J Polym Res (2013) 20:59
DOI 10.1007/s10965-012-0059-3

ORIGINAL PAPER

Synthesis, characterization, and micellization of cholesteryl-modified amphiphilic poly(L-lactide)-*block*-poly (glycidyl methacrylate) as a nanocarrier for hydrophobic drugs

Massoumeh Bagheri · Forough Motirasoul

Received: 15 June 2012 / Accepted: 12 October 2012 / Published online: 23 January 2013

Abstract The biodegradable polymer cholesteryl-(L-lactic acid)$_{50}$, CLA_{50}, was synthesized via ring-opening polymerization of L-lactide in the presence of cholesterol as an initiator and a catalytic amount of $Sn(Oct)_2$. The resulting monohydroxyl-terminated CLA_{50} was subsequently converted to a bromine-ended macroinitiator (CLA_{50}–Br) by esterification with 2-bromisobutyryl bromide. The amphiphilic diblock copolymer CLA_{50}-b-PGMA was then synthesized via atom transfer radical polymerization of glycidyl methacrylate (GMA). The resulting polymers were characterized by FTIR, ^{1}H NMR, GPC, and DSC. Polymeric micelles were prepared by the co-solvent evaporation method. The aqueous self-assembly of the copolymer CLA_{50}-b-PGMA was investigated by TEM and DLS. Using naproxen as a hydrophobic model drug, drug-loaded micelles were prepared. TEM images of naproxen-loaded micelles of the copolymer (which exhibited a loading efficiency of 76.5 % and a loading capacity of 15.3 %) showed that the micelles were spherical and had diameters of 29–40 nm. An in vitro release study of naproxen was performed using the dialysis method in a phosphate-buffered solution at 37 °C. According to the results obtained in this work, these polymeric micelles could be tailored (by modifying the copolymer composition and molecular weight of blocks) to act as effective drug carriers that facilitate the release of various drugs.

Keywords L-lactide · Cholesterol · Glycidyl methacrylate · ATRP · Micellization · Controlled drug release

M. Bagheri (✉) · F. Motirasoul
Chemistry Department, Science Faculty,
Azarbaijan Shahid Madani University, P.O. Box: 53714-161,
5375171379 Tabriz, Iran
e-mail: massoumehbagheri@yahoo.com

Introduction

Polymeric amphiphiles can form nanosized self-assemblies—spherical micelles—with an inner core of hydrophobic segments and an outer shell of hydrophilic segments in aqueous media, due to the intra- and/or intermolecular interactions of hydrophobic segments [1]. These polymeric micelles that form through the self-assembly of amphiphilic block copolymers exhibit many merits, such as nanoscale dimensions, core–shell structure, relatively high stability due to their low critical micelle concentration (CMC), and prolonged circulation because of their high water solubility [2]. In recent years, they have attracted wide scientific and technological interest due to their potential use as nanosized carriers of drugs that show poor solubility in water [3]. Controlled release of the loaded drug can be achieved through diffusion from the micelles or by the biodegradation of amphiphilic polymers. Many investigations [4–6] have reported that these self-assemblies, when used as drug-delivery systems, can reduce unwanted toxic side effects, increase the solubility of drugs that are poorly water soluble (by storing them within the hydrophobic core of the micelle), prolong the circulation time, reduce uptake by the reticuloendothelial system (RES), and enhance the therapeutic indices of drugs. Among the various polymeric amphiphiles that could potentially act as drug carriers, block copolymers of biodegradable poly-L-lactic acid (PLA) are the most attractive [7, 8]. Aliphatic polyesters such as PLA have high potential for use as biomaterials and environmentally friendly materials because of their hydrolytic and/or enzymatic degradation into products that are ultimately metabolized in most cases [9]. PLA is a biodegradable material with low toxicity and excellent biocompatibility; it has therefore been incorporated into the cores of micelles and used as a matrix for controlled drug release [1]. It

has been reported that copolymers that include PLA can be synthesized through a combination of atom transfer radical polymerization (ATRP) and other polymerization methods such as chemical ring-opening polymerization (ROP) [10, 11]. In recent years, interest has grown in epoxy-based copolymers such as glycidyl methacrylate (GMA), which have been used in advanced biotechniques such as DNA separation, enzyme immobilization, and targeted drug delivery [12–14]. Controlled/"living" radical polymerization procedures can be used to prepare copolymers with predetermined molecular weights and narrow molecular weight distributions. Importantly, polymer chains prepared by atom transfer radical polymerization (ATRP) are highly end-functionalized and can therefore participate in various post-polymerization modifications and serve as macroinitiators in the synthesis of block copolymers [15, 16].

Amphiphilic acrylate- and lactone-based block copolymers find application in the fabrication of polymer systems for a variety of biomedical applications, ranging from controlled release systems used in drug delivery [17] to the fabrication of degradable surgical implants. The acrylate group allows the synthesis of systems that are nondegradable but readily tunable—in terms of hydrophilicity [18], pH- and temperature-induced phase behavior [19], and loading with therapeutic agents [20], for instance—through simple variation of the acrylate substituent. Further advantages of combining these blocks include the selective introduction of large numbers of functional groups via the polyacrylate block, the generation of amphiphilic block copolymers, and the creation of partially biodegradable structures. Nevertheless, only a few examples of the synthesis of polyester-block-polyacrylate copolymers via ROP of a lactone and ATRP of an acrylate have been described in the literature so far [10, 11, 17, 18, 21, 22]. Among the vast number of potential comonomer combinations, block copolymer systems based on lactide and glycidyl methacrylate (GMA) have not been reported so far, even though each of these polymers has been successfully and usefully employed in biomedical applications.

