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Micelle formation and drug release behavior of polypeptide graft copolymer and its mixture with polypeptide block copolymer

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Abstract

Self-association behavior of polypeptide graft copolymer and its mixture with polypeptide block copolymer and drug carrier capability of the formed micelles was examined. The results gained through fluorescence spectroscopy, transmission electron microscopy and nuclear magnetic resonance spectroscopy revealed that both polypeptide graft copolymer and its mixture with polypeptide block copolymer can self-assemble to form polymeric micelles in aqueous media. The molecular structure of the graft copolymer and blending the graft with block copolymer exert marked effects on the critical micelle concentration and the shape of formed micelles. It was found that the hydrophobic inner core of the micelles formed either by graft copolymer or mixture of graft and block copolymers can act as an incorporation site for the hydrophobic drugs. The drug loading content of the graft copolymer micelles tends to be larger when the content of the polypeptide segments in the copolymer increases. The results obtained from the drug-release studies showed that the drug-release rates are dependent on the chemical nature of the graft copolymer, the composition of the graft and block copolymer mixture, and also the pH value of the release media.
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Keywords: Polypeptide; Micelle; Self-assembly; Drug delivery

1. Introduction

The concept of selective delivery of drugs to their site of action was first proposed by Ehrlich (1906). Since, then delivery systems, such as liposomes, microspheres and nanoparticles have been developed for this purpose. Among various drug carries used for controlled drug delivery, there has been a rising interest in micelles formed through self-assembly of copolymers, especially block copolymers recently (Kwon and Okano, 1996; Kabanov and Kabanov, 1998; Torchilin, 2001; Lin et al., 2006b; Pan et al., 2006).

Due to the amphiphilic characteristics, block or graft copolymers, containing hydrophobic and hydrophilic components, exhibit surfactant behavior and can form micelles with a core–shell structure. The hydrophobic inner core can act as a drug-incorporation site, in which the hydrophobic drugs are entrapped through hydrophobic interactions. The hydrophilic outer shell may be cloaked to avoid being quickly taken up by the reticuloendothelial system and clearable organs, such as liver, spleen, lungs, and kidneys.

Polypeptide block and graft copolymers are suitable copolymers for preparing the micelle drug carrier. Under certain conditions, the polypeptide copolymers can form core–shell structure micelles with various shapes. Besides this characteristics, they are also biocompatible and biodegradable (Cho and Kim, 1988). The large number of amino acids along with their range of physical and chemical properties render this class of polymers useful for the design of novel drug delivery systems. By appropriate modification of the molecular structure, a variety of polypeptide copolymers can be designed to possess varying degrees of hydrophobicity, structural attributes, and electrostatic properties. Various kinds of micelles can be further obtained through self-assembly of these polypeptide copolymers.

Some studies of the drug delivery systems based on the polypeptide block copolymers have already been reported in the literatures (Lavasanifar et al., 2002). For instance, it was found that diblock copolymers composed of poly(β-benzyl-L-aspartate) (PBLA) and poly(ethylene glycol) (PEG) form

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Table 1
Characteristics of polypeptide graft copolymers

Sample	PBLG-*g*-PEG1	PBLG-*g*-PEG2	PBLG-*g*-PEG3
M_η of original polypeptide	20,000	60,000	110,000
M_w of PEG side chain	350	350	350
Grafting rate (mol%)	43.86	27.42	20.05
PBLG content in the copolymer (mol%)	69.47	78.51	83.21

micelles through self-association in water. The formed micelles can act as hydrophobic drug carries such as for the anticancer agent adriamycin. Enhanced tumor accumulation, long blood circulation times, and effective treatment of solid tumors of those drug-load micelles have been reported (Yokoyama et al., 1991; Kwon et al., 1994, 1995, 1997; Kataoka et al., 2000). Nah et al. reported the drug-delivery systems based on core–shell type micelles formed by poly(γ-benzyl-L-glutamate)-*block*-poly(ethylene glycol) (Nah et al., 1998, 2000; Oh et al., 1999). The results show that the molecular structures of the polypeptide block copolymers have a marked effect on the self-association behaviors and drug loading and releasing properties.

So far widely used copolymers for the preparation of the micelle drug carries are block copolymers. The studies regarding the drug carries of graft copolymer micelles are limited (Chiu et al., 1998; Sugimoto et al., 2004). For example, Sugimoto et al. recently have studied aggregate formation and release behavior of hydrophobic drugs of amphiphilic graft copolypeptide. It was found that the graft copolypetides can form aggregates in aqueous medium and exhibit ability to uptake hydrophobic drugs into hydrophobic moiety (Sugimoto et al., 2004). In the present work, drug delivery systems based on the micelles formed by polypeptide graft copolymer and its mixture with polypeptide block copolymer were first reported. Influence of the molecular structure of the polypeptide graft copolymer and blending the graft with block copolymer on the self-associations was studied. The in vitro release profiles of the naproxen, a model drug, from the polypeptide micelles were examined. The physicochemical characteristics of the polypeptide micelles were found to have marked effect on their drug loading and releasing abilities.

2. Materials and methods

2.1. Materials

Polyethylene glycol monomethylether (mPEG) ($M_w = 350$) and methoxypolyethylene glycol amine ($M_w = 5000$) were purchased from Sigma Inc., and used without further purification. Hexane, tetrahydrofuran (THF) and 1,4-dioxane are of analytical grade and dried with sodium to remove water before use. All other solvents are of analytical grade and used without further purification.

