Preparation of Core–Shell Type Nanoparticles of Diblock Copolymers of Poly(L-lactide)/Poly(ethylene glycol) and Their Characterization *In Vitro*

JEONG-JUN YU,[1] YOUNG-IL JEONG,[2] YONG-HO SHIM,[3] GYUN-TAEK LIM[1]

[1] Department of Polymer Engineering, College of Engineering, Chonnam National University, 300, Yongbong-Dong, BukGu, Kwangju 500-757, Korea

[2] Research Institute of Medical Science, Chonnam National University Medical School, Kwangju 501-746, Korea

[3] Structure et Fonction de Molecules Bioactive, Universite Pierre et Marie Curie, Paris Cedex 05, France

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ABSTRACT: Core–shell type nanoparticles of poly(L-lactide)/poly(ethylene glycol) (LE) diblock copolymer were prepared by a dialysis technique. Their size was confirmed as 40–70 nm using photon correlation spectroscopy. The ^{1}H-NMR analysis confirmed the formation of core–shell type nanoparticles and drug loading. The particle size, drug loading, and drug release rate of the LE nanoparticles were slightly changed by the initial solvents that were used. The drug release behavior of LE core–shell type nanoparticles showed an initial burst during the first 12 h and then a sustained release until 100 h. The degradation behavior of LE block copolymer nanoparticles was divided into three phases: the initial rapid degradation phase, the stationary phase, and the rapid degradation phase until complete degradation. It was suggested that lidocaine release kinetics were predominantly governed by the diffusion mechanism in the initial burst phase and after that by both of the diffusion and degradation mechanisms. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 85: 2625–2634, 2002

Key words: poly(L-lactide)/poly(ethylene glycol) diblock copolymer; core–shell type nanoparticles; organic solvent; lidocaine; biodegradation; *in vitro*

INTRODUCTION

Nanoparticles[1] have been widely used for targeted drug delivery and other biomedical applications.[1–5] Because these drug carrier systems are able to be used for intravenous injection of drugs for site-specific drug delivery, nanoparticles or colloidal carriers have great potential in the therapy of several fatal diseases without unwanted side effects.[2,6] To achieve these objectives, a series of nanosized particles or colloidal carriers such as nanospheres,[1–6] polymeric micelles,[7–10] liposomes,[11–13] and surface-modified nanoparticles[14,15] have been developed and suggested. However, some problems, which are still presently not fully understood, are the distribution of drugs and carriers in the body, undesirable side effects, rapid clearance by macrophages, thermal instability, structural fragility, lower drug loading efficiency, and so forth.

On the other hand, block copolymers exhibit surfactant behavior and then form polymer micelles[7–10] or core–shell type nanoparticles[16,17] in an aqueous environment because of their am-

Correspondence to: G.-T. Lim (gtlim@chonnam. ac.kr).

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phiphilic characteristics. In these structures each segment of the block copolymers has different functions. Hydrophobic blocks form the inner core of the structure, which acts as a drug incorporation site, especially for hydrophobic drugs. Hydrophobic drugs may be easily physically entrapped within the inner core of the structures by hydrophobic interactions.[7–16] Hydrophilic blocks form a hydrated outer shell that may cloak the hydrophobic core to avoid its quick uptake by the reticular endothelial system (RES) and more active clearing organs such as the liver, spleen, lung, and kidneys. Therefore, a hydrated outer shell can increase the blood circulation time of nanoparticles. The predominant characteristics of this system that have been reported are the reduced toxic side effects of antitumor agents, passive targeting to the specific sites, solubilization of hydrophobic drugs, stable storage of drugs, long blood circulation, favorable biodistribution, thermal stability, and lower interactions with the RES.

Several groups[7–10] extensively investigated polymeric micelles as hydrophobic drug carriers, such as the anticancer agent Adriamycin. They reported that diblock copolymers composed of poly(β-benzyl L-aspartate) (PBLA) and poly(ethylene oxide) (PEO) form micelles through self-association in water and are on the order of several 10s of nanometers in size, which is a size range similar to viruses. They also reported enhanced tumor accumulation of antitumor agents, long blood circulation times, and the effective treatment of solid tumors by micelle-forming block copolymer–Adriamycin conjugates.[18,19] Gref and collaborators[3,16] reported that core–shell type nanoparticles of polylactide/poly(ethylene glycol) (PEG) diblock or multiblock copolymer and poly(ϵ-caprolactone-*co*-ethylene glycol) diblock copolymers were circulated in blood for a long tiem and hydrophobic drugs were released in a sustained manner.