In our previous work, we synthesized and characterized liquid crystalline cholesteryl-(L-lactic acid)$_n$, CLA$_n$ (n=30), via an Sn(Oct)$_2$-catalyzed bulk ROP method [23]. Although this method is not strictly a "living" process, the molecular weight of the copolymer can be adjusted by varying the L-lactic acid/cholesterol ratio [24]. The main purpose of the present study was to produce a new micellar vehicle to deliver the hydrophobic drug naproxen. This vehicle was prepared from the amphiphilic copolymer PCLA-b-PGMA. It is expected that PCLA-b-PGMA micelles possess a high loading capacity and good controlled-release properties in addition to their good biocompatibility due to the notable self-assembly capacity of the cholesteryl groups [25, 26]. In the work described in this paper, the synthesis and characterization of CLA$_{50}$ and its block copolymer with glycidyl methacrylate via the ATRP method were achieved. In particular, we discuss initial studies on micellization and the in vitro release of naproxen as a hydrophobic model drug.

Experimental

Material

L-lactide, tin(II) bis(2-ethylhexanoate) (Sn(oct)$_2$), and triethylamine (TEA) were obtained from Alfa Aesar (Ward Hill, MA, USA). 2-Bromisobutyryl bromide, copper(I) chloride (CuCl), 2,2′-bipyridine (bpy), glycidyl methacrylate (GMA), naproxen, and cholesterol were purchased from Merck (Darmstadt, Germany). Dialysis membrane (MWCO=10,000) was purchased from Sigma–Aldrich (St. Louis, MO, USA). TEA was refluxed for 12 h in the presence of CaH_2 and distilled in vacuo. GMA, dichloromethane, and DMF were distilled over calcium hydride (CaH_2) in vacuo before use. CuCl was purified by precipitation from glacial acetic acid to remove Cu^{2+}, filtered and washed with ethanol, and then dried. L-lactide, Sn(oct)$_2$, 2-bromisobutyryl bromide, cholesterol, and bpy were used without further purification.

Cholesteryl-(L-lactic acid)$_{50}$ (CLA$_{50}$)

A mixture of L-lactide (1.5 g, 0.01 mol) and cholesterol (0.161 g, 0.4 mmol) was placed in a preheated oil bath at 150 °C and stirred until everything was molten. A solution of Sn(Oct)$_2$ in toluene (1 mL, 0.0043 g Sn (Oct)$_2$/mL) was then added, and the reaction mixture was stirred at 150 °C under an argon atmosphere. After 5 h, the reaction mixture was allowed to cool to room temperature, and the residual solid was triturated with MeOH (15 mL) and diethyl ether (15 mL). Solids were collected by filtration and finally vacuum dried at room temperature. The yield was 1.05 g (68 %).

Synthesis of the bromine-terminated macroinitiator (CLA$_{50}$–Br)

The resulting CLA$_{50}$ (0.3 g, 0.102 mmol) was dissolved in 5 mL of dry dichloromethane and then cooled in an ice bath (0 °C). To this solution, 0.094 mL (1.02 mmol) of TEA were added. After 5 min of stirring, 0.084 mL (1.02 mmol) of 2-bromisobutyryl bromide in 5 mL of dry dichloromethane were added dropwise to the solution over a period of 0.5 h. The reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 22 h. The color of the solution changed from white to yellow.

The precipitated by-product was removed by filtration and then the filtrate was evaporated to dryness. The crude product was dissolved in 30 mL of dichloromethane, and the organic phase was thoroughly washed successively with 5 % aqueous $NaHCO_3$ and deionized water before being dried over $MgSO_4$. The concentrated solution was poured into methanol to precipitate the product. The resulting white solid was dried for 24 h in vacuo. The yield was 0.23 g (76 %).

Synthesis of AB-type diblock copolymer

A dry flask equipped with a magnetic stirrer was charged with 0.024 g (0.08 mmol) of CuCl, 0.111 g (0.24 mmol) of bpy, and 0.2 g (0.015 mmol) of the macroinitiator CLA_{50}–Br. The reaction mixture was immersed in an ice–water/NaCl mixture at about −10 °C and degassed using vacuum and argon three times, and then 18.3 mL (46.6 mmol) of the monomer GMA and 5.58 mL (30 %v/v of the monomer) of the solvent DMF were degassed using vacuum and argon three times. After the CLA_{50} macroinitiator had completely dissolved, polymerization was carried out under continuous stirring at 50 °C for 3 h. Finally, the reaction mixture was opened to the air and cooled to room temperature. The catalyst was removed by passing the polymer solution through a short aluminum oxide column. The crude polymer was purified by precipitation in methanol and then diethyl ether and dried in a vacuum oven overnight. The yield was 0.08 g (40 %).

