Carbohydrate Polymers 79 (2010) 119–124

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Synthesis and characterization of glucose-grafted biodegradable amphiphilic glycopolymers P(AGE-glucose)-*b*-PLA

Zhiguo Hu *, Xiaoshan Fan, Guisheng Zhang

College of Chemistry & Environmental Science, Henan Normal University, Xinxiang 453007, PR China

ARTICLE INFO

Article history:
Received 3 June 2009
Received in revised form 24 June 2009
Accepted 17 July 2009
Available online 23 July 2009

Keywords:
Biodegradable
Amphiphilic
Glycopolymer
Free-radical addition
Micelle

ABSTRACT

Novel glucose-grafted biodegradable amphiphilic glycopolymers P(AGE-glucose)-*b*-PLA were synthesized through a facile and efficient way. First, the block copolymer intermediates PAGE-*b*-PLA bearing double bonds in the side chains were synthesized by ring-opening polymerization of LA using PAGE as macroinitiator and $Sn(Oct)_2$ as catalyst; Then, 2-mercaptoethyl-β-glucoside (MEGlu) was conjugated to the side chains of PAGE-*b*-PLA via free-radical coupling reaction to give the glycopolymer P(AGE-glucose)-*b*-PLA. The micellization behavior of the glycopolymers P(AGE-glucose)-*b*-PLA in aqueous media was investigated by fluorescence (FL), ^{1}H nuclear magnetic resonance spectroscopy (^{1}H NMR), dynamic light scattering (DLS), and transmission electron microscope (TEM). The results showed that these glycopolymers P(AGE-glucose)-*b*-PLA formed spherical micelles with diameters about 200 nm.

1. Introduction

Amphiphilic copolymers, referred to “hybrid polymers”, may self-assemble into micelles with a hydrophobic inner core and a hydrophilic outer shell in aqueous media. Due to their unique structure, polymeric micelles have great potential applications in drug delivery or tissue engineering (Akiyoshi, Maruichi, Kohara, & Kitamura, 2002; Discher & Eisenberg, 2002; Gaucher et al., 2005; He, Li, Simone, & Lodge, 2006). Recent studies in molecular biology revealed that cell-surface carbohydrates from glycoproteins and glycolipids are involved in a variety of recognition events including fertilization, immunological protection, nervous system and virus infection (Dwek, 1996; Varki, 1993). The recognition processes have been proven to involve several simultaneous contacts between carbohydrates that are clustered on cell surfaces and protein receptors that contain multiple binding sites (Mammen, Choi, & Whitesides, 1998; Sacchettini, Baum, & Brewer, 2001). Thus, considerable efforts have been focused on the synthesis of amphiphilic glycopolymers for their potential applications as models for investigating carbohydrate–protein interactions and targeted drug delivery.

Over the past decades, many amphiphilic glycopolymers with carbon–carbon bonds in the main chains have been synthesized by copolymerizing vinyl monomers with pendant saccharide residues or by direct attaching saccharide residues onto a carbon–carbon polymer backbone (Ohno, Izu, Yamamoto, Miyamoto, & Fukuda, 1999; Ye, Wells, & DeSimone, 2001; You & Schlaad, 2006). However, this kind of amphiphilic glycopolymers are not biodegradable and may be limited in biomedical applications (Lu et al., 2006). Recently, more and more attention has been paid to the synthesis of amphiphilic glycopolymers containing biodegradable polyesters, such as polylactide (PLA), poly(glycolic acid) (PGA), and poly(ε-caprolactone) (PCL). Several examples of sugar-capped poly(ethylene glycol)-*b*-poly(D,L-lactide) biodegradable amphiphilic glycopolymers have been reported in the literature (Jule, Nagasaki, & Kataoka, 2003; Nagasaki et al., 1998; Rieger et al., 2007; Yasugi, Nkamura, Nagasaki, Kato, & Kataoka, 1999). However, amphiphilic glycopolymers end-capped with only one sugar residue at the end of hydrophilic segment have weaker binding capacity to target cells than saccharide-grafted amphiphilic glycopolymers (DeFrees, Gaeta, Lin, Ichikawa, & Wong, 1993; Nishimura, Matsuoka, & Furita, 1990). As the result, the synthesis of carbohydrate-grafted biodegradable amphiphilic glycopolymers has been the focus of many groups in recent years. Studies about the synthesis of saccharide-grafted biodegradable amphiphilic glycopolymers are still rare due to the synthetic difficulties. Although such glycopolymers have been prepared, the synthesis methods suffered from some drawbacks. For example, Xiabin Jing and co-workers synthesized a glucose-grafted biodegradable amphiphilic glycopolymer by a tedious reaction pathway (Lu et al., 2006). They first synthesized a block copolymer intermediate bearing pendant carboxyl groups by ring-opening copolymerization of L-lactide and (3s)-benzoxylcarbonylethylmorpholine-2,5-dione (molar ratio 10:1) with dihydroxyl PEG as macroinitiator, and then catalytic hydrogenation. The glucose residues were attached onto the polymer

---

* Corresponding author. Tel.: +86 373 3326335.
E-mail address: zhiguohu@yahoo.com (Z. Hu).