For this study we synthesized diblock copolymers composed of poly(L-lactide) (PLLA) and PEG (LE). Core–shell type nanoparticles of LE as hydrophobic drug carriers were prepared and lidocaine was used as a hydrophobic drug model. PLLA is a well-defined nontoxic biodegradable polymer with a hydrophobic character. PEG is a nonimmunogenic, nontoxic water-soluble polymer and it has the ability to prevent protein adsorption and attack of the RES.[20] There are a number of studies on nanoparticles or polymeric micelles using LE diblock copolymers; however, their particle size, drug loading capacity, and physicochemical properties against various conditions, such as the initial solvent and drug feeding ratio, was not sufficiently investigated *in vitro*. Also, the biodegradable behavior of LE diblock copolymer nanoparticles against PLLA block domain size was investigated *in vitro*.

EXPERIMENTAL

Materials

Monomethoxy PEG (MePEG, MW 5000), lidocaine, and stannous 2-ethylhexanoate were purchased from Sigma. The L-lactide [LLA, (3S)-cis-3,6-dimethyl-1,4-dioxane-2,5-dione] was purchased from Aldrich. 1,4-Dioxane, acetone, dimethylformamide (DMF), dimethylsulfoxide (DMSO), dimethylacetamide (DMAc), tetrahydrofuran (THF), dichloromethane, methanol, and diethyl ether were reagent grade and were used without further purification.

Synthesis of LE Diblock Copolymer

The LE diblock copolymer was synthesized by ring-opening polymerization of LLA to the one end of the hydroxyl group of MePEG as reported by Zhu et al.[21] The preweighed amounts of LLA and MePEG were mixed in a round-bottomed flask and melted at 100°C in an oil bath. Then 0.5 wt % of stannous 2-ethylhexanoate was added into the round-bottomed flask and evacuated with a vacuum pump. The flask was then placed in an oil bath at 180°C to start the polymerization. After 6 h the resultant product was dissolved in methylene chloride and precipitated into diethyl ether several times. The precipitants were harvested by filtration and the resultant product was dried in a vacuum oven at 40°C for 3 days.

The molecular weight was estimated by ^{1}H-NMR measurement using $CDCl_3$. The copolymer composition and number-average molecular weight was estimated from the characteristic peaks of PLLA (5.1 and 1.5 ppm of methine and methylene protons, respectively) and PEG (3.7 ppm of methylene protons).

^{1}H-NMR Spectrometry

In order to estimate the copolymer compositions and the molecular weights of the PLLA blocks, the ^{1}H-NMR spectra of the copolymers were measured in $CDCl_3$ using a 300-MHz NMR spectrometer (FT-NMR, Bruker AC-300F). Because the

number-average molecular weight of PEG is known (5000), one can estimate the number-average molecular weights of the PLLA block and the copolymer composition as calculated from the peak intensities in the spectrum assigned to both polymers.

To approve the core–shell type structure of the LE block copolymer the ^{1}H-NMR spectra were measured in $CDCl_3$ and D_2O. The concentration of the polymeric core–shell type nanoparticles was 1.0 wt % in $CDCl_3$ and 0.5 wt % in D_2O.

Wide Angle X-Ray Diffractometry

X-ray powder diffractograms were obtained with a Rigaku D/Max-1200 apparatus using Ni-filtered CuKα radiation (35 kV, 15 mA).

Differential Scanning Calorimetry

The melting temperature was measured by a Mettler DSC-30 differential scanning calorimeter. The measurement was carried out in a range from room temperature to 200°C under nitrogen at a scanning rate of 10°C/min.

Gel Permeation Chromatography (GPC)

The MW of PLLA/PEG was measured with a Waters LC system coupled with a Waters 410 differential refractometer using Waters Styragel™ HR1, HR2, and HR4 columns at a flow rate of 1 mL/min. THF was used as an eluent. The average MW was evaluated with polystyrene as a standard.