Micelle formation and drug encapsulation

Polymeric micelles were prepared using a precipitation method. In brief, CLA_{50}-b-PGMA (10 mg) and naproxen (2 mg) were dissolved in 5 mL of THF, and this solution was added to 10 mL of distilled water. After removing the THF, a dispersion of micelles in solution was prepared. Empty micelles (not loaded with the drug) were prepared using the same method as described above.

Unencapsulated naproxen was removed by centrifugation at 4,000 rpm for 10 min. The precipitate containing the unloaded drug was dissolved in a 50 % ethanol solution, and the amount of drug present was analyzed by UV-visible spectrophotometry at 330 nm. Standard solutions were prepared at concentrations ranging from 0.02 to 0.10 g L^{-1}. The correlation coefficient (R^2) was at least 0.998.

It was found that ~76.5 wt% of the free drug naproxen was loaded into the polymeric micelles (W_{total}=2 mg). The drug-loading efficiency (76.5 %) and drug-loading capacity (15.3 %) were calculated as follows:

$$\text{Loading efficiency}\,(\%) = (\mathrm{A} - \mathrm{B})/\mathrm{A} \times 100 \quad (1)$$

$$\text{Loading capacity}\,(\%) = (\mathrm{A} - \mathrm{B})/\mathrm{C} \times 100, \quad (2)$$

where A is the total mass of naproxen used, B is the mass of unloaded naproxen in the precipitate after centrifugation, and C is the mass of the copolymer.

In vitro drug release test

The in vitro release of naproxen from the micelle was determined using the dialysis membrane diffusion technique. Three milliliters of the drug-loaded micelle solution were transferred into a dialysis tube (MWCO=10,000) and immersed in 30 L of release media (pH 7.4 buffer solution) at 37 °C.

The mixed solution was monitored by UV-visible spectroscopy at 330 nm to determine the amount of drug released. At predetermined intervals, 3 mL of the medium were taken, and 3 mL of fresh PBS were added after each removal. The concentration of the drug released was determined using an UV-visible spectrophotometer at 330 nm, and all experiments were carried out in triplicate. Standard aqueous solutions were prepared at concentrations ranging from 0.003 to 0.02 g L^{-1}. The correlation coefficient (R^2) was at least 0.996. The release percentage of naproxen was calculated from the following equation:

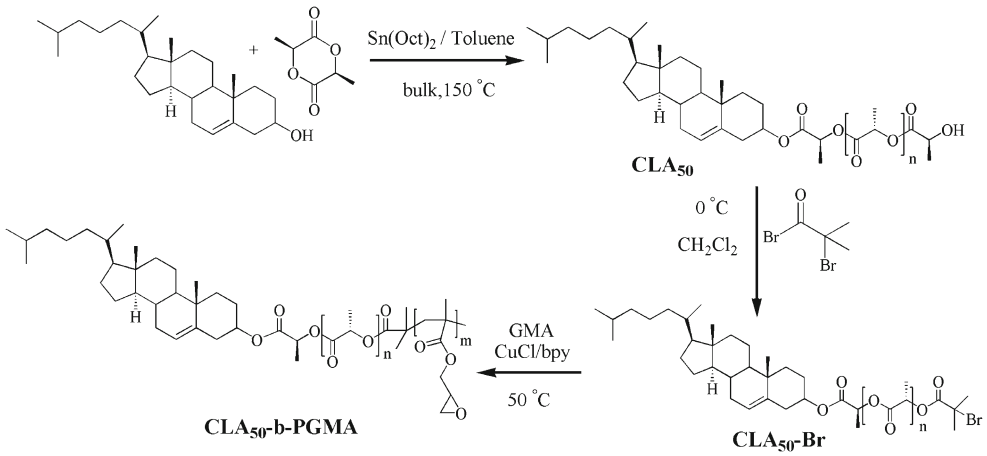
$$\%\,\text{Released} = (\mathrm{W_t})/(\mathrm{W_{total}}) \times 100, \quad (3)$$

where W_t is the mass of released naproxen at time t and W_{total} is the total mass of absorbed naproxen in the polymeric micelle structure. W_{total} was calculated as the mass of the free drug (i.e., the total mass of the drug used in this work, A, which was 4 mg) minus the mass of unloaded drug (B).

Methods

Melting points were recorded with a model 9100 melting point apparatus (Electrothermal, Rochford, UK). FT-IR spectra were recorded on a PS-15 spectrometer (Bruker Optics, Ettlingen, Germany). ^{1}H NMR spectra were taken on a 400 MHz SP-400 Avance spectrometer (Bruker Biospin, Rheinstetten, Germany) using chloroform as solvent and tetramethylsilane as the internal standard. UV spectrometry was carried out using a T80 UV–vis spectrometer (PG Instruments, Lutterworth, UK). A model 822 differential scanning calorimeter from Mettler Toledo (Columbus, OH, USA) was used to determine phase transition temperatures at heating and cooling rates of 10 °C/min. The instrument was calibrated for temperature and enthalpy using indium. Thermogravimetric analysis (TGA) was carried out using a Mettler Toledo 822 instrument. The number-average and weight-average molecular weights were determined using gel permeation chromatography (GPC, 6A instrument, Shimadzu, Kyoto, Japan), with a Waters (Milford, MA, USA)

Scheme 1 Synthetic route to the amphiphilic diblock copolymer CLA_{50}-b-PGMA



Ultrastyragel 10^3 Å column, chloroform used as eluent at 40 °C, and a differential refractive index detector, performing calibration with polystyrene standards.

