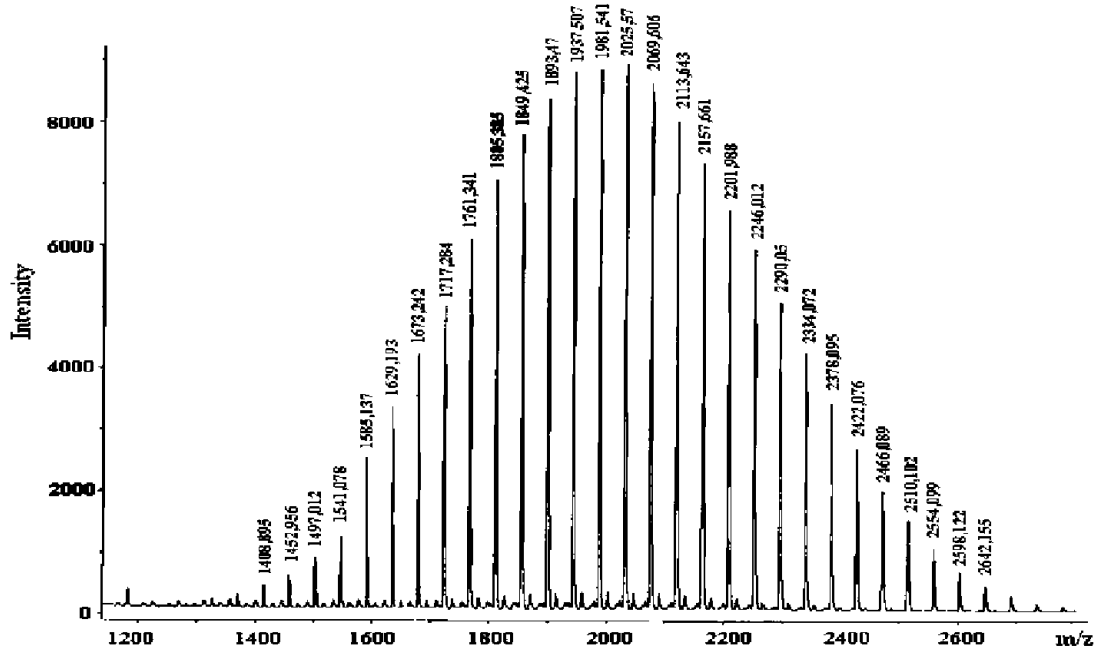


Fig. 4. *^{1}H NMR spectrum of PEO(OH)$_2$.*

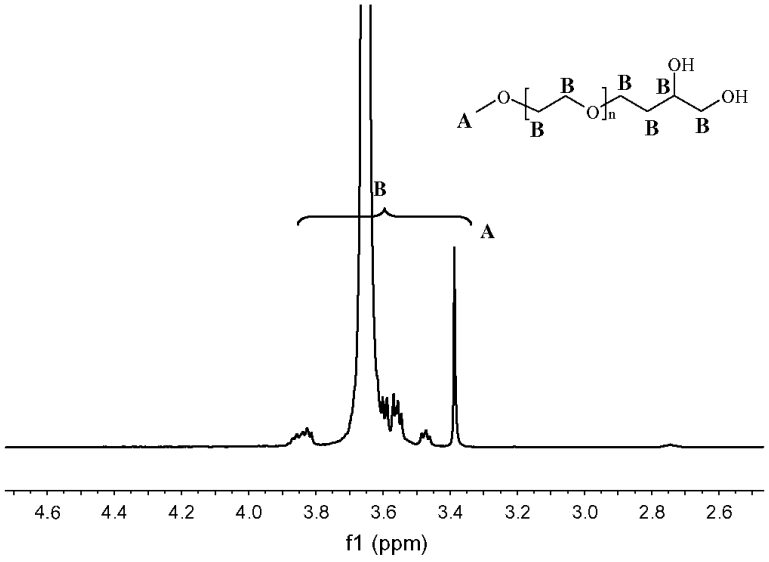


***Fig. 5**. Size exclusion chromatography curves of (a) PEO-epoxide (lb, in Table 1), (b) PEO(OH)$_2$ (1c, in Table 1).*