2.2. Syntheses of polypeptide copolymers

Poly(γ-benzyl-L-glutamate) (PBLG) were prepared by a standard *N*-carboxyanhydride (NCA) method as adopted in our previous work (Lin et al., 1996, 2000). Briefly, NCA was prepared first, polypeptide was then obtained by the ring-opening polymerization of NCA initiated by triethylamine in 1,4-dioxane at room temperature. The reaction mixture was poured into a large volume of anhydrous ethanol. The precipitated product was dried under vacuum and then purified twice by repeated precipitation from a chloroform solution into a large volume of anhydrous methanol. The molecular weights of polypeptide were estimated from the intrinsic viscosity measured in dichloroacetic acid (DCA) (Lin et al., 1996).

PBLG graft copolymers were prepared by the ester exchange reaction of PBLG with PEG in 1,2-dichloroethane with *p*-toluenesulfonic acid as a catalyst according to the method described in our previous work (Tang et al., 2004; Lin et al., 2006a). In all the cases, the mixture reacted at 55 °C for 72 h and then was precipitated into a large volume of anhydrous ethanol. The resulting product was purified twice from a chloroform solution in a large volume of anhydrous methanol and dried under vacuum. PBLG-*b*-PEG block copolymer was obtained by the ring-opening polymerization of *N*-carboxyl-γ-benzyl-L-glutamate anhydride (γ-BLG-NCA) using methoxypolyethylene glycol amine ($M_w = 5000$) as an initiator. The molecular weight of the block copolymer and the grafting rate of the graft copolymers were estimated by nuclear magnetic resonance (NMR) measurements (Avance 550). It was calculated by the peak intensities of the methylene proton signal (5.1 ppm) of polypeptide and the ethylene proton signal (3.6 ppm) of PEG in the ^{1}H NMR spectrum. The molecular weight of the block copolymer, according to the NMR analysis, is 65,000. The characteristics of the obtained polypeptide graft copolymers are shown in Table 1.

2.3. Preparation of polypeptide copolymer micelles with and without drug loaded

Micelles of PBLG-*g*-PEG and its mixture with PBLG-*b*-PEG were prepared according to the method reported in our previous work (Tang et al., 2004). Briefly, the polypeptide copolymer and its mixture were dissolved in a mixed solvent of tetrahydrofuran (THF)/*N*,*N*-dimethylformamide (DMF). The solution was stirred at room temperature until the polymer was dissolved completely. Then the solution was dialyzed against deionized water using dialysis tubing (3500 molecular weight cut-off) to remove the organic solvents for about 48 h at room temperature. It was preferred that the deionized water was exchanged at intervals of 3–4 h. The solution was diluted with deionized water to the desired concentration.

The drug-loaded micelles were also prepared by the dialysis method. The polypeptide copolymer and its mixture PBLG-*b*-PEG were dissolved in a mixed solvent of THF/DMF and

subsequently naproxen was added. After the samples were completely dissolved, the solution was dialyzed using dialysis tubing with molecular weight cut-off of 3500 against deionized water, which was exchanged at intervals of 4 h during 72 h. The solution was then freeze-dried.

To evaluate the drug-loading content, the freeze-dried sample was put into a dialysis tubing and dialyzed against DMF for 48 h to release the naproxen completely. Then the solution was taken out for the measurement of the drug concentration using ultraviolet (UV) spectrophotometer (UV-2102PCS, Unico) at 331 nm.

2.4. Measurements of fluorescence spectroscopy

To prove the formation of the micelles, fluorescence measurements were carried out using pyrene as a probe (Wilhelm et al., 1991; Kwon et al., 1993; Tang et al., 2004). The fluorescence spectra of pyrene in aqueous solution were recorded at room temperature on a Varian Cary Eclipse fluorescence spectrophotometer. The sample solutions were prepared by first adding known amounts of pyrene in acetone to a series of flasks. After acetone evaporated completely, measured amounts of micelle solutions with various concentrations of PBLG graft and block copolymers and their mixtures were added to each of the flasks and mixed by vortexing. The concentration of pyrene in the final solution was 6×10^{-7} M. The flasks were heated for 3–4 h at 60 °C to equilibrate the pyrene and the micelles. Then the solutions cooled down to room temperature, and equilibrated for 3–4 days before measurements. The emission wavelength was 390 nm for excitation spectra, and excitation bandwidth was 5 nm.

2.5. Observation of transmission electron microscope

The morphologies of the micelles were observed by TEM (JEM-1200-EXII). Drops of micelle solution were placed on a carbon film coated copper grid, and then were dried at room temperature. Before the observations, the sample was stained by phosphotungstic acid. The TEM bright field imaging was performed with 120 kV accelerating voltage.

2.6. Dynamic light scattering (DLS) measurements

Size and distribution of the polypeptide micelles were analyzed by means of a DLS instrument (Zetasizer 3000, Malvern Instruments) with an argon laser beam at a wavelength of 633 nm at 25 °C. The results are expressed in volume-averaged scales as unimode. The scattering angle used is 90°.