The polymeric micelles were analyzed by transmission electron microscopy (TEM). TEM observations were recorded with a Philips (Amsterdam, The Netherlands) SM10 TEM and Epson (Suwa) HP8300 photo flatbed scanner operated at an accelerating voltage of 150 keV. The TEM sample was prepared by placing a drop of the micellar dispersion on a copper grid coated with carbon film and staining with a 2 % (w/v) phosphotungstic acid aqueous solution. The average size and the size distribution of the polymeric micelles were determined by dynamic light scattering (DLS) using a light scattering spectrometer (SEM-633, SEMATech, Nice, France) at 25 °C.

Results and discussion

Synthesis and structural characterization

The synthetic paths to CLA_{50}, the macroinitiator CLA_{50}–Br, and the amphiphilic diblock copolymer CLA_{50}-b-PGMA are presented in Scheme 1.

The synthesis of cholesteryl-(L-lactic acid)$_n$ with n=10, 24, 37 in bulk using $Sn(Oct)_2$ as a catalyst has been reported previously [27]. According to that report, in the absence of an alcohol used as a co-initiator, this ROP procedure does not permit accurate control over the molecular weight of the copolymer. However, in the presence of cholesterol and a catalytic amount of $Sn(Oct)_2$, polymers with narrow molecular weight distributions can be prepared; in this case, the average molecular weight corresponds to the L-lactide/alcohol ratio. In our previous work, liquid-crystalline CLA_{30} was synthesized with accurate control over the molecular weight via the ROP method with a catalyst concentration of 100–1,000 ppm in 5 h [23]. The number-average degree of polymerization of CLA_{30} was evaluated by ^{1}H NMR spectroscopy. Cholesteryl-terminated poly-L-lactic acid, CLA_{50}, with a tightly controlled molecular weight was prepared according to our previously reported procedure [23], and was characterized by FT-IR and ^{1}H NMR spectroscopy. The concentration of water in the reaction medium needs to be minimized because this determines the molecular weight distribution and the degree of incorporation of the initiator cholesterol into the CLA_n chain terminus. The number-average degree of polymerization of CLA_{50} was evaluated by ^{1}H NMR spectroscopy and GPC methods (Table 1).

The ^{1}H NMR spectrum of CLA_{50} is shown in Fig. 1. In addition to the dominant PLA signals, the characteristic signal of the cholesterol moiety (a) is evident at 5.4 ppm, thus confirming the cholesterol-initiated ROP of L-lactide. Quartet signals at 5.2 ppm (b) derive from the main-chain

Table 1 Results for CLA_{50} and the CLA_{50}-b-PGMA diblock copolymer

Sample	$[M]_0/[I]_0$	Mn_{NMR} (g/mol)[a]	Mn_{GPC} (g/mol)[b]	Mw/Mn [b]	Composition (L-lactide/GMA)[c]	Yield (%)
CLA_{50}	25/1	4346	3628	1.14	–	68
CLA_{50}-b-PGMA	3100/1	14712	14106	1.37	54/73	40

[a] Determined by ^{1}H NMR analysis

[b] Determined from GPC measurements

[c] Degree of polymerization of CLA_{50}/PGMA calculated from the ^{1}H NMR spectra