Photon Correlation Spectroscopy (PCS)

The PCS was measured with a Zetasizer 3000 (Malvern Instruments) with an He-Ne laser beam at a wavelength of 633 nm at 25°C (scattering angle of 90°). A nanoparticle solution prepared by the dialysis method was used for particle size measurement (0.1 wt % concentration) and was measured without filtering.

Preparation of LE Nanoparticles

The preparation of the LE core–shell type nanoparticles was carried out by the dialysis method. Briefly, 20 mg of LE diblock copolymer was dissolved in 4 mL of DMF. Subsequently, 20 mg of lidocaine was added into the above solution. The solution was introduced into a dialysis tube (12,000 g/mol molecular cutoff) and dialyzed 6 times against 1 L of distilled water for 12 h. Then the solution was analyzed or freeze-dried.

For an evaluation of the drug loading content, 5 mg of lidocaine-loaded LE nanoparticles was dissolved in 0.1 mL of dichloromethane and then 9.9 mL of ethanol was added. The precipitated LE block copolymer was removed by centrifugation at 12,000 $\times$ g. The supernatant was used for the evaluation of drug loading by a UV spectrophotometer (Shimadzu UV-1201) at 240 nm. The drug loading contents and loading efficiency were calculated as follows: drug loading contents = [(amount of remaining drug in nanoparticles)/(total amount of nanoparticles)] $\times$ 100; loading efficiency = [(amount of remaining drug in nanoparticles)/(initial amount of drug)] $\times$ 100.

In Vitro Release Studies

The *in vitro* release experiment was carried out as follows: 10 mg of lidocaine-loaded LE nanoparticles and 5 mL of phosphate buffered saline (PBS, 0.1*M*, pH 7.4) were put in a dialysis tube and then the dialysis tube was introduced into a vial with 95 mL of PBS. At specific time intervals the whole medium was taken out and replaced with fresh PBS. The concentration of the released lidocaine was determined by using a UV spectrophotometer (Shimadzu UV-1201) at 240 nm.

In Vitro Degradation Test of LE Block Copolymer Nanoparticles

In order to study the degradation behavior of the LE core–shell type nanoparticles,[22] the dialyzed nanoparticles were incubated in PBS (0.1*M*, pH 7.4). Then 100 mg of the LE triblock copolymer was dissolved in 20 mL of organic solvent. The solution was dialyzed using a 2000 g/mol molecular cutoff dialysis tube and then dialyzed against PBS (0.1*M*, pH 7.4) for 2 days with an exchange of fresh PBS at intervals of 3–6 h. The resulting dialyzed aqueous solution was adjusted to 50 mL with PBS solution and 10 mL (i.e., 10 mL of aqueous solution contain 20 mg of LE triblock copolymer nanoparticles) was subsequently introduced into the dialysis tube (2000 g/mol molecular weight cutoff). The dialysis tubes were then introduced into a 100-mL bottle with 50 mL of PBS and incubated at 100 rpm in 37°C. The whole media was exchanged with fresh PBS media at intervals of 2 days. At specific time intervals the dialyzed polymer solution in the dialysis tube was taken and dialyzed against distilled water for 6 h

Table I Characterization of Poly(L-lactide)/Poly(ethylene glycol) Diblock Copolymer

	Feeding Amount (mol%)	Total Molecular Weight				
				MW by GPC		
	L-lactide/PEG	Calculated[a]	Number Average MW[b]	M_n	M_w	Polydispersity[c]
LE-1	200	33,800	23,300	18,200	29,400	1.62
LE-2	100	19,400	18,500	9,400	17,500	1.86
LE-3	50	12,200	8,100	6,600	9,500	1.44

[a] Molecular weight of block copolymer was calculated from the M_w of PEG (5,000) measured by Sigma Co., USA.
[b] Molecular weight was evaluated by ^{1}H-NMR
[c] Polydispersity was calculated from GPC data.

to remove trace elements. The resultant solution was freeze-dried for the GPC analysis of molecular weight changes of the PLLA block as described above.