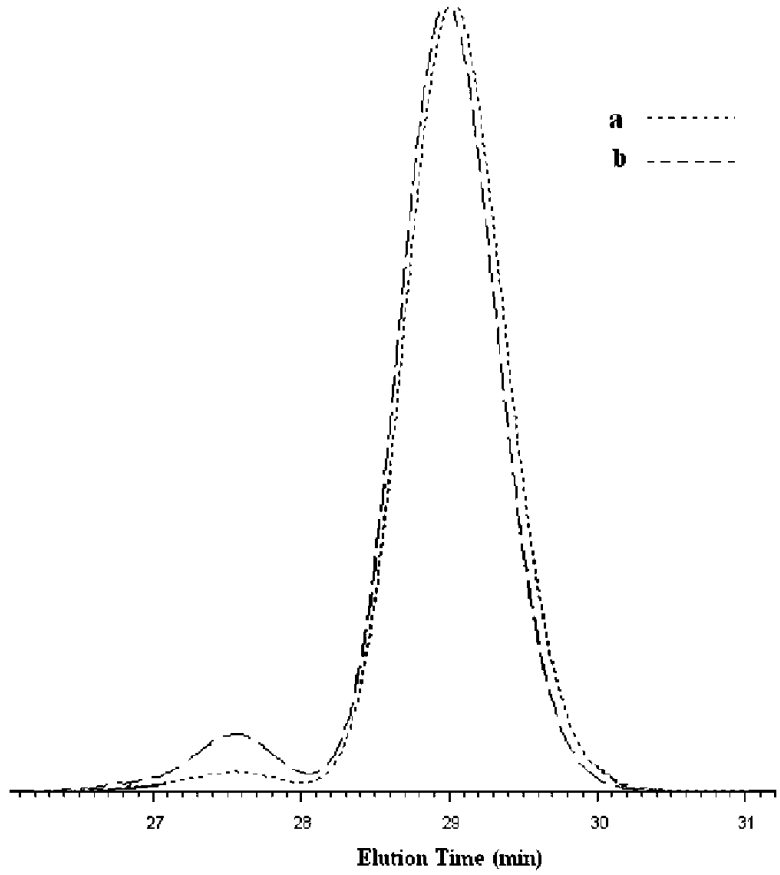


***Fig. 6.** MALDI-TOF spectrum (linear mode) for the PEO(OH)$_2$ macroinitiator (1c, in Table 1)*

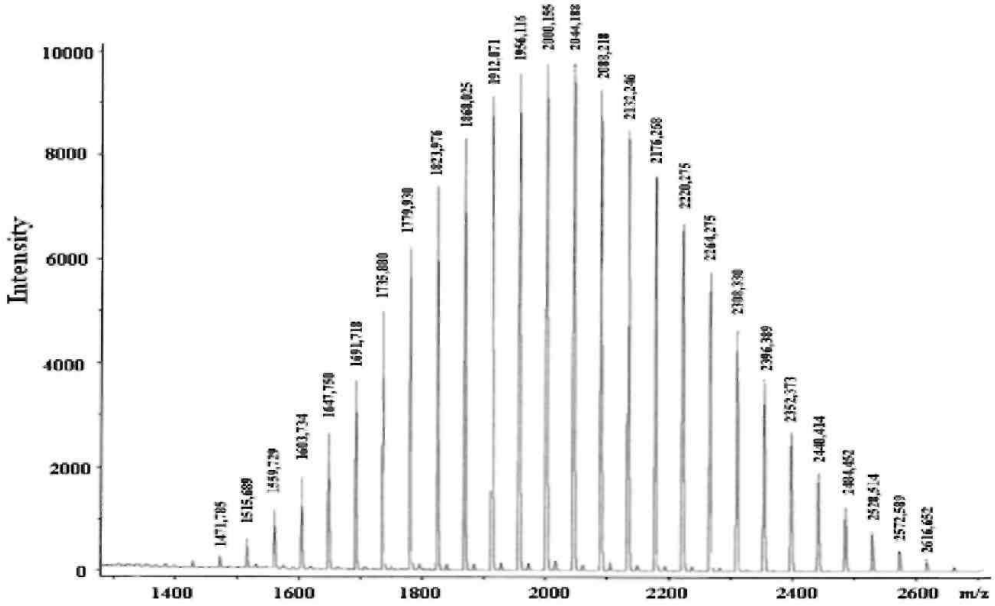
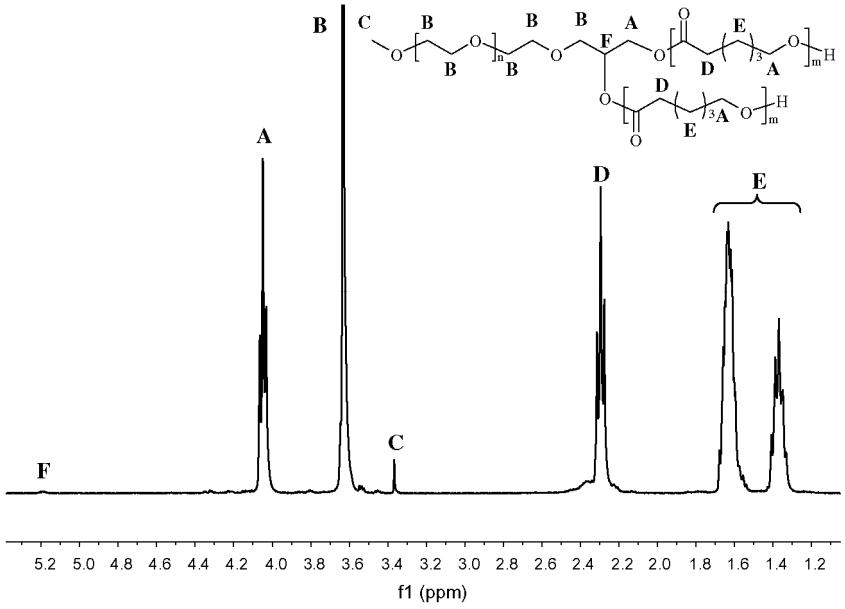


***Fig. 7**. 'H NMR spectrum for the AB_2 PEO(PCL)$_2$ star-shaped copolymer in $CDC1_3$.*



3.3. Synthesis of AB_2 star-shaped copolymers PE0(PCL)$_2$, (4)

The AB_2 triarm star-shaped copolymers PEO(PCL)$_2$ were successfully synthesized by the ring-opening-polymerization of εCL initiated by PEO(OH)$_2$ in the presence of Sn(Oct)$_2$ as a catalyst. Different ratios of εCL/macroinitiator were used to obtain different copolymers with different PCL block molecular-weights. The composition of the copolymer, structure and molecular weight were characterized by ^{1}H NMR and SEC analyses.

A typical ^{1}H NMR spectrum for the star-shaped copolymer, recorded in $CDC1_3$, is shown in the Fig. 7. The ^{1}H NMR spectrum for the purified copolymer shows signals typical of PEO and PCL. The methylene protons of PEO were observed at 3.65 ppm (peak B) and the characteristic methylene protons of PCL were detected at 4.05 (peak A), 2.30 (peak D), 1.63 and 1.37 (peak E). The M_n of the PEO(PCL)$_2$ triarm star-shaped copolymers was determined by ^{1}H NMR and has been calculated by the Eq. (3):

$$M_{n(NMR)}PEO(PCL)_2 = (I_A/2)/(I_B/4) \times DP_{PE0} \times 114.14 + M_{n(NMR)}PEO(OH)_2 \quad (3)$$

where I_A and I_B stand for the integral values of the methylene protons of PCL marked as A (Fig. 7) and for the methylene protons of PEO at 3.65 ppm B. About 114.14 is the molecular weight of εCL unit, DP_{PEO} is the degree of polymerization of the PEO(OH)$_2$ and $M_{N(NMR)}$ PEO(OH)$_2$ is the molecular weight of the macroinitiator. The experimental degree of εCL polymerization agrees well with the theoretical value (Table 2).