0144-8617/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carbpol.2009.07.041

backbone via an amide linkage. But the density of carbohydrate residues in the side chain was relative lower. Chang–Ming Dong synthesized a star-shaped biodegradable amphiphilic glycopolymer via the ring-opening polymerization of ε-caprolactone followed by the direct ATRP of unprotected lactobionamidoethyl methacrylate glycomonomer (Zhou, Dai, & Dong, 2008). However, the superfluous free hydroxyl groups of carbohydrate residues within glycopolymers restricted the ATRP process to some extent and the glycomonomer conversion was only in the range of 20–40%. Therefore, a relatively simple and efficient strategy is needed to prepare carbohydrate-grafted biodegradable glycopolymers with well-defined structure.

In this study, a series of novel glucose-grafted biodegradable amphiphilic glycopolymers were prepared via a facile and efficient pathway (Fig. 1). The well-defined copolymers PAGE-*b*-PLA were synthesized first through controlled polymerization techniques, then the unprotected MEGlu was attached onto the polymeric backbone via free-radical coupling reaction. This reaction not only tolerates the presence of most functional groups (—OH, —NH_2, —COOH, etc.), but also can proceed in quantitative yields under mild conditions (Boustany, 1972; Griesbaum, 1970). The composition, structure and self-assembly of this biodegradable amphiphilic glycopolymer have been thoroughly characterized by ^{1}H NMR, gel permeation chromatography (GPC), dynamic light scattering (DLS) and transmission electron microscopy (TEM).

2. Experimental

2.1. Materials

Allyl glycidyl ether(AGE) was dried over CaH_2 for 24 h at room temperature and distilled under reduced pressure. Tin(II) bis(2-ethylhexanoate) was purchased from Alfa Aesar and was used as received. DL-Lactide was obtained from GLACO LTD without further purification prior to use. Dimethylformamide(DMF) was dried by refluxing over P_2O_5 and was distilled under reduced pressure before use. 2,2′-Azobisisobutyronitrile (AIBN) (Aldrich) was recrystallized twice from ethanol. Dialysis tubing (Cutoff 2000 Da) was purchased from Shanghai Green Bird & Technology Development Co., Ltd. 2-mercaptoethyl-β-D-glucoside (MEGlu) was synthesized according to the literature (Dahmén et al., 1983; Murakami, Hirono, Sato, & Furusawa, 2007). Other reagents and solvents used were of the analysis grade and were dried according to the conventional methods.

2.2. Measurements

^{1}H NMR Spectra were measured on a Bruker-400 NMR instrument using $CDCl_3$, DMSO-d_6 and D_2O-DMSO-d_6 (6:1 v/v) as solvents. The molecular weight and molecular weight distribution of polymer samples were determined by gel permeation chromatography (GPC) using a LC-10AVP apparatus equipped with three columns (SHIMADZU Shim-pack GPC-803) in series (eluent, DMF; a flow rate of 1.0 mL/min). The GPC chromatogram was calibrated against standard polystyrene samples at 40 °C. Fluorescence spectra were recorded on a CARY Eclipse FL spectrometer in the right-angle geometry (90° Collecting optics) at 25 °C. The hydrodynamic diameter of micelles was measured using Malvern Zetasizer nano-ZS-90. The whole experiment was conducted in water-bath at 25 °C. Transmission electron microscope (TEM) images were obtained using a TecnaiG220 S-TWIN operating at an acceleration voltage of 200 kv. The dialyzed solution of the copolymers P(AGE-glucose)-*b*-PLA (0.4 mg/mL) were used for TEM detection. A drop of the solution was placed onto TEM copper/carbon grid and the excess solution was blotted up using a strip of filter paper, then the sample was allowed to dry at room temperature before observation.

2.3. Synthesis of poly(allyl glycidyl ether) (PAGE) homopolymers

A typical procedure for the polymerization: Under nitrogen, 0.50 g (7.38 mmol) freshly prepared C_2H_5ONa and 2 mL anhydrous xylene were introduced to a flame-dried and nitrogen-purged Schlenk tube equipped with a stirrer, followed by sonication for 15 min. When C_2H_5ONa was scattered evenly into xylene, 15.26 mL (0.13 mol) AGE was injected using a glass syringe. The reaction mixture was heated at 100 °C for 24 h. After that, 0.42 mL acetic acid (7.38 mmol) was added to stop the polymerization and the system was cooled to room temperature.