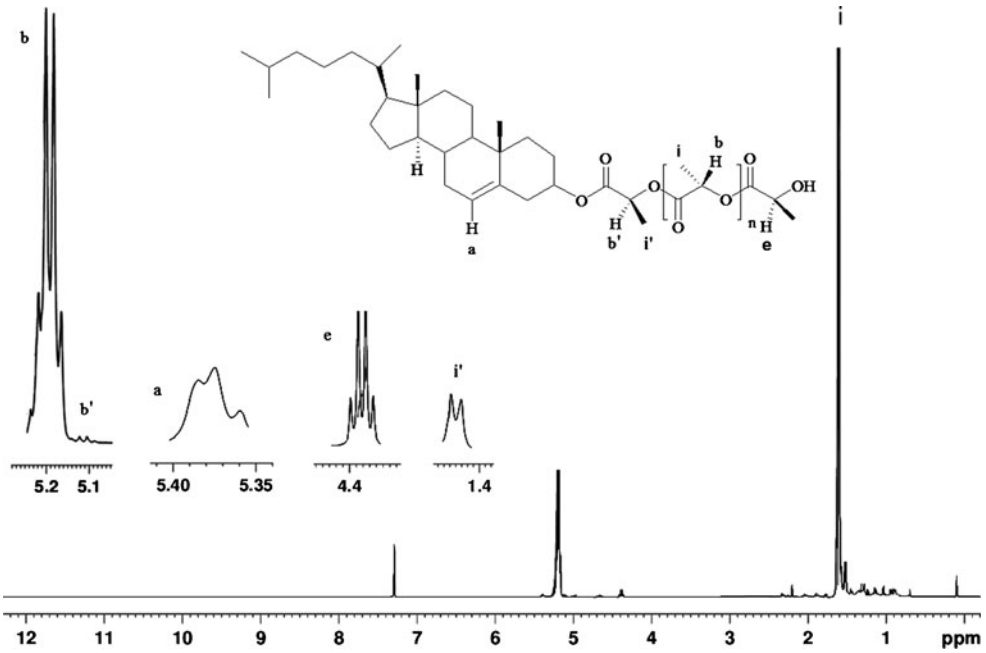


Fig. 1 ^{1}H NMR spectrum of CLA_{50}

methine protons of the PLA, while the doublet signals at 1.53 ppm (i) correspond to the methyl protons of the PLA main chain. Very small peaks from the protons of the methine and methyl groups closest to the cholesteryl moiety at around δ 5.1 and 1.45 ppm (Fig. 1), respectively, in the ^{1}H NMR spectrum of CLA_{50} are also visible.

The number-average degree of polymerization of CLA_{50} was estimated from end-group analysis by ^{1}H NMR spectroscopy. The intensity of the vinyl proton peak of the cholesterol moiety (at 5.4 ppm) was used for this purpose. Consequently, a number-average degree of polymerization of 54 was calculated.

The macroinitiator CLA_{50}–Br for ATRP was obtained from the subsequent esterification reaction between the terminal hydroxyl group of the resulting CLA_{50} and 2-bromisobutyryl bromide. In the associated ^{1}H NMR spectrum, new signals at 1.94 and 1.97 ppm were assigned to the diastereotopic methyl protons adjacent to the active bromide. In addition, the disappearance of the signal from the methine proton at the α position to the terminal –OH group of CLA_{50} (see Fig. 1, peak e) indicated the complete substitution of the end hydroxyl groups.

The prepared macroinitiator was subsequently used for bromoester-mediated GMA polymerization. ATRP of GMA from CLA_{50}–Br was carried out at 50 °C in DMF (30 %v/v of the monomer) with CuCl/bpy as the catalytic system. The ^{1}H NMR spectrum of copolymer CLA_{50}-b-PGMA is shown in Fig. 2. It is apparent that besides the dominant CLA_{50} signals, there are new peaks (d) and (e) at 3.23 ppm and at 2.64 and 2.84 ppm, respectively, which were assigned to the methine proton and the methylene protons of the epoxy group. The signals at 4.33 and 3.79 ppm arise through the splitting of the signal due to methylene protons in the –CH_2OCO– group of the GMA unit by the methyne proton of the epoxy group. In addition, the resonance signal from the α-CH_3 splits into three well-resolved peaks at 0.94, 1.10, and 1.26 ppm, which are assigned to isotactic, heterotactic, and syndiotactic triads (stereochemical configuration of monomeric units along the PGMA chains), respectively. The composition of the copolymer was also obtained from the ^{1}H NMR spectrum. For example, the intensities of the peaks at 0.94, 1.10, and 1.26 ppm and at 1.57 ppm for the copolymer CLA_{50}-b-PGMA, due to the methyl protons of the PGMA block and the methyl protons of the PLA backbone, respectively, were used for this purpose (see Figs. 1 and 2). The molar masses, the average degree of polymerization (DP), and the copolymer composition are listed in Table 1.

Figure 2 shows the related FT-IR spectra of CLA_{50}, CLA_{50}–Br, and the CLA_{50}-b-PGMA diblock copolymer. CLA_{50} contains an end hydroxyl group that yields a broad peak from 3,300 to 3,600 cm^{-1}, which were assigned to O–H stretching vibrations (Fig. 3). As seen in the FT-IR spectrum of CLA_{50}–Br, the attachment of 2-bromisobutyryl bromide to CLA_{50} resulted in a significant decrease in the OH-group absorbance peak at 3,510 cm^{-1} (Fig. 3).

For CLA_{50} and the CLA_{50}–Br macroinitiator, a characteristic absorption band occurs at 1,759 cm^{-1}, which was assigned to the ester carbonyl group of the PLA main chain. Comparison of the IR spectra of CLA_{50} and CLA_{50}–Br with that of the CLA_{50}-b-PGMA copolymer showed that the ester carbonyl absorption is shifted to 1,721 cm^{-1}. This is probably due to the high content of PGMA in the copolymer (~70 mol %), because the C=O stretching peak from the ester group of PGMA is observed at a lower wavenumber than it is for PLA