***Table 2** Characteristics of the AB_2 triarm star-shaped copolymers.*

N°	Sample	$[M]_0/[I]_0$	M_n[a] (th)	M_n[b] (NMR)	M_wM_n[c] (SEC)
2a	PEO(PCL)$_2$ 1	4	3000	2700	1.10
2b	PEO(PCL)$_2$ 2	8	4000	3700	1.35
2c	PEO(PCL)$_2$ 3	17	6000	5700	1.10
2d	PEO(PCL)$_2$ 4	26	8000	7500	1.30

[a] M_n (th) = $[M]_0/[I]_0$ X $M_{w\,\varepsilon cL}$ + M_n[MPEO(OH)$_2$].
[b] M_n was calculated by 'H NMR spectroscopy according to Eq. (3).
[c] M_w/M_n was determined by SEC calibrated by PS standards.

***Fig. 8**. Size exclusion chromatography curves of (a) $PEO(OH)_2$ (1c, in Table 1), (b) $PEO(PCL)_2$ triarm star-shaped copolymer (2a, in Table 2).*

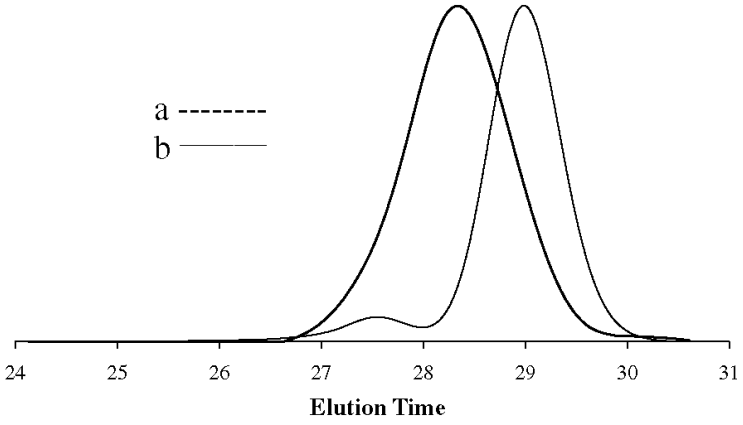


***Fig. 9.** TEM image of a micelle sample from a $[PEO(PCL)_2]$ star block copolymer solution (2b in Table 2).*

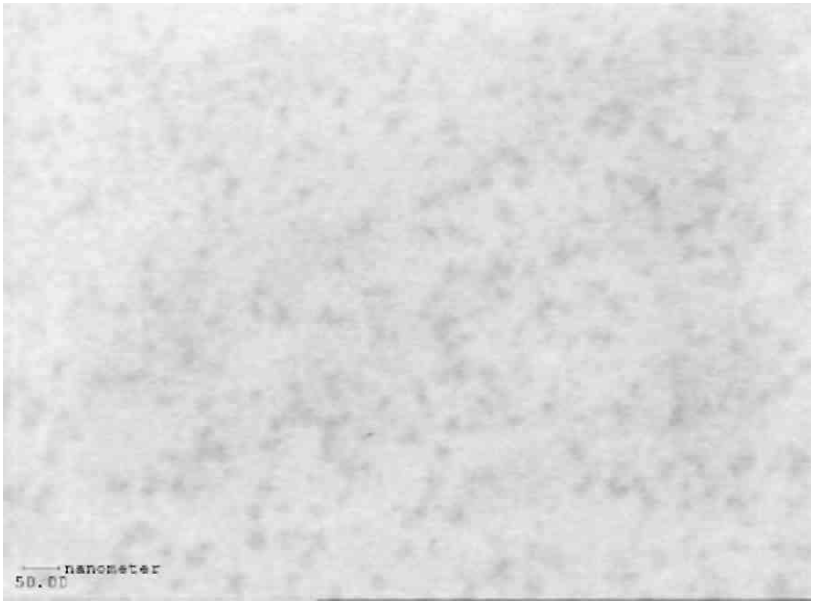
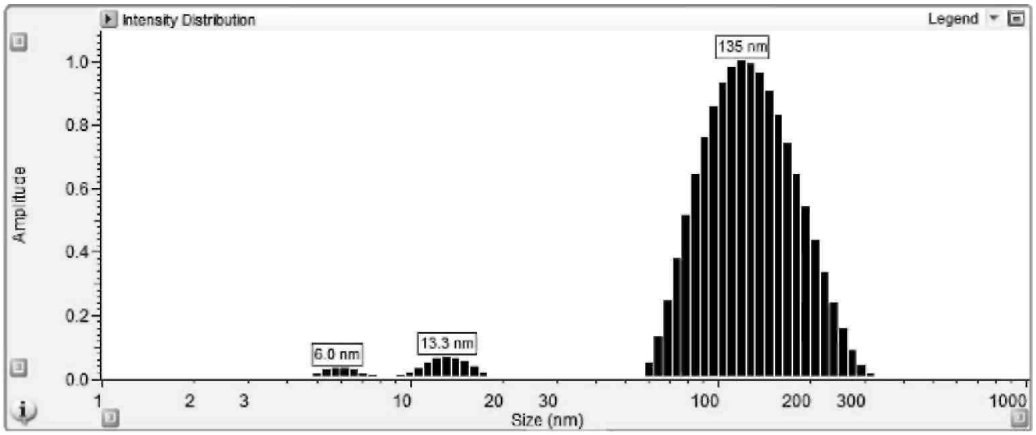