The crude PAGE was dissolved in CH_2Cl_2 and was dried with Na_2CO_3 over night and filtered. The filtrate was concentrated under reduced pressure and the solution was precipitated with hexane to give a light yellow viscous liquid. The results are summarized in Table 1.

2.4. Synthesis of poly(allyl glycidyl ether)-b-polylactide (PAGE-b-PLA) copolymers

PAGE-*b*-PLA copolymers were prepared by ring-opening polymerization of LA with PAGE in the presence of $Sn(Oct)_2$ as catalyst. 4.72 g LA (32.78 mmol), 2.22 g $PAGE_{2k}$ (0.58 mmol) and 0.34 mL $Sn(Oct)_2$ in xylene (1.7×10^{-1} mol/mL) were charged into a dried Schlenk tube equipped with a stirrer. The flask was purged with nitrogen and degassed several times. The flask was then sealed under vacuum and put into a pre-heated oil bath. The reaction was carried out at 130 °C for 20 h and was stopped by removing the flask from the oil bath. Purification was performed by dissolving the reaction mixture in a small amount of CH_2Cl_2 and pouring it into an excess of hexane with stirring. The copolymers were collected and dried in vacuum. The results are summarized in Table 1.

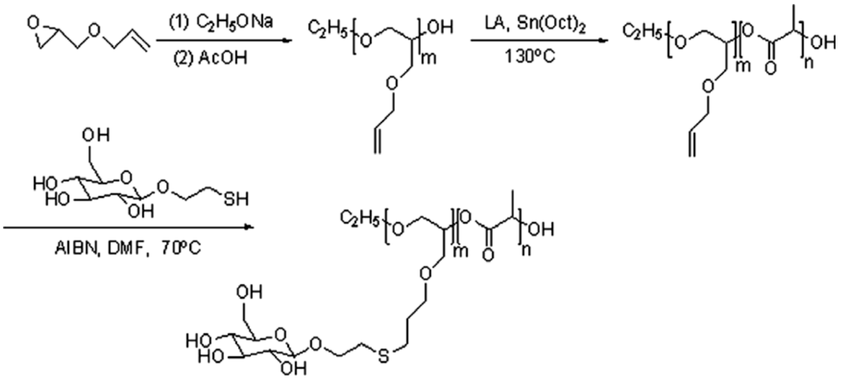

Fig. 1. The synthesis of glycopolymer P(AGE-glucose)-*b*-PLA.

Table 1
Preparation and characteristics of the PAGE homopolymers and PAGE-*b*-PLA copolymers.

Sample	Initiator (g)	Monomer (g)	Molar ratio (initiator/monomer)	Mn[a]	Mn[b]	Mn[c]	Mw/Mn[c]
$PAGE_{2k}$	0.50	14.46	1/17.5	2000	1820	8335	1.04
$PAGE_{4k}$	0.40	23.70	1/35.0	4000	3800	9830	1.08
$PAGE_{2k}$-*b*-PLA_{2k}	4.30	4.57	1/13.5	4000	4200	7500	1.46
$PAGE_{2k}$-*b*-PLA_{4k}	2.67	5.36	1/25.3	6000	5480	6545	1.78
$PAGE_{4k}$-*b*-PLA_{4k}	4.22	4.43	1/28.0	8000	7470	8000	1.56

[a] Calculated from the monomer/initiator ratio.
[b] Determined by ^1H NMR.
[c] Measured by GPC in DMF with polystyrene as calibration standard.

2.5. Synthesis of glucose-grafted glycopolymers poly(allyl glycidyl ether-glucose)-b-polylactide (P(AGE-glucose)-b-PLA)

11.29 g MEGlu (46.90 mmol-SH) was dissolved in 35 mL DMF, and the solution was added to a Schlenk tube which contained the solution of 1.00 g $PAGE_{4k}$-*b*-PLA_{4k} (4.69 mmol C═C) in 5 mL DMF. Then 0.46 g AIBN (2.82 mmol) was added. The stirred solution was degassed under nitrogen flow for 1 h and heated to 70 °C for 48 h. The reaction mixture was concentrated to 10 mL by partial evaporation of the solvent, then was transferred into a membrane (Mw cutoff 2000 Da) and dialyzed against deionized water for 3 days. Finally, the resulting copolymer solution was dialyzed against acetone to remove the water in dialyzed solution and evaporation of acetone afforded the product as a light yellow powder.