2.7. In vitro release studies

The freeze-dried sample was put into dialysis tubing and then dialyzed against the phosphate buffered saline solution (PBS, pH 7.4). At specific time intervals, the whole medium was taken out and replaced with fresh PBS to prevent saturation of the drug. The concentration of the released naproxen was determined by the UV spectrophotometer at 331 nm. For the studies of the influence of the pH value on the release rate, the PBS solution was replaced by HCl solution, potassium acid phthalate buffered solution, and sodium borate buffered saline solution. The pH values of those solutions are 1.1, 4.0, and 10.0, respectively.

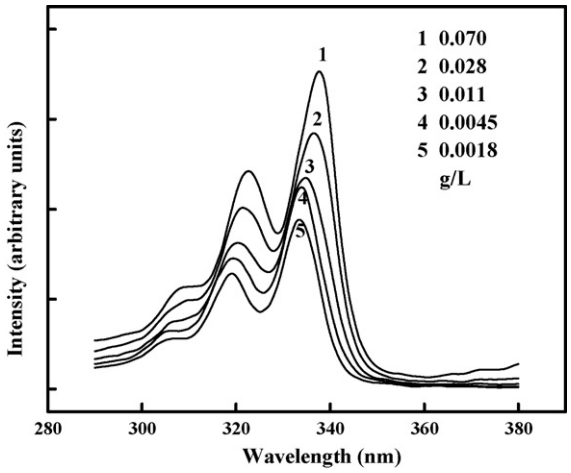

Fig. 1. Excitation spectra of pyrene as a function of PBLG-*g*-PEG3 concentrations in deionized water.

3. Results and discussion

3.1. Micellization of polypeptide graft copolymer and its mixture with block copolymer

Fig. 1 presents a typical fluorescence excitation spectra obtained for pyrene in PBLG graft copolymer solutions with various polymer concentrations. The fluorescence intensity increases with increasing the concentration. Concomitantly with the increase in the fluorescence intensity, a red shift from 333 to 338 nm is shown for the pyrene (0, 0) band. This effect indicates that micellization takes place for the PBLG graft copolymer above a critical polymer concentration. Upon the formation of the micelles, pyrene molecules transfer from the water environment to the microenvironment within the micelles. Such a change of the surrounding environment could cause the change

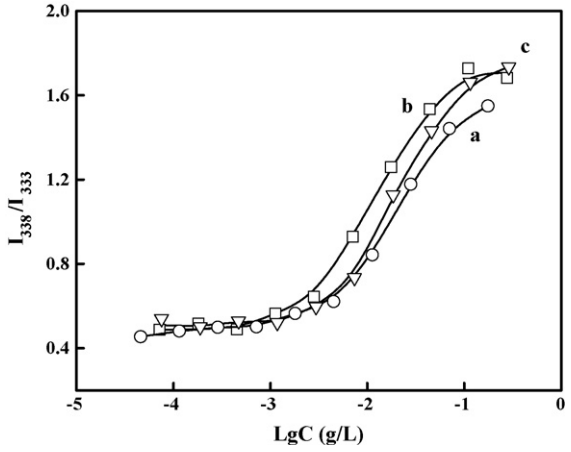

Fig. 2. Plots of I_{338}/I_{333} vs. log *C* for PBLG-*g*-PEG3 (a), PBLG-*b*-PEG (b), and mixture of PBLG-*g*-PEG3 and PBLG-*b*-PEG with ratio of 1:1 by weight (c).

Table 2
CMC values for PBLG graft and block copolymers and their mixtures determined by fluorescence spectroscopy measurements

Sample	PBLG-*g*-PEG1	PBLG-*g*-PEG2	PBLG-*g*-PEG3	PBLG-*b*-PEG	PBLG-*g*-PEG1/PBLG-*b*-PEG (1:1 by weight)	PBLG-*g*-PEG3/PBLG-*b*-PEG (1:1 by weight)
PBLG content (mol%)	69.47	78.51	83.21	70.68	69.75	75.33
CMC (g/l)	1.79×10^{-2}	2.48×10^{-3}	2.40×10^{-3}	1.77×10^{-3}	5.60×10^{-3}	2.15×10^{-3}

in the photophysical properties of pyrene, which can provide information both about the critical micelle concentration (CMC) and the locus of the pyrene probe in the system (Dowling and Thomas, 1990; Zhao et al., 1990). Similar phenomena were also observed for PBLG block copolymers and the mixed systems of PBLG graft and block copolymers.

Curve (a) in Fig. 2 illustrates a plot of I_{338}/I_{333} versus log C for PBLG graft copolymer. At the low concentration, negligible changes in the magnitude of I_{338}/I_{333} were observed. As the polymer concentration is increased, at a certain concentration (i.e., the CMC) the value of I_{338}/I_{333} increases dramatically in a sigmoid manner. According to the method adopted by Wilhelm et al. (1991), the CMC value is taken as the intersection of the tangent to the curve at the inflection with the horizontal tangent through the points at low polymer concentrations. The I_{338}/I_{333} values obtained for PBLG block copolymer and mixture of PBLG graft and block copolymers are shown by curves (b) and (c). They exhibit similar pattern to that of PBLG graft copolymer. Moreover, the single CMC value shown for the mixed systems indicates that PBLG-PEG graft and block copolymers may take part in the hybridization together and form hybrid micelle. One CMC point was also observed for self-association of mixed amphiphilic copolymers by Chu et al. (Liu et al., 1999) In their work, two oxyalkylene triblock copolymers can self-associate to