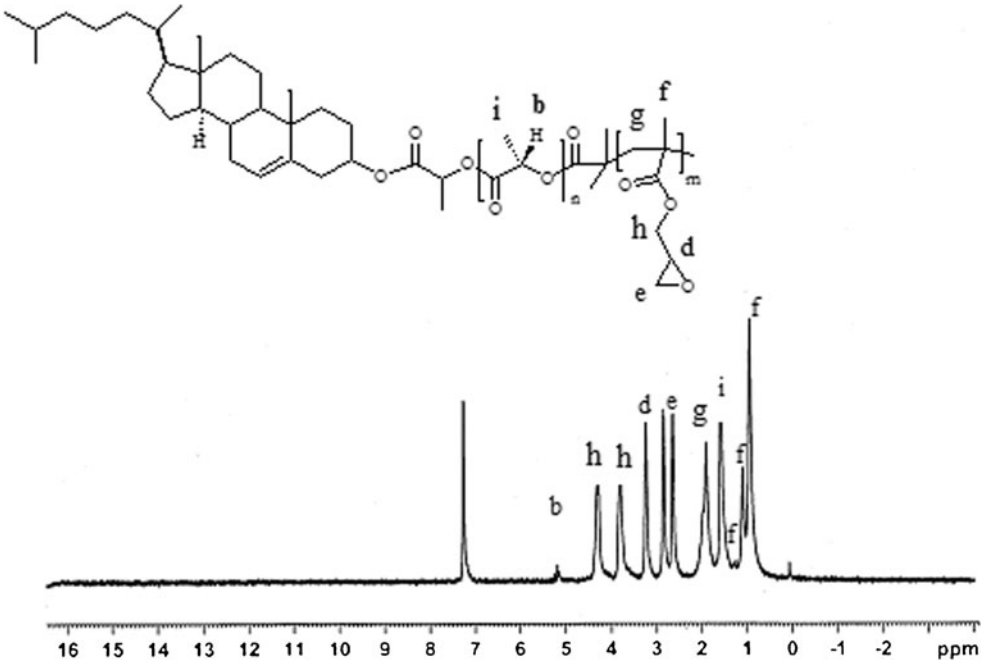


Fig. 2 ^{1}H NMR spectrum of the CLA_{50}-b-PGMA diblock copolymer

[27, 28]. In addition, the spectrum of CLA_{50}-b-PGMA shows new absorption bands at wavenumbers of approximately 848, 908, and 993 cm^{-1}, which were ascribed to the epoxy group (Fig. 3). The characteristic bands at 2,851 and 2,930 cm^{-1} were assigned to the stretching of methyl groups in the α position with regard to the ester groups. Another variation associated with the GMA blocks in the copolymer was an increase in C–H stretching resonances from methyl groups, which resonate at 2,851 and 2,930 cm^{-1} (Fig. 3).

Thermal analysis

The second DSC heating curve of CLA_{50} (heating rate 10 °C min^{-1}, Fig. 4) shows a glass transition at 50 °C, a cold crystallization at 93.8 °C (16.4 Jg^{-1}), and an endothermic transition peak at 133 °C with a total enthalpy of −47 Jg^{-1}. For CLA_{50}-Br, the corresponding transitions were observed at 55 °C, 105 °C (36.6 Jg^{-1}), and 143 °C (−49 Jg^{-1}), respectively. The glass transition temperatures (T_g) for these materials were still below the T_g for PLA, which is known to be 57 °C. Thus, the results obtained for CLA_{50} and CLA_{50}–Br clearly demonstrate the inability of the cholesterol segment to induce self-assembly in these polymers. The DSC curve for the block copolymer CLA_{50}-b-GMA is also presented in Fig. 4. No melting or crystallization peaks were observed for the block copolymer. PGMA is an amorphous material without any crystallization temperature; the crystallinity of the block copolymer was attributed to the CLA_{50}

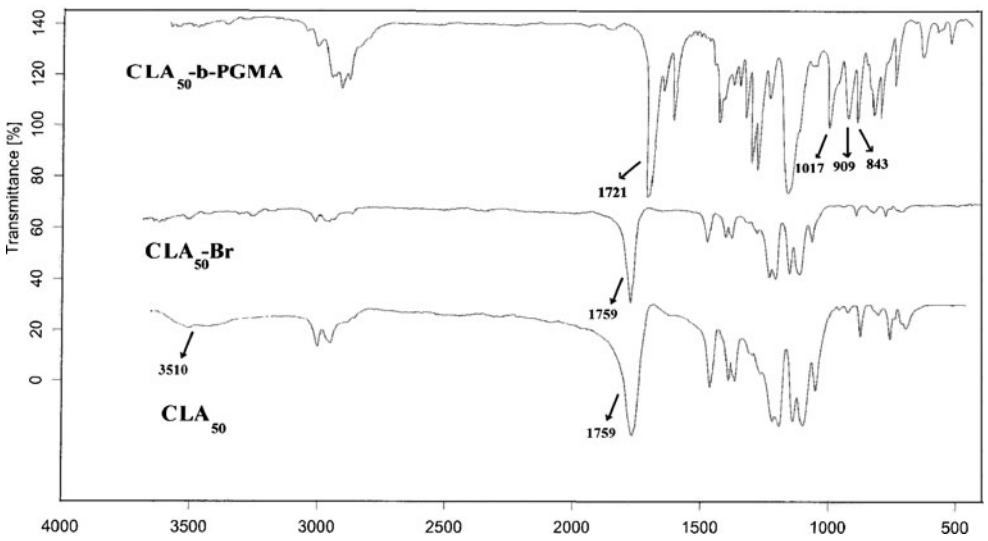


Fig. 3 FT-IR spectra of CLA_{50}, CLA_{50}–Br, and the CLA_{50}-b-PGMA diblock copolymer