RESULTS AND DISCUSSION

Characterization of Core–Shell Type Nanoparticles of LE Diblock Copolymer

The composition and molecular weights of the polymers were determined by ^{1}H-NMR spectroscopy and the unit ratio of MePEG and LLA was calculated from the peak intensities of the methylene proton of the PEG and the methylene proton of the LLA units. Values of 4.13 and 1.5 ppm were assigned to the methylene proton peaks of PEG and PLLA, respectively. The composition of the LE block copolymer was estimated from each of the number-average molecular weights of the PLLA and PEG blocks as a monomeric unit. The LE diblock copolymers with different molecular weights were prepared by changing the molar ratio of the PEG homopolymer/LLA monomer. The calculated results of the molecular weight and the composition of LE are summarized in Table I.

It was expected that LE diblock copolymers in aqueous solutions could self-associate into nanoparticles with a core–shell structure via the dialysis procedure. Core–shell type nanoparticles of LE diblock copolymers were prepared by dissolving LE-2 diblock copolymer followed by dialysis against distilled water, and the particle size was measured to confirm the formation of nanoparticles of the LE-2 diblock copolymer. The particle size distribution of LE-2 core–shell type nanoparticles is shown in Figure 1. The mean particle size of the LE-2 diblock copolymer was 51.0 ± 4.9 nm. As expected, the LE-2 core–shell type nanoparticles have a small particle size. As reported elsewhere,[3,7,10] polyester–polyether block copolymers are simply made as nanoparticle drug carriers by the dialysis procedure or the oil/water emulsion solvent evaporation method. In these results, however, LE-2 core–shell type nanoparticles have significant secondary aggregation (439.7 ± 300.9), although their fraction is so small (1.2%) and thus can be ignored. Secondary aggregation behavior during preparation of nanoparticles using diblock copolymer was reported by several authors.[9,17] The secondary aggregation behavior is still unclear. Several possibilities are generally considered: the individual nanoparticles are further associated by the hydrophobic–hydrophobic interactions between exposed cores, there is a multilayer structure with alternating concentric layers of solvated and undissolved blocks, second-

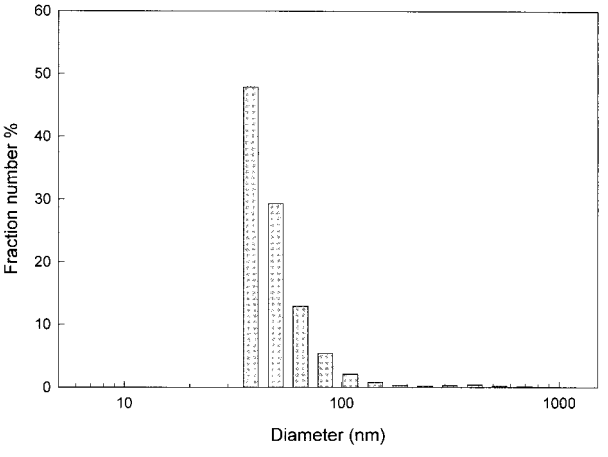


Figure 1 The particle size distribution of LE-2 core–shell type nanoparticles.

ary aggregates are formed with time due to the weak steric stabilization of PEO chains, there is a mixture of micelles, and there is a considerable amount of secondary aggregates.[9,17,23–25]

Further evidence of core–shell type nanoparticles of the LE-2 block copolymer and the limited mobility of the PLLA chain and drug loading in the core of the nanoparticles were obtained with ^{1}H-NMR in $CDCl_3$ and D_2O as shown in Figure 2. Because both of the PLLA and PEG blocks are easily dissolved in $CDCl_3$ or DMSO (*d* form) and exist in the liquid state (Fig. 2, spectrum b), the core–shell structure was not expected. In $CDCl_3$ or DMSO (*d* form) the characteristic peak of the methyl protons of the PLLA segment are shown at about 1.5 and 5.1 ppm, respectively. Also, in that solvent the protons of the ethylene oxide of the PEG segment were shown at 3.6–3.7 ppm. However, in D_2O the characteristic peaks of the PLLA block had completely disappeared whereas the peculiar peaks of the PEG block remained as shown in spectrum c in Figure 2. These results indicated that the protons of PLLA block display restricted motions within the inner core and the PLLA block has a rigid solid structure whereas PEG blocks existed as a liquid state in the aqueous environment. This behavior of LE core–shell type nanoparticles is in contrast to low molecular amphiphiles and PEO-poly(propylene oxide)-PEO block copolymers, which typically exhibit liquid-like cores and relatively higher mobility. It was also reported that a PBLA/PEO diblock copolymer has a rigid PBLA core,[8] but in their results the peaks of 7.4 and 5.2 ppm had not completely disappeared and this result suggested that PBLA/PEO diblock copolymer micelles may have a relatively less rigid core when compared with LE core–shell type nanoparticles. Also, drug entrapment into the inner core of the core–shell type nanoparticles was approved with ^{1}H-NMR in $CDCl_3$ and D_2O. The characteristic peaks of the drug itself (Fig. 2, spectrum a) disappeared in D_2O (Fig. 2, spectrum e) whereas peaks of PEG remained. However, in $CDCl_3$ both characteristic peaks of the LE diblock copolymer and drug appeared as shown in spectrum d in Figure 2. These results clearly showed that the hydrophobic drug was successively entrapped in the inner core of the core–shell type nanoparticles with the hydrated outer shell of PEG.