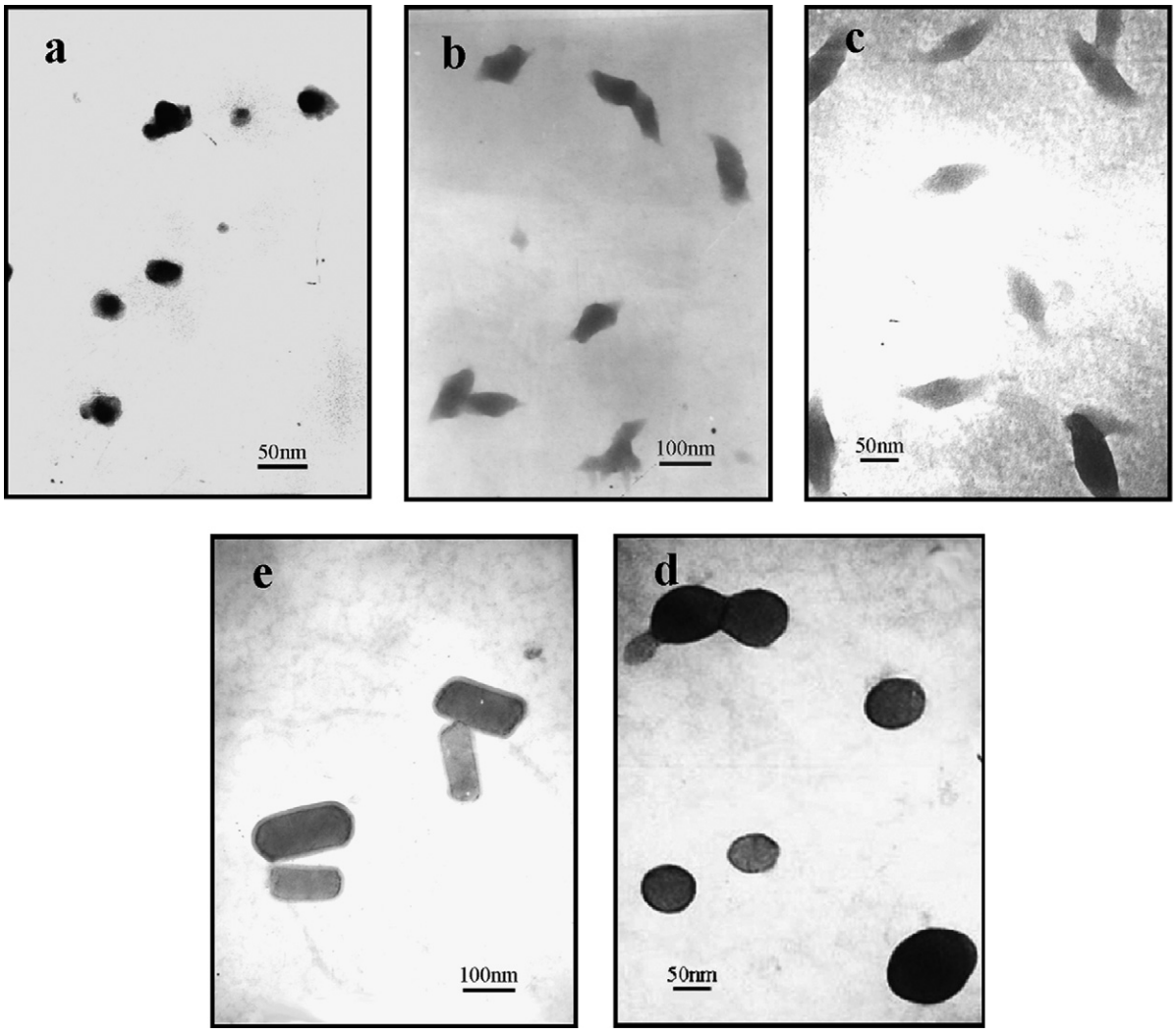

Fig. 3. TEM photographs of micelles formed by PBLG-*g*-PEG1 (a), PBLG-*g*-PEG2 (b), PBLG-*g*-PEG3 (c), PBLG-*b*-PEG (d), and PBLG-*g*-PEG3/PBLG-*b*-PEG mixture with ratio of 1:1 by weight (e).