2.6. Preparation of the aqueous micellar solutions

In the present study, we employed the dialysis method to prepare the polymeric micelles of the amphiphilic block copolymers P(AGE-glucose)-*b*-PLA. The P(AGE-glucose)-*b*-PLA copolymer (100 mg) was dissolved in analytically pure DMF (5 mL) in a 50-mL round-bottom flask with a stirrer and 40 mL twice-distilled water was added dropwise with stirring (ca one drop/15 s). Then, the solution was dialyzed against twice-distilled water using a dialysis membrane tube (Mw cutoff 2000 Da) for 3 days to remove DMF. The micellar solution and twice-distilled water were added to a 100-mL volumetric flask to make polymer solution of 1 mg/mL. The samples were sonicated to homogenize the solution.

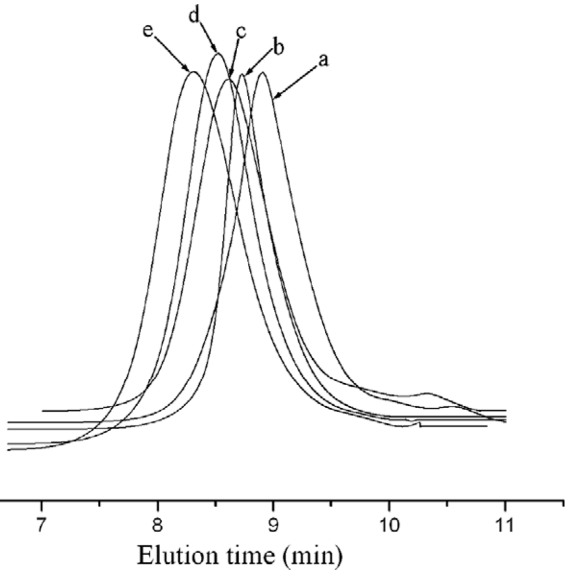

Fig. 3. GPC traces of (a) $PAGE_{2k}$, (b) $PAGE_{4k}$, (c) $PAGE_{2k}$-*b*-PLA_{2k}, (d) $PAGE_{2k}$-*b*-PLA_{4k} and (e) $PAGE_{4k}$-*b*-PLA_{4k}.

3. Results and discussion

3.1. Synthesis of P(AGE-glucose)-b-PLA biodegradable amphiphilic glycopolymers

As illustrated in Fig. 1, the copolymers PAGE-*b*-PLA bearing pendant double bonds, which provided the reactive possibility with –SH groups, were synthesized first by ring-opening polymerization of LA using PAGE as macroinitiator and $Sn(Oct)_2$ as catalyst. The carbohydrate molecules MEGlu were attached onto the copolymers PAGE-*b*-PLA via free-radical coupling reaction to give the amphiphilic glycopolymers P(AGE-glucose)-*b*-PLA.

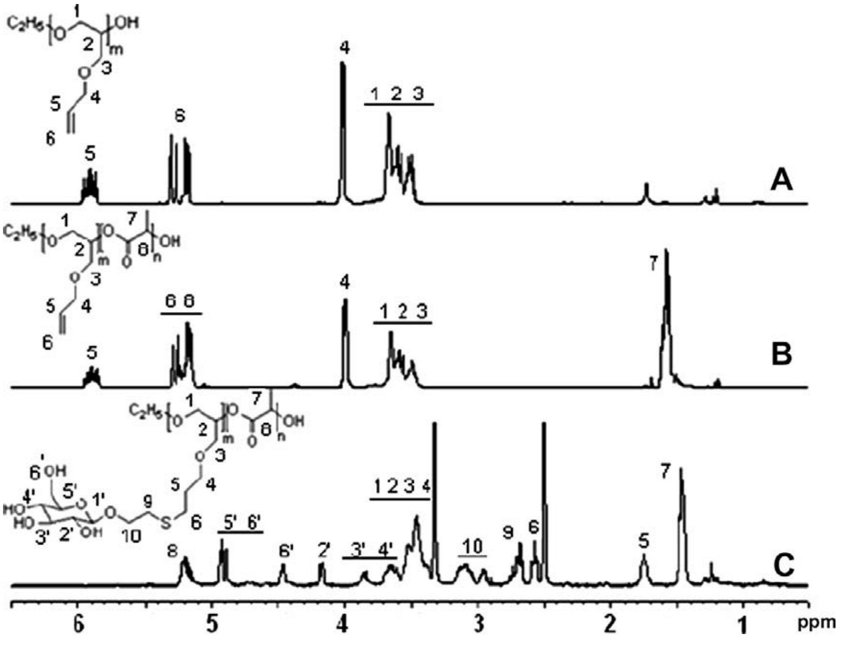

Fig. 2. ^1H NMR spectra of (A) $PAGE_{4k}$ in $CDCl_3$, (B) $PAGE_{4k}$-*b*-PLA_{4k} in $CDCl_3$ and (C) P(AGE_{4k}-glucose)-*b*-PLA_{4k} in DMSO-d_6.