To investigate the physicochemical characteristics of lidocaine-loaded LE-2 core–shell type nanoparticles, X-ray powder diffraction was utilized. Figure 3 shows the X-ray powder diffraction scans of lidocaine-loaded LE-2 core–shell type nanoparticles and the corresponding physical blend. It can be observed that the X-ray diffraction patterns showed sharp peaks in the lidocaine drug crystals, and in the physical blend similar drug crystal peaks appeared. However, when lidocaine was entrapped in LE-2 core–shell type nanoparticles, the specific drug crystal peaks were not observable in the X-ray diffraction patterns. It was thought that the crystalline drugs showed a sharp, specific crystal peak, but after the drug became entrapped in the nanoparticles it could exist as a molecular dispersion in the nanoparticles.[16] These results also showed that the drug was successfully entrapped in the nanoparticles as molecular dispersions.

Drug Loading and Release Study

In block copolymer nanoparticles the selected solvent used to dissolve the block copolymer can affect the formation of nanoparticles because of the polymer solubility in the solvent, the dissimilarity of the diffusion rate of the solvent into the aqueous environment, the differences of each block of the copolymer in the solvent/water mixtures, the solubility of the drug, and so forth.[9,10] These parameters can also affect the particle size and drug loading contents of the LE block copolymer nanoparticles. Various water miscible solvents such as 1,4-dioxane, acetone, DMF, DMSO, DMAc, and THF can be used to prepare the core–shell type nanoparticles of LE-2 block copolymers by the dialysis method, and the results are summarized in Table II. When DMF and THF were used as the initial solvents for the preparation of nanoparticles in water, the particle sizes were relatively smaller than those of other solvents, although the particle sizes of the solvents was not significantly different. The use of acetone resulted in increased particle size. Among them, DMF resulted in a relatively high drug loading with small particle size and was used in the following experiment.

The drug loading contents, loading efficiency, and particle size of LE core–shell type nanoparticles against the block copolymer composition and initial drug amount are summarized in Table III. As shown in the table, the particle sizes of the LE diblock copolymers were 40–70 nm and were not significantly different from the molecular weight of the LE block copolymer and the drug loading contents. The drug loading contents in the LE block copolymer were slightly increased