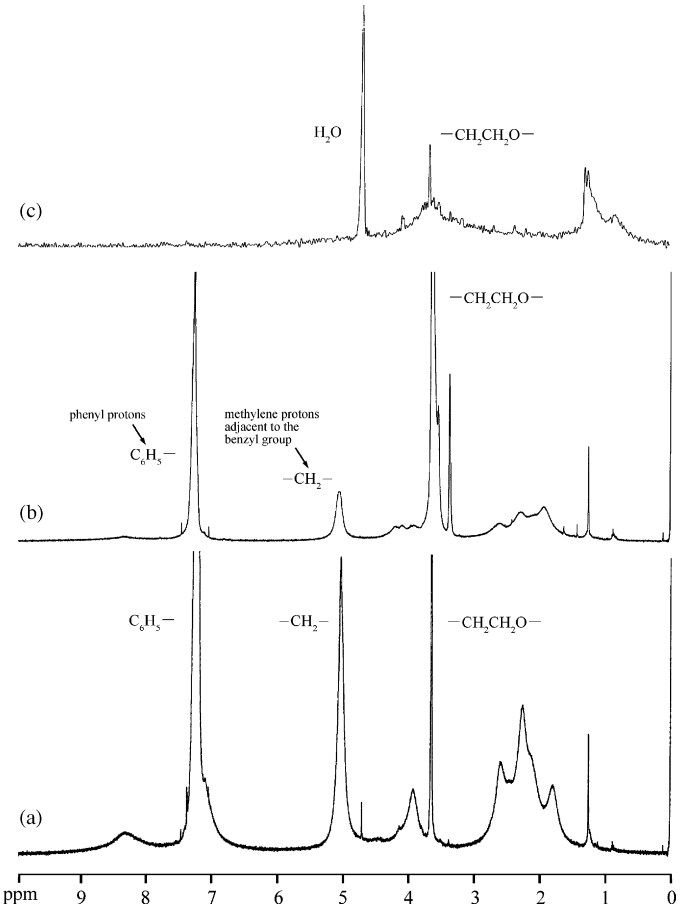

Fig. 4. ^{1}H NMR spectra for PBLG-*g*-PEG3 in $CDCl_3$ (a), PBLG-*b*-PEG in $CDCl_3$ (b), and PBLG-*g*-PEG3/PBLG-*b*-PEG mixture (1:1 by weight) in D_2O (c).

form hybrid micelles in aqueous solution, and one CMC point exhibits.

The CMC data for PBLG copolymers and the mixtures of the graft and block copolymers determined by fluorescence spectroscopy measurements are collected in Table 2. As for the PBLG graft copolymers, with increasing polypeptide content in the copolymer, the CMC value becomes smaller. This suggests that the self-assembly tendency of the PBLG graft copolymer increases with increasing hydrophobic segment content in the copolymer. With respect to the mixture systems, the CMC value is determined by both graft and block copolymers. It was shown to be between the values of the individual copolymers as it can be seen from Table 2.

Fig. 3 presents the morphologies of the micelles formed by PBLG graft and block copolymers and their mixture. Shown in Fig. 3a–c are the results observed for the graft copolymers with various molecular structures. Spherical micelles are shown for PBLG-*g*-PEG1 that has short length of polypeptide chain and low content of PBLG segment (Fig. 3a). With increase in the length of the polypeptide backbone and the content of PBLG in the copolymer, the morphologies of the formed micelles tend to be rhombic as shown by Fig. 3b. Spindly shaped micelles can be seen in Fig. 3c for PBLG-*g*-PEG3 sample, which has longest PBLG chain length and highest PBLG content among the three graft samples. It is well known that PBLG can take α-helix or random coil conformation depending on solvent, temperature, etc. In aqueous solution, the PBLG main chain takes rigid α-helix conformation. Due to the rigid α-helix chain structure, the polypeptide chains are expected to favor ordered packing with their long axis aligned within the micelle core. The soluble PEG chains are excluded outside to form corona (some PEG segments may exist in the core). As a result, rhombic and spindly shaped micelles are observed. However, when the PEG content is higher and PBLG chain length is shorter in the graft copolymer, the micelles are spherical (Fig. 3a). This can be attributed to the formation of larger PEG corona with randomly chains packing, and the smaller micelle core with shorter PBLG chains. The micelles formed by the block copolymer exhibit spherical shapes (Fig. 3d), which are the same as those reported in the literatures (Nah et al., 1998, 2000). Fig. 3e gives a typical example of the morphologies for the micelles formed by PBLG-*g*-PEG3 and PBLG block copolymer mixture (weight ratio is 1:1). Cylindrical micelles are demonstrated. The morphologies are neither spindly-shaped micelles of PBLG-*g*-PEG3 nor spherical micelles of PBLG block copolymer, which further suggests that the graft and block copolymers associate into hybrid micelles together.

Further information regarding the hybrid micelle formation of PBLG-*g*-PEG/PBLG-*b*-PEG is provided by ^{1}H NMR spectra. Fig. 4a and b shows the ^{1}H NMR spectra of PBLG-*g*-PEG3 and PBLG-*b*-PEG in $CDCl_3$ where the micelle formations are not expected. The characteristic peaks of the phenyl protons in the PBLG segment and the methylene protons adjacent to the benzyl

Table 3
Drug-loading content of micelles formed by PBLG graft and block copolymers and their mixtures[a]

Sample	Final drug concentration (mg drug/7 mg polymer)	Loading content (wt.%)	Loading efficiency (%)
PBLG-*g*-PEG1	0.242	3.34	6.05
PBLG-*g*-PEG2	0.546	7.24	13.65
PBLG-*g*-PEG3	1.013	12.64	25.33
PBLG-*b*-PEG	0.294	4.03	7.35
PBLG-*g*-PEG3/PBLG-*b*-PEG (1:1 by weight)	0.452	6.07	11.30
PBLG-*g*-PEG3/PBLG-*b*-PEG (4:1 by weight)	0.494	6.59	12.35
PBLG-*g*-PEG3/PBLG-*b*-PEG (1:4 by weight)	0.266	3.66	6.65

[a] Value of the initial solvent was 25 ml. Seven milligrams of copolymer and 4 mg naproxen were added. The loading efficiency was defined as the ratio of the weight of loaded drug to the initially added drug.