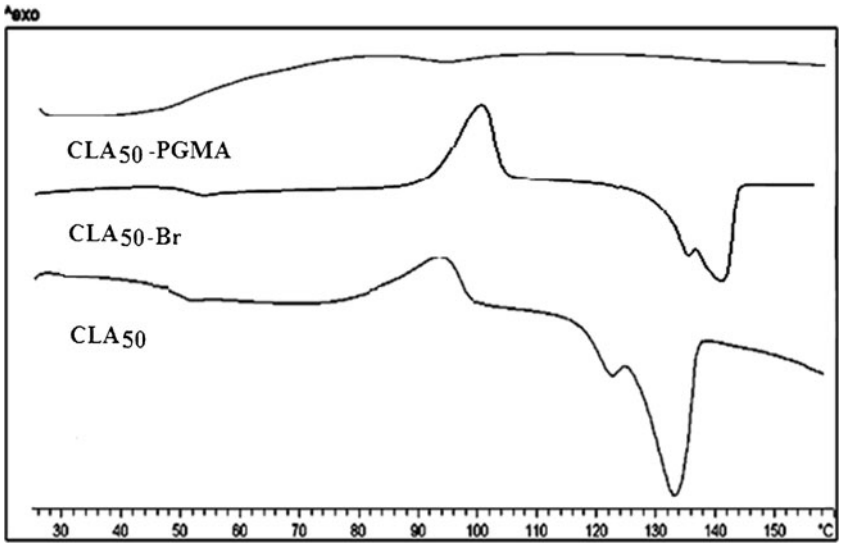


Fig. 4 DSC thermograms for CLA_{50}, CLA_{50}–Br, and CLA_{50}-b-PGMA at the second heating, obtained at a scan rate of 10 °C/min

block. However, its melting enthalpy reflects the amount of crystallinity in the sample. Due to the short CLA_{50} block in the copolymer, a melting transition was not observed for the CLA_{50} block, which could be due to a very small melting peak for the CLA_{50} block. The glass transition temperature of the PGMA block was 74 °C,

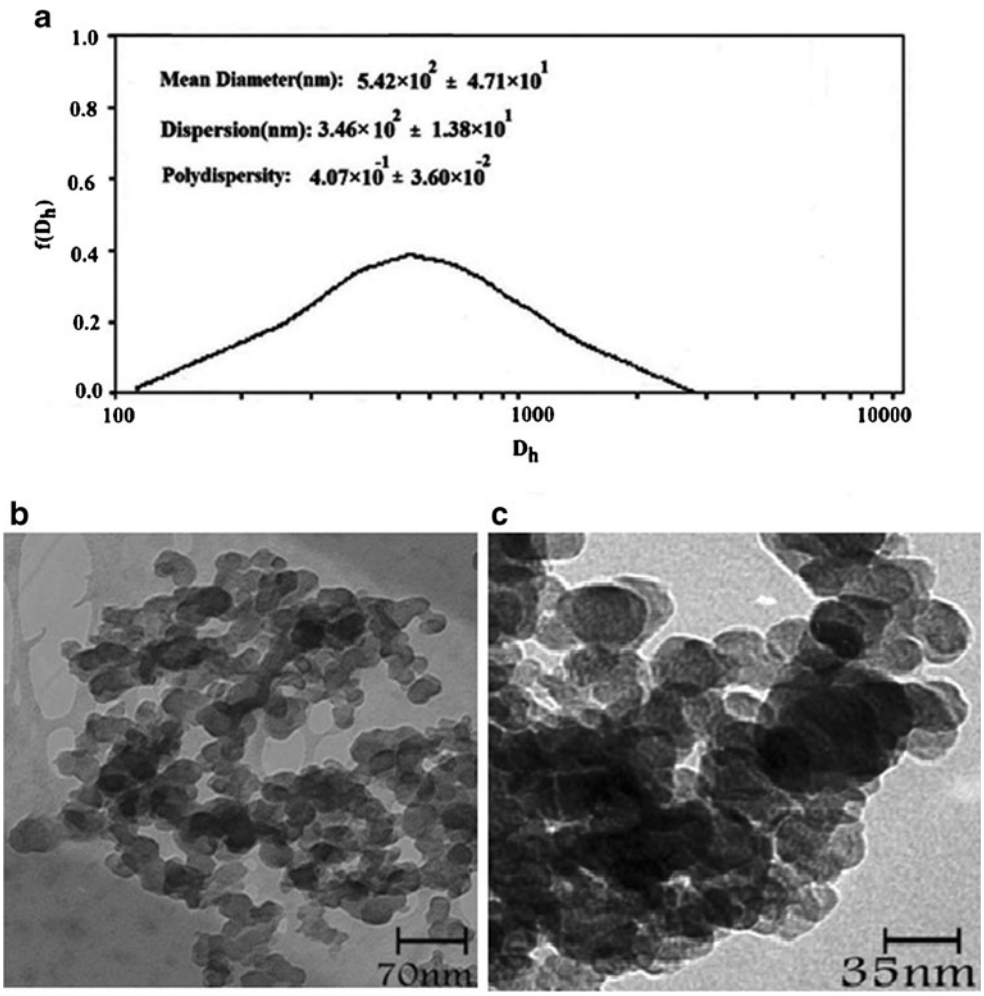


Fig. 5 **a** Size distribution of polymeric micelles of CLA_{50}-b-PGMA. **b** TEM image of polymeric micelles of CLA_{50}-b-PGMA. **c** TEM image of polymeric micelles of drug-loaded CLA_{50}-b-PGMA