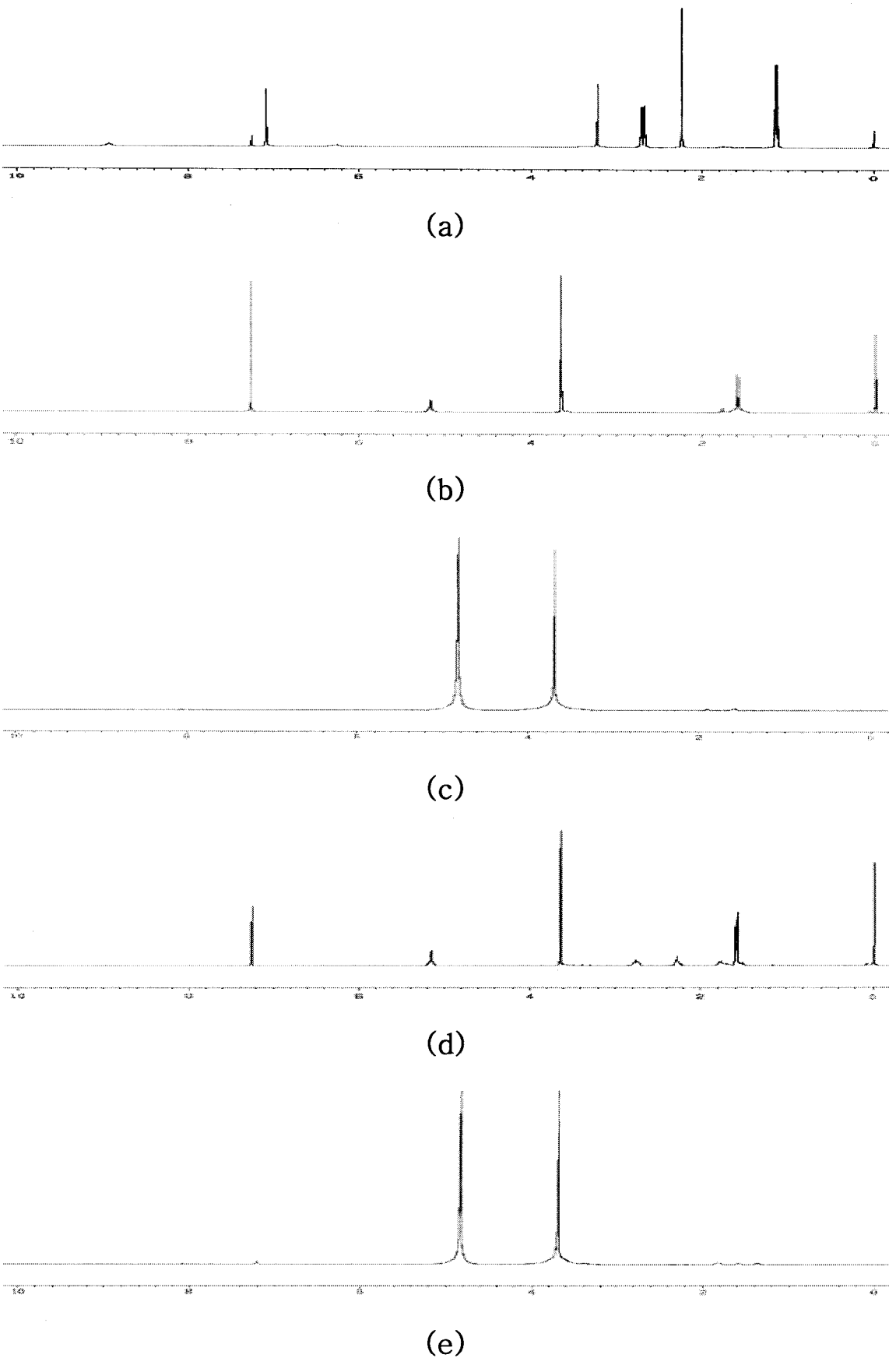


Figure 2 The ^{1}H-NMR spectra of LE-2 core–shell type nanoparticles. Lidocaine (spectrum a), LE-2 empty nanoparticles (spectrum b), and lidocaine-loaded LE-2 nanoparticles (spectrum d) were dissolved in $CDCl_3$. LE-2 empty nanoparticles (spectrum c) and lidocaine-loaded LE-2 nanoparticles were redistributed in D_2O (spectrum e).