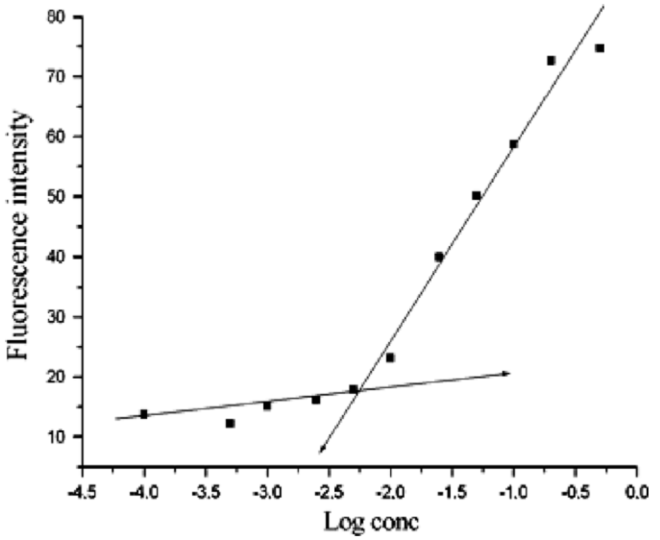

Fig. 4. Plot of the fluorescence intensity of the $\boldsymbol{I}_1$ band (λ emission = 373 nm; the first peak on the emission spectra with λ exc = 335 nm) versus the logarithm of the P(AGE_{2k}-glucose)-*b*-PLA_{2k} concentration.

Table 2
Characteristics of the micelles of P(AGE-glucose)-*b*-PLA glycopolymers.

Glycopolymer	D_h[a] (nm)	PDI[a]	cmc[b] (mg/mL)
P(AGE_{2k}-glucose)-*b*-PLA_{2k}	207	0.246	5.62×10^{-3}
P(AGE_{2k}-glucose)-*b*-PLA_{4k}	183	0.282	3.16×10^{-3}
P(AGE_{4k}-glucose)-*b*-PLA_{4k}	199	0.302	7.94×10^{-3}

[a] Mean hydrodynamic diameters by dynamic light scattering at 25 °C. In this measurement, the copolymers concentration was 1 mg/mL; PDI: polydispersity index.
[b] Measured in water at 25 °C.

The PAGE homopolymers were synthesized by the "living" anionic polymerization of AGE, initiated by sodium ethoxyl. The degree of polymerization was determined by ^{1}H NMR from the relative integration intensity of the proton signals of the unsaturated bonds ($-C\boldsymbol{H}{=}CH_2$) at 5.84 ppm and the end methyl group ($-C\boldsymbol{H}_3$) at 1.15 ppm (Fig. 2A). Mn determined from ^{1}H NMR spectra was close to the theoretical. It can be seen that the GPC traces of PAGE homopolymers showed monomodal peaks (Fig. 3a and 3b), which indicated that the polymerization proceeded successfully.

The PAGE-*b*-PLA copolymers were synthesized by ring-opening polymerization of LA with monohydroxyl PAGE as a macroinitiator in the presence of $Sn(Oct)_2$. The length of PLA block was tuned by the molecular ratio of the monomer to the macroinitiator. Fig. 2B shows the ^{1}H NMR spectrum of the copolymer $PAGE_{4k}$-*b*-PLA_{4k}. Compared to the spectrum of $PAGE_{4k}$ homopolymer (Fig. 2A), the new signal at 1.54 ppm can be assigned to the protons of the methyl groups ($-C\boldsymbol{H}_3$) of PLA segments. Resonances in the range of 5.1 to 5.3 ppm become more intense, which was attributed to the signal of the methenyl protons ($-COC\boldsymbol{H}(CH_3)O-$) of PLA segments overlapping with that of the methylene ($-CH = C\boldsymbol{H}_2$) of the double bonds of PAGE segments. The GPC traces of the copolymers (Fig. 3c–e) showed narrow and monomodal peaks and shifted to the higher molecular weight regions. The results from ^{1}H NMR and GPC demonstrated that the copolymers PAGE-*b*-PLA with narrow molecular weight distribution were obtained. The degree of polymerization of PLA segment was estimated from the PLA methyl proton signal ($-C\boldsymbol{H}_3$) at 1.54 ppm and signal at 5.84 ppm assigned to pendant double bonds ($-C\boldsymbol{H} = CH_2$) of PAGE segments.

Finally, MEGlu was conjugated to the pendant double bonds of the copolymer PAGE-*b*-PLA via free-radical addition reaction to give the amphiphilic glycopolymers. In the ^{1}H NMR spectrum of the resulting glycopolymers (Fig. 2C), the signals of glucose residues in the range of 3.6–5.0 ppm were observed clearly, and the signals at 5.84 ppm ($-C\boldsymbol{H}{=}CH_2$), characteristic of the pendant double bonds of PAGE block, disappeared completely, indicating the successful attachment of MEGlu onto the polymer backbone.