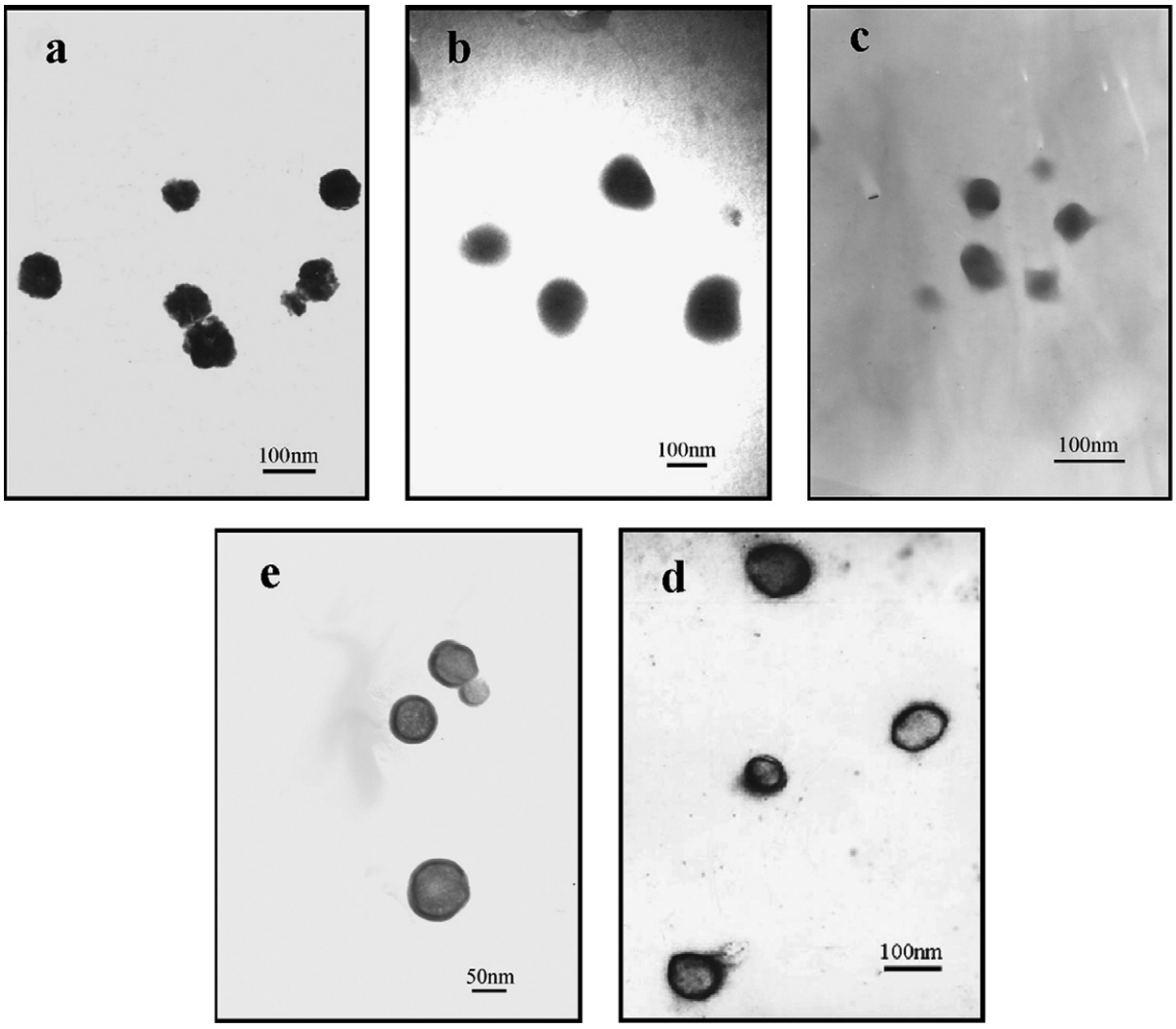

Fig. 5. TEM photographs of drug-loaded micelles formed by PBLG-*g*-PEG1 (a), PBLG-*g*-PEG2 (b), PBLG-*g*-PEG3 (c), PBLG-*b*-PEG (d), and PBLG-*g*-PEG3/PBLG-*b*-PEG mixture with ratio of 1:1 by weight (e).

group of PBLG segment appear at 7.2 and 5.1 ppm, respectively. The characteristic peak of ethylene protons of PEG is shown at 3.6 ppm. The ^{1}H NMR spectrum of PBLG-*g*-PEG3/PBLG-*b*-PEG mixture in D_2O is shown by curve (c) in Fig. 4. It shows a striking difference in comparison with the spectra of PBLG-*g*-PEG3 and PBLG-*b*-PEG measured in $CDCl_3$. The peaks of the phenyl protons (7.2 ppm) of the PBLG segment and the methylene protons (5.1 ppm) adjacent to the benzyl group of PBLG segment disappear. The peak of the ethylene protons of PEG is still visible. Such changes in the ^{1}H NMR spectra indicate that the graft copolymer and block copolymer could assemble into micelles with the hydrophobic PBLG segments aggregating as the inner core of the micelles surrounded by PEG chains. The restriction of the proton motions of the PBLG segments results in the disappearance of the PBLG characteristic peaks (Kwon et al., 1993; Jeong et al., 1999).