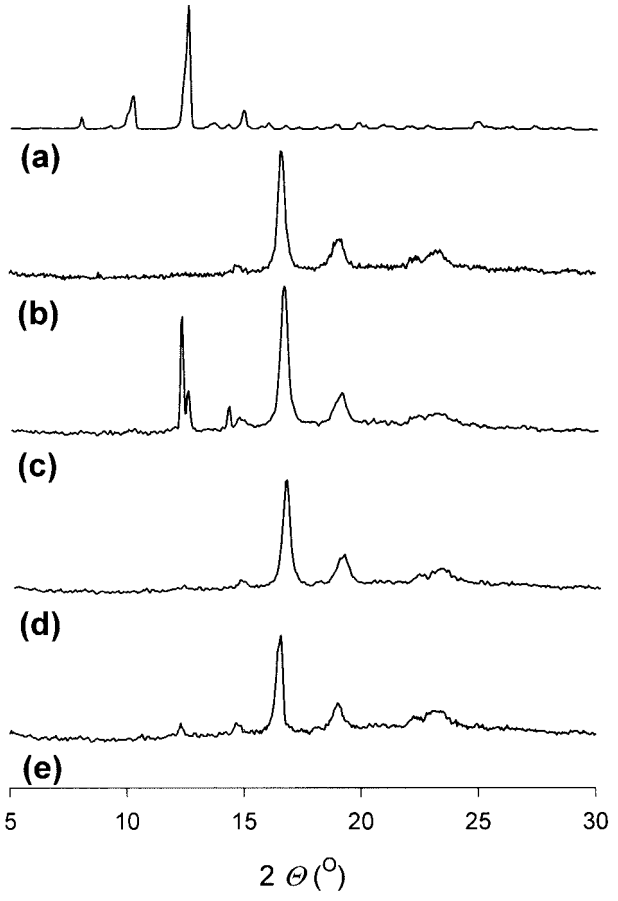


Figure 3 X-ray powder diffraction patterns of LE-2 core–shell type nanoparticles. Lidocaine (spectrum a), LE-2 empty nanoparticles (spectrum b), a physical mixture (LE empty nanoparticles/lidocaine = 10:1, spectrum c), lidocaine-loaded LE-2 nanoparticles (drug contents = 8.3 wt %, spectrum d), and lidocaine-loaded LE-2 nanoparticles (drug contents = 12.1 wt %, spectrum e).

with increased drug feeding, but the loading efficiency was decreased. When the initial drug amounts were different, a higher initial amount induced higher drug loading contents and lowered the loading efficiency in the LE-2 block copolymer core–shell type nanoparticles.

The lidocaine-loaded nanoparticles of LE block copolymer were simply redistributed into PBS (pH 7.4, 0.1*M*), and a drug release study was performed *in vitro*. Figure 4 shows the drug release from the core–shell type nanoparticles of LE diblock copolymers versus the molecular weight. There was a significant initial burst release of drug during the first 12 h and then a continuously sustained release up to 100 h. Figure 5 shows the drug release from the core–shell type nanoparticles of LE-2 diblock copolymers versus the drug loading contents. Similar to the results of Figure 4, the drug release pattern resulted in an initial burst for 12 h. It was observed that the higher drug loading contents resulted in slower drug release kinetics. These phenomena were reported by several authors.[3,10,16,17] A hydrophobic drug can be crystallized inside the nanoparticles at higher drug loading contents and then a phase separation occurs, leading to the crystallization of a part of the drug in the nanoparticles.[16] Hydrophobic drugs entrapped in nanoparticles are released more slowly at higher drug loading contents. Additionally, the lidocaine release rate from the nanoparticles was shown to be slow at higher drug loading contents. On the other hand, at low drug loading, lidocaine (CNZ) is relatively present as a molecular dispersion inside the nanoparticles.[16] The crystallized drug should dissolve and diffuse more slowly into the outer aque-

Table II Particle Size of Core–Shell Type Nanoparticles of LE-2 Diblock Copolymer Against Used Initial Solvent

Solvent	Particle Size (nm)	Drug Loading Contents (wt %)	Loading Efficiency (wt %)
DMF	51 ± 4.9 (98.7%)		
	439.7 ± 300.9 (1.2%)	15.82	37.57
	128.1 ± 15.3 (52.1%)		
DMSO	605.4 ± 342.7 (43%)	12.19	27.76
	437.5 ± 116.6 (71%)		
DMAc	761.9 ± 189.3 (29%)	13.68	31.70
	448.9 ± 109 (48.2%)		
Acetone	716.5 ± 160.2 (41.4%)	12.35	28.28
	412.8 ± 127.6 (80.4%)		
THF	739.6 ± 232.2 (19.6%)	12.65	28.96
	169.4 ± 66.5 (19.3%)		
1,4-Dioxane	409.4 ± 154.3 (70.2%)	16.6	39.8

Table III Drug Loading Content, Drug Loading Efficiency, and Particle Size Distribution of Core–Shell Type Nanoparticles of LE Diblock Copolymer