3.2. Self-assembly properties of P(AGE-glucose)-b-PLA amphiphilic glycopolymers

In this study, a dialysis method was employed to prepare the polymeric micelles. The micellar formation of these amphiphilic glycopolymers was characterized by FL technique using pyrene as probe. Fig. 4 shows the relationship of the intensities of the first peak ($\boldsymbol{I}_1$) in the emission spectra of pyrene as a function of polymer concentration at the room temperature (Lee, Shin, Na, & Bae, 2003). It can be seen that at low concentration, the intensities of $\boldsymbol{I}_1$ remained nearly unchanged, and started to increase dramatically as the concentration of the polymer increased. This is a reflection that pyrene molecules transfered from a water media to the hydrophobic core of micelles. The critical micellar concentration (cmc) is an important parameter characterizing the stability of polymeric micelles. The cmc value was obtained from the crossover point of

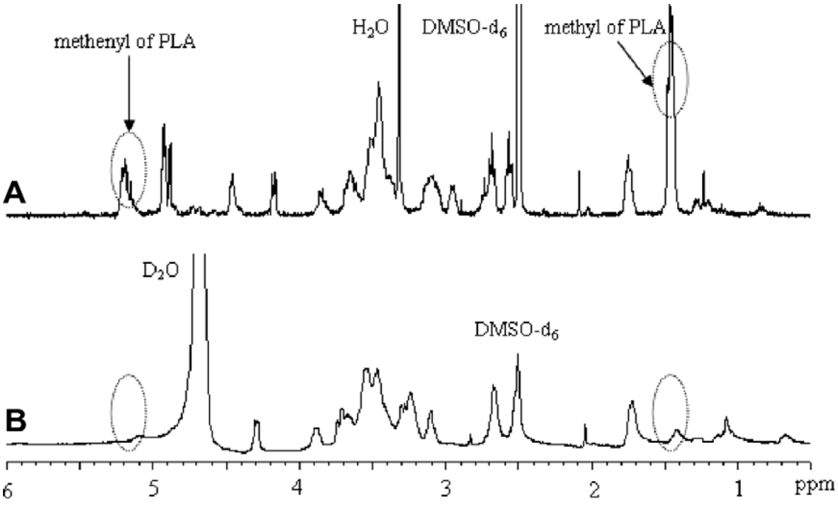

Fig. 5. ^{1}H NMR of (A) P(AGE_{4k}-glucose)-*b*-PLA_{4k} in DMSO-d_6 and (B) its corresponding in mixed solvent D_2O-DMSO-d_6 (6:1, v/v).

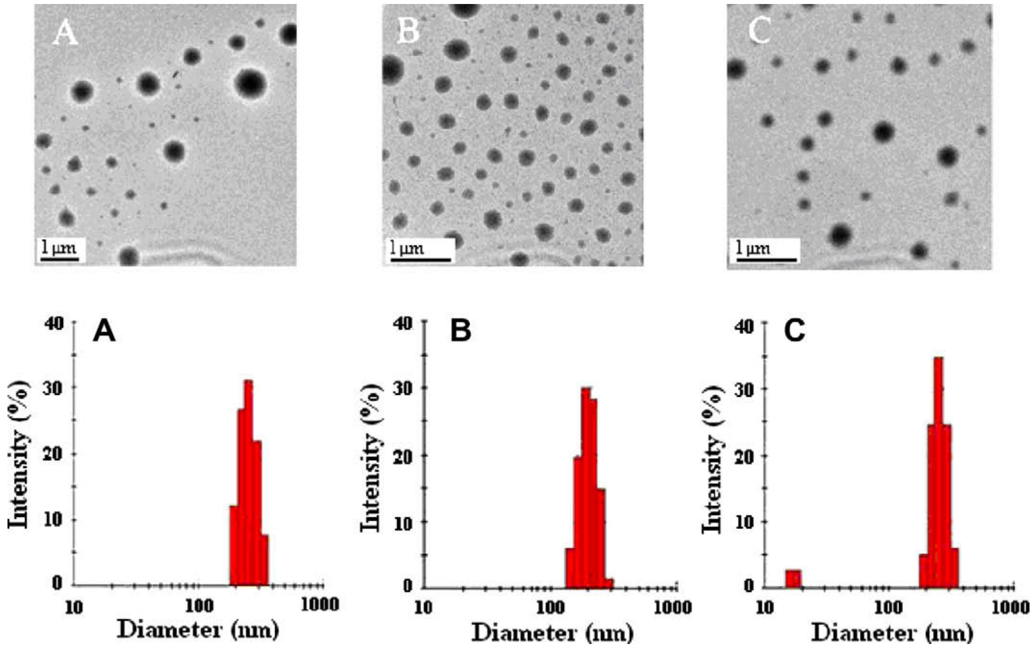

Fig. 6. TEM images and size distribution of the micelles determined by DLS of (A) P(AGE$_{2k}$-glucose)-*b*-PLA$_{2k}$, (B) P(AGE$_{2k}$-glucose)-*b*-PLA$_{4k}$ and (C) P(AGE$_{4k}$-glucose)-*b*-PLA$_{4k}$.