3.2. Drug loading and releasing studies

Table 3 shows the drug-loading contents of the micelles formed by PBLG graft copolymers, block copolymer and their mixtures. The mol contents of the PBLG segments in the graft copolymers are 69.47, 78.51 and 83.21% for PBLG-*g*-PEG1, PBLG-*g*-PEG2, and PBLG-*g*-PEG3, respectively. As it can be seen from Table 3, the loading content increases with increasing PBLG segment content. This can be explained that the more hydrophobic part in the polymer chain makes it possible to have more hydrophobic interaction points in the formed micelles, giving rise to a higher loading content. Such an observation is in line with the result observed for PBLG block copolymer (Nah et al., 1998, 2000; Oh et al., 1999). The loading content was found to increase when the PBLG chain length in the block copolymer becomes longer. As for the mixture systems of PBLG graft and block copolymers, the loading content shows a tendency to be between those of graft and block copolymers.

TEM photographs of the micelles after loading drug are shown in Fig. 5. Comparing with the results demonstrated in Fig. 3, the micelles sizes become larger when the drug is incorporated. The drug loading also shows effect on the shape of the formed micelles. Rhombic-shaped and spindle-like micelles turn spherical after the incorporation of the naproxen. The effect of the drug loading on the micelle size and distribution was also

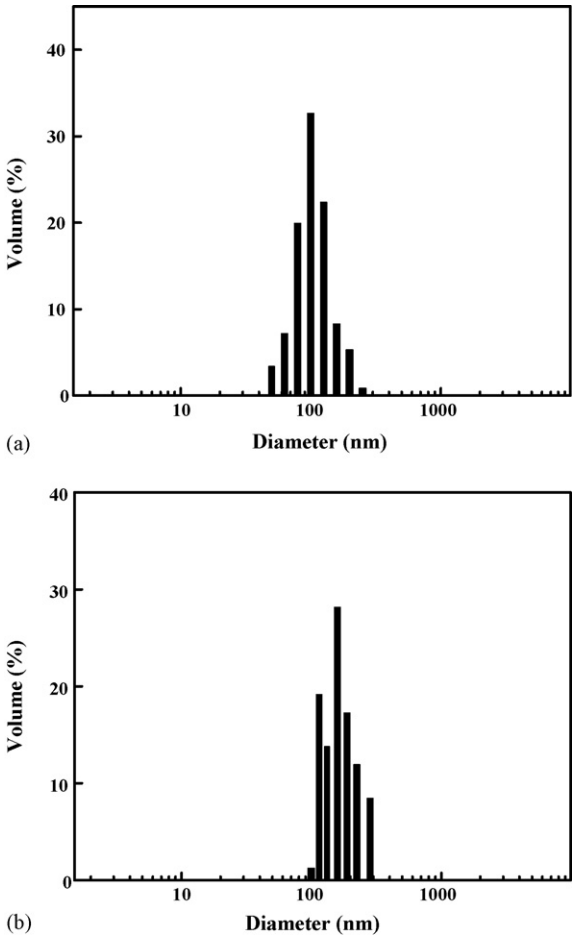

Fig. 6. Particle-size distribution of micelles formed by PBLG-*g*-PEG3 without (a) and with (b) drug loaded.

studied by DLS. Although the micelles formed by some graft copolymers are asymmetry in shape, the DLS results still give interesting information to corroborate the TEM observations. Shown in Fig. 6 is a typical result of the particle size distribution for the PBLG-*g*-PEG3 micelles with and without naproxen loaded. The particle size based on volume average is 159 nm for the micelles without drug loaded. It becomes 192 nm when the naproxen is incorporated.

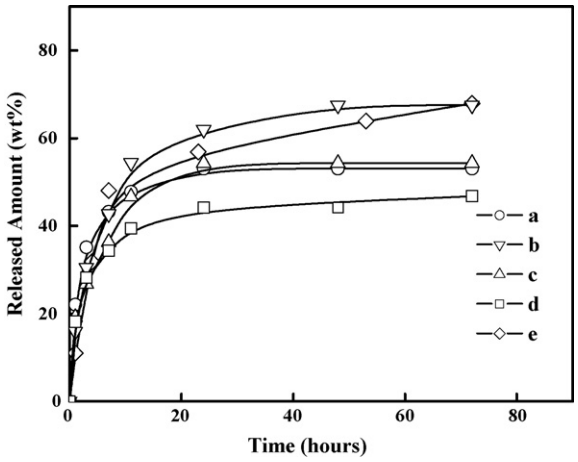

Fig. 8. Release of naproxen from micelles formed by mixtures of PBLG-*g*-PEG3/PBLG-*b*-PEG with ratios of 4:1 (a), 1:1 (b), 1:4 (c), PBLG-*g*-PEG3 (d), and PBLG-*b*-PEG (e). The pH value of the release media is 7.4.

Fig. 1 shows the release kinetics of naproxen from the micelles of PBLG graft copolymers as a function of time. The release profile was characterized by a rapid release in the initial stage, followed by slow and sustained release. At the same release time the amount of the released naproxen tends to be larger when the content of the PBLG segment in the graft copolymer decreases. Such a dependence on the polypeptide content in copolymer was also observed in the polypeptide block copolymer systems. It was found that the higher polypeptide content could result in a slower drug release rate (Nah et al., 1998, 2000; Oh et al., 1999).