Sample	Polymer Amount (mg)	Drug Amount (mg)	Drug Loading Content (wt %)	Loading Efficiency (wt %)	Particle size (nm)
LE-1	60	30	12.08	27.3	48.8 ± 5.2 (99.2%)
LE-2-1	60	15	9.14	40.2	155.8 ± 70.2 (25.5%)
					410.1 ± 164 (61.4%)
LE-2-2	60	30	12.62	28.9	415.4 ± 122 (79.2%)
					723.6 ± 228 (17.6%)
LE-2-3	60	60	15.10	17.8	73.4 ± 12.6 (95.3%)
					459.1 ± 220.4 (4.7%)
LE-3	60	30	11.13	25.1	40.2 ± 6.1 (99.8%)

ous phase than in the molecular dispersion. Moreover, because of differences in the diffusivity of the drug molecules to the outer aqueous phase, the drug loading contents, the nature of the polymer used, and the size of the nanoparticles affects the drug release kinetics.

Degradation Behavior of Core–Shell Type Nanoparticles of LE Diblock Copolymers

To elucidate the release mechanism of lidocaine from the nanoparticles, a degradation test of the LE nanoparticles was performed *in vitro*. PLLA is known to degrade slowly due to its hydrophobic properties, which do not allow fast water penetration. Polyesters such as PLLA degrade by random hydrolytic chain scission of the ester linkages. The PLLA homopolymer itself is degraded slowly when compared with poly(glycolic acid) and poly(glycolic acid-*co*-lactic acid) and is suitable for long-term delivery systems. There were reports that the biodegradability of PLLA homopolymer can be enhanced or controlled by copolymerization with less hydrophobic materials such as diglycolide PEG. It is expected that the biodegradability of PLLA can be greatly enhanced by block copolymerization with the hydrophilic polymer PEG. Because the PEG block is not biodegradable matter and the PLLA block is biodegradable, the molecular weight of PEG is consistent during the degradation test, although the PLLA block can be expected to continuously degrade. The residual molecular weight of the LE diblock copolymer was calculated by GPC and the results are summarized in Figure 6. In spite of the very large surface area of the nanoparticles, the LE diblock copolymer was degraded slower than we expected (i.e., after 120 h), and only below 20% of the initial MW

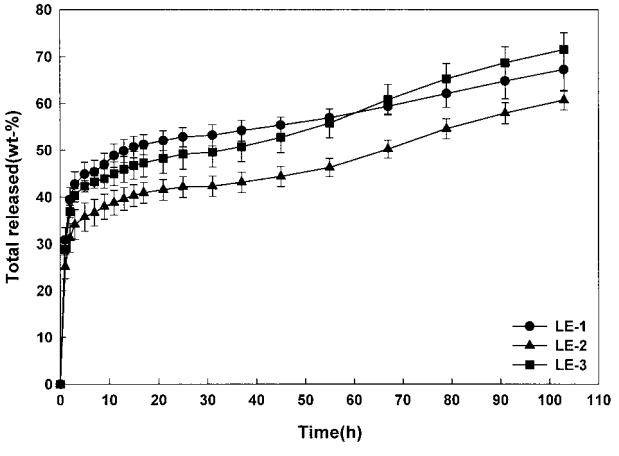


Figure 4 The effect of the molecular weight of the LE block copolymer on the drug release from core–shell type nanoparticles.

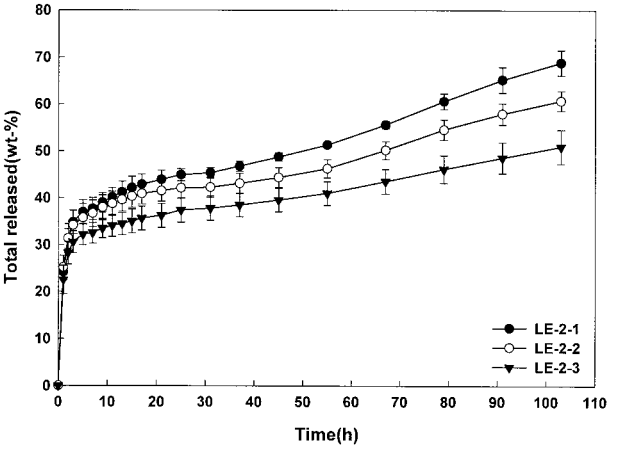