the two lines as shown in Fig. 4 and summarized in Table 2. The formation of micelles was further confirmed by ^{1}H NMR (Fig. 5). The signals of methyl protons (—C$\boldsymbol{H}_3$) at 1.5 ppm and methenal protons (—COC $\boldsymbol{H}$ (CH_3)—) at 5.1 ppm of the hydrophobic PLA segment can be seen clearly in DMSO-d$_6$, however, these signals were very weak in the mixed solvent D_2O-DMSO-d$_6$ (6:1, v/v). The observation suggested that the hydrophobic PLA segments were located within the core of the resulted polymeric micelles and its mobility was restricted.

The morphology and average size of the polymeric micelles were studied by TEM and DLS, as shown in Fig. 6. It can be seen from the TEM images that the micelles took a spherical morphology. The average hydrodynamic diameters of the micelles determined by DLS were about 200 nm (Table 2), which was nearly consistent with the TEM images. Obviously, these micelles were bigger than conventional polymeric micelles usually with a diameter of less than 100 nm, and they were probably aggregates formed by the strong aggregations between simple core–shell micelles. According the literature reports, larger complex micelles are often formed by the further aggregation of simple micelles, which is induced by hydrogen banding or van der Waals interactions among the hydrophilic shell (Hong, Mai, Zhou, Yan, & Cui, 2007; Zhang & Eisenberg, 1996).

4. Conclusions

In this work, we described a relatively simple and efficient approach to carbohydrate-grafted biodegradable amphiphilic glycopolymers with well-defined structure. Through free-radical coupling reaction of ω-mercaptoalkyl glycoside with the double bonds, the glucose residues were attached onto the polymer backbone without the resource to protecting groups chemistry. This method is not only suitable for the synthesis of glucose-grafted biodegradable amphiphilic glycopolymers, but also for other carbohydrate derivatives-grafted biodegradable glycopolymers. These glucose-grafted amphiphilic glycopolymers can self-assemble into core–shell micelles surfaced by a glucose shell. Such structure may enhance the binding affinity of the polymeric micelles to targeted cells. Therefore, these glycopolymers are interesting as models for targeted drug carrier and for investigation carbohydrate–protein interactions.

Acknowledgements

We are thankful the financial support from the National Natural Science Foundation of China (No. 20473026); the SRF for ROCS, SEM (No. [2007] 1108), and the program for Innovative Research Team (in Science and Technology) in Henan Province (2008IRTSTHN002, 084100510002).

References

Akiyoshi, K., Maruichi, N., Kohara, M., & Kitamura, S. (2002). Amphiphilic block copolymer with a molecular recognition site: Induction of a novel binding characteristic of amylose by self-assembly of poly(ethylene oxide)-block-amylose in chloroform. *Biomacromolecules, 3*, 280–283.

Boustany, K. (1972). Chemistry of sulfur compouds. Selectivity of addition of thiyl radicals to terminal olefins. *Journal of Chemical & Engineering Data, 17*, 104–106.

Dahmén, J., Frejd, T., Gronberg, G., Lave, T., Magnusson, G., & Noor, G. (1983). 2-Bromoethyl glycosides: Synthesis and characterisation. *Carbohydrate Research, 116*, 303–307.

DeFrees, S. A., Gaeta, F. C. A., Lin, Y. C., Ichikawa, Y., & Wong, C. H. (1993). Ligand recognition by E-selectin: Analysis of conformation and activity of synthetic monomeric and bivalent sialyl Lewis X analogs. *Journal of American Chemistry Society, 115*, 7549.

Discher, D. E., & Eisenberg, A. (2002). *Polymer vesicles*. Science.

Dwek, R. A. (1996). Glycobiology: Toward understanding the function of sugars. *Chemical Reveiws, 96*, 683–720.

Gaucher, G., Dufresne, M. H., Sant, V. P., Kang, N., Maysinger, D., & Leroux, J. C. (2005). Block copolymer micelles: Preparation, characterization and application in the drug delivery. *Journal of Controlled Release, 109*, 169–188.

Griesbaum, K. (1970). Problems and possibilities of the free-radical addition of thiols to unsaturated compounds. *Angewandte Chemie International Edition in English, 9*, 273–287.