***Fig. 10**. Micelle size distribution of $[PEO(PCL)_2]$ (2b, in Table 2).*



The Fig. 8 shows the SEC curves of $PEO(OH)_2$ and the AB_2 star-shaped copolymer (la, in Table 1 and 2a, in Table 2). The SEC analysis of the triarm star-shaped copolymer showed a monomodal and narrow molecular weight distribution. The values of each M_w/M_n for all the samples are listed in Table 2. It is worth noting that the present strategy is based on the initiation of both PCL arms by two different hydroxyl groups (a primary and a secondary alcohol). Thus, the initiation rate might be different for both arms leading to two PCL arms of different length. Nevertheless, the comparison of the hydrodynamic volumes measured by SEC of the AB_2 star-shaped copolymer and linear PEO-b-PCL with an identical composition confidently confirms the star-shaped AB_2 structure. Indeed, the hydrodynamic volume of the star-shaped copolymer is lower than its linear counterpart, the M_n star-shaped/M_n linear ratio being equals to 0.8 which is significant for copolymers of an identical composition but different architectures [34]. However, we presently cannot give further details on the relative length of both PCL arms.

The amphiphilic nature of AB_2 star-shaped copolymers enables them to self-assemble in aqueous solution. The morphology of micelles was investigated by TEM. The Fig. 9 shows TEM image of well-defined spherical micelles in aqueous media from the $PEO(PCL)_2$ star-shaped copolymer with aM_n~1000g/mol per arm for the PCL block. Further investigation was carried out by DLS. The size distribution (Fig. 10) is bimodal and the average diameter of the micelles, measured by dynamic light scattering, were in the range from 13.3 to 135 nm.

4. Conclusions

A series of AB_2 triarm block copolymers were successfully synthesized by the ring-opening polymerization of εCL. For this purpose, a well-defined α-methoxy-ω-epoxy-poly(ethylene oxide) was obtained by a coupling reaction with epichlorohydrin. Then α-methoxy-ω,ω'-dihydroxy poly(ethylene oxide) was prepared upon selective hydrolysis of the epoxy ring of the α-methoxy-ω-epoxy-poly(ethylene oxide). $MPEO(OH)_2$ was designed as a macroinitiator for the sequential controlled ring-opening polymerization of εCL in the presence of $Sn(Oct)_2$. The various ratios of ε-caprolactone/hydroxyl were used to obtain copolymers with different PCL block lengths. The ability of these amphiphilic $PEO(PCL)_2$ copolymers to form micelles in aqueous media was investigated by DSL. By changing the length of the hydrophobic PCL block at constant content of hydrophilic PEO block in the copolymer, the size of the self-assembled micelles could be modulated. Additionally, such copolymers exhibit well-defined biodegradability and biocompatibility with an architectural diversity for various biomedical applications including controlled delivery and tissue engineering.

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