The release profiles of the naproxen from the micelles formed by mixtures of PBLG graft and block copolymers are shown in Fig. 8. The results obtained for the PBLG graft and block copolymers are also included. The release curves of the mixture systems exhibit similar pattern to those of graft and block copolymers. The release rates of naproxen from the mixture systems tend to be between those of graft and block copolymer systems.

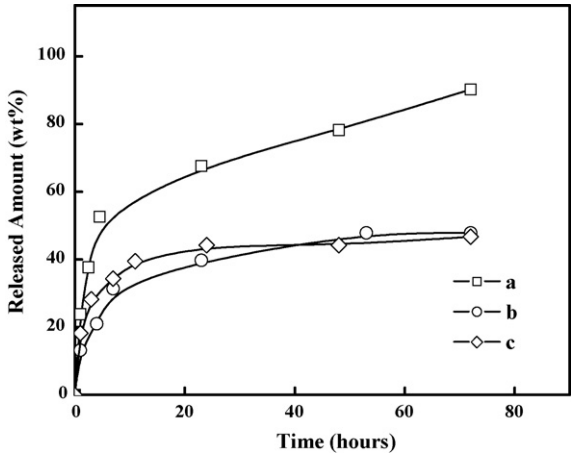

Fig. 7. Release of naproxen from micelles formed by PBLG-*g*-PEG1 (a), PBLG-*g*-PEG2 (b), and PBLG-*g*-PEG3 (c). The pH value of the release media is 7.4.

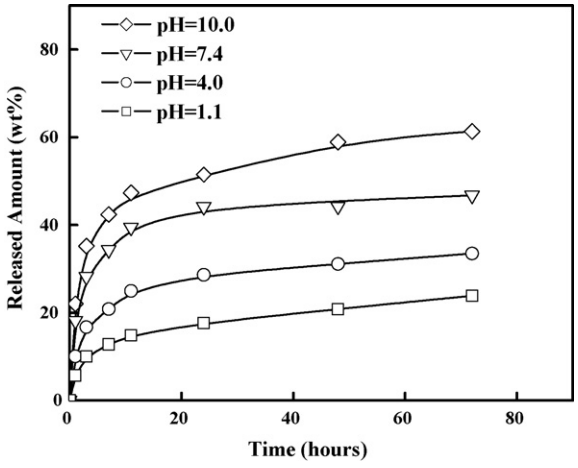

Fig. 9. Effect of the pH values on the release rates of naproxen from micelles formed by PBLG-*g*-PEG3.

Fig. 9 shows a typical result of the effect of pH value of release medium on the release kinetics. The release rate of naproxen from the PBLG-*g*-PEG3 micelles increases with increasing pH value. Similar phenomenon was also observed for other graft copolymer samples, block copolymer sample, and the mixture systems. It is likely due to that the solubility of naproxen increases with increasing pH value in aqueous media. Such pH value dependence may find some useful applications, since the drug-load micelles can achieve preferential drug release at some place where the local pH is quite different from those of normal tissue (Hoes et al., 1993).

4. Conclusions

The micellization behaviors of PBLG-*g*-PEG and its mixtures with PBLG-*b*-PEG in aqueous media were studied by fluorescence spectroscopy, TEM and NMR. The micelles formed throughout self-assembly were found to be able to act as a drug-carrier. Influence of the molecular structure of the graft copolymer, composition of the graft and block copolymer mixture, and pH values of the release media on the drug loading and releasing abilities were examined. The obtained experimental results are summarized as followings:

(1) Both PBLG-*g*-PEG and its mixture with PBLG-*b*-PEG can self-associate to form polymeric micelles in water. Higher PBLG segment content in the graft copolymer could lead to lower critical micelle concentration. For the mixed systems containing PBLG graft and block copolymers, the CMC values are between the values of the individual copolymers.
(2) Spherical micelles were observed for the PBLG graft copolymers with low polypeptide content and short length of PBLG backbone. As the polypeptide content and PBLG backbone length increase, the shape of the formed micelles turns rhombic and further increase in the polypeptide content and the backbone length results in a spindle-like morphology. For the mixed systems, the morphologies of the micelles are dependent on both graft and block copolymers, since the graft and block copolymers associate together to form hybrid micelles.
(3) The drug-loading content of the PBLG-*g*-PEG micelles was found to increase as the PBLG content in the copolymer increases. As for the mixture systems of the PBLG graft and block copolymers, the loading content tends to be between those of individual graft and block copolymers.
(4) The drug-release kinetic studies showed that the higher polypeptide content in the graft copolymer could result in a slower release rate. The pH value of the release media has marked effect on the release kinetics. The release rate increases with increasing pH value.

The micelles based on the polypeptide copolymers are of interest as drug delivery platforms because of their capacity to be both biocompatible as well as biodegradable to naturally occurring biological products. The experimental results gained throughout present studies have provided a useful way to control the formation of the delivery platforms and release kinetics. Such a way could be realized by optimizing the chemical nature of the polypeptide copolymers, and also simply blending two kinds of the polypeptide copolymers with different molecular structures.

Acknowledgements

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