He, Y. Y., Li, Z. B., Simone, P., & Lodge, T. P. (2006). Self-assembly of block copolymer micelles in an ionic liquid. *Journal of American Chemical Society, 128*, 2745–2750.

Hong, H., Mai, Y., Zhou, Y., Yan, D., & Cui, J. (2007). Self-assembly of large multimolecular micelles from hyperbranched star copolymers. *Macromolecular Rapid Communication, 28*, 591–596.

Jule, E., Nagasaki, Y., & Kataoka, K. (2003). Lactose-installed poly(ethylene glycol)-poly(D,L-lactide) block copolymer micelles exhibit fast-rate binding and high affinity toward a protein bed simulating a cell surface. *A surface plasmon resonance study. Bioconjugate Chemistry, 14*, 177–186.

Lee, E. S., Shin, H. J., Na, K., & Bae, Y. H. (2003). Poly(L-histidine)-PEG block copolymer micelles and PH-induced destabilization. *Journal of Controlled Release, 90*, 363–374.

Lu, C. H., Chen, X. S., Xie, Z. G., Lu, T. C., Wang, X., Ma, J., & Jing, X. B. (2006). Biodegradable amphiphilic triblock copolymer bearing pendant glucose residues: Preparation and specific interaction with concanavalin A molecules. *Biomacromolecules, 7*, 1806–1810.

Mammen, M., Choi, S.-K., & Whitesides, G. M. (1998). Polyvalent interactions in biological systems: Implications for design and use of multivalent ligands and inhibitors. *Angewandte Chemie International Edition, 37*, 2754–5794.

Murakami, T., Hirono, R., Sato, Y., & Furusawa, K. (2007). Efficient synthesis of ω-mercaptoalkyl 1,2-*trans*-glycosides from sugar peracetates. *Carbohydrate Research, 342*, 1009–1020.

Nagasaki, Y., Okada, T., Scholz, C., Iijima, M., Kato, M., & Kataoka, K. (1998). The reactive polymeric micelle based on an aldehyde-ended poly(ethylene glycol)/poly(lactide) block copolymer. *Macromolecules, 31*, 1473–1479.

Nishimura, S. I., Matsuoka, K., & Furita, K. (1990). Synthetic glycoconjugates: Simple and potential glycoprotein models containing pendant *N*-acetyl-D-glucosamine and *N*,*N*′-diacetylchitobiose. *Macromolecules, 23*, 4182–4184.

Ohno, K., Izu, Y., Yamamoto, S., Miyamoto, T., & Fukuda, T. (1999). Nitroxide-controlled free radical polymerization of a sugar-carrying acrylogl monomer. *Macromolecular Chemistry and Physics, 200*(7), 1619–1625.

Rieger, J., Stoffelbach, F., Cui, D., Imberty, A., Lameignere, E., Putaux, J. L., Jérôme, R., Jérôme, C., & Auzély-Velty, R. (2007). Mannosylated poly(ethylene oxide)-*b*-poly(ε-caprolactone) diblock copolymers: Synthesis, characterization, and interaction with a bacterial lectin. *Biomacromolecules, 8*, 2717–2725.

Sacchettini, J. C., Baum, L. G., & Brewer, C. F. (2001). Multivalent protein–carbohydrate interactions. A new paradigm of supermolecular assembly and signal transduction. *Biochemistry, 40*, 3009–3015.

Varki, A. (1993). Biological roles of oligosaccharides: All of the theories are correct. *Glycobiology, 3*, 97–130.

Yasugi, K., Nkamura, T., Nagasaki, Y., Kato, M., & Kataoka, K. (1999). Sugar-installed polymer micelles: Synthesis and micellization of poly(ethylene glycol)-poly(D,L-lactide) block copolymers having sugar groups at the PEG chain end. *Macromolecules, 32*, 8024–8032.

Ye, W. J., Wells, S., & DeSimone, J. M. (2001). Well-defined glycopolymer amphiphiles for liquid and supercritical carbon dioxide appications. *Journal of Polymer Science Part A: Polymer Chemistry, 39*, 3841–3849.

You, L. C., & Schlaad, H. (2006). An easy way to sugar-containing polymer vesicles or glycosomes. *Journal of American Chemical Society, 128*, 13336–13337.

Zhang, L., & Eisenberg, A. (1996). Multiple morphologies and characteristics of "crew-cut" micelle-like aggregates of polystyrend-*b*-poly(acrylic acid) diblock copolymers in aqueous solutions. *Journal of American Chemical Society, 118*, 3168–3181.

Zhou, W., Dai, X. H., & Dong, C. M. (2008). Biodegradable and biomimetic poly(ε-caprolactone)/poly(lactobionamidoethyl methacrylate) biohybrids: Synthesis, lactose-installed nanoparticles and recognition properties. *Macromolecular Bioscience, 8*, 268–278.