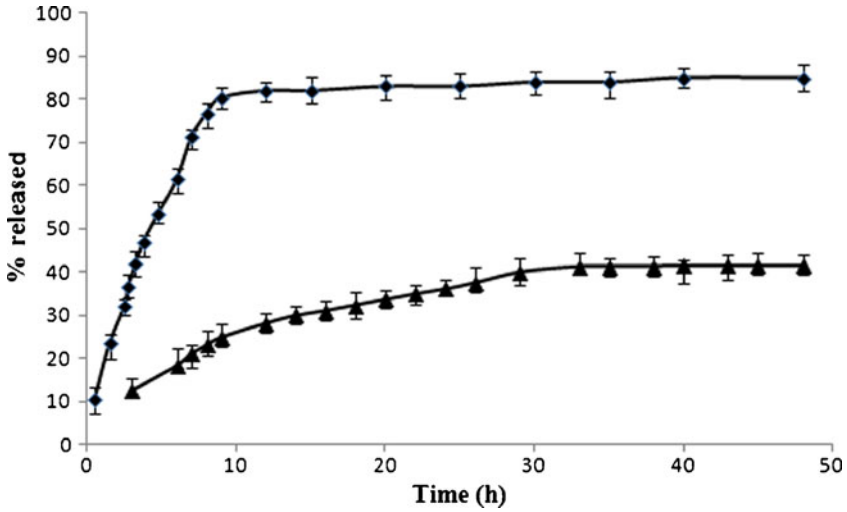


Fig. 6 Profiles for the release of free naproxen (*filled circles*) and naproxen from CLA_{50}-b-PGMA copolymer micelles (*filled triangles*) at 37 °C and pH 7.4

similar to that of the homopolymer. There was no observable glass transition in the region between 50 and 74.8 °C, suggesting that the CLA_{50} segments and PGMA segments were immiscible.

Characterization of polymeric micelles

The amphiphilic block copolymer CLA_{50}-b-PGMA, which consists of a potentially hydrophilic PGMA block and a biodegradable hydrophobic CLA_{50} block, provides the possibility of unique micellar formation in aqueous media. The precipitation method was therefore employed to prepare polymeric micelles [29]. The copolymer was first dissolved in THF and micellization was induced by the dropwise addition of water. The formation of nanoscale micelles in aqueous solution was judged based on the bluish tinge of such a solution. The aqueous self-assembly of the amphiphilic copolymer was monitored by DLS and TEM. The mean diameter of the copolymer in water was 239± 2.8 nm and the polydispersity index was 0.244±0.03 (see Fig. 5a), as measured by the DLS method TEM can be used to probe the size and shape of the micelles in the solid state, which eliminates any perturbations caused by swelling in solvent. Figure 5b shows TEM images of micelles of the CLA_{50}-b-PGMA diblock copolymer. A micrograph of the copolymer shows the presence of spherical micelles with diameters of 25–38 nm.

Drug-loaded copolymer micelles were prepared using naproxen as a hydrophobic model drug. A TEM image of naproxen-loaded copolymer micelles (loading efficiency 76.5 %) showed that the micelles were spherical with diameters of about 29–40 nm (Fig. 5c). However, compared with the blank nanoparticles (Fig. 5b), the drug-loaded polymeric micelles were slightly larger. This increase in the average diameter of the nanoparticles may suggest that naproxen molecules were physically entrapped in the nanoparticles.

In vitro drug release study

Naproxen, which shows poor solubility in water, was used as a model drug to investigate the drug loading and release properties of the polymer carrier. The naproxen was encapsulated in the hydrophobic micelle cores. The release behavior of naproxen from polymer micelles was studied in vitro by the dynamic dialysis method in PBS solution (0.1 M, pH 7.4) at 37 °C. Figure 6 presents the in vitro release profile of naproxen-loaded micelles in PBS. Naproxen was released at a relatively slow rate; only 40 % of the naproxen was released in 48 h. However, during the same time period, about 80 % of the naproxen permeated into the solution when the drug was added without being encapsulated in micelles. Thus, the drug was released more slowly from the micelles, which suggests that this polymer is an effective drug carrier for controlling the release of this drug.

Conclusions

In conclusion, an amphiphilic block copolymer consisting of cholesteryl-modified poly-L-lactide and poly(glycidyl methacrylate) was synthesized via ROP and ATRP. The number-average molecular weight of the mPLA and the copolymer composition were obtained using ^{1}H NMR spectroscopy in accordance with the GPC results. DSC analyses showed that the high content of PGMA in the copolymer causes its amorphous structure. The amphiphilic, well-defined diblock structure self-associated in water to form core–shell micelles. Based on TEM observations, these micelles were found to be spherical with a mean diameter of 25–38 nm. Finally, the results of a study of the release of naproxen from these micelles indicated that this block copolymer could be used for controlled drug delivery.

Acknowledgments The authors would like to thank the Research Vice Chancellor of Azarbaijan Shahid Madani University for financial support of this research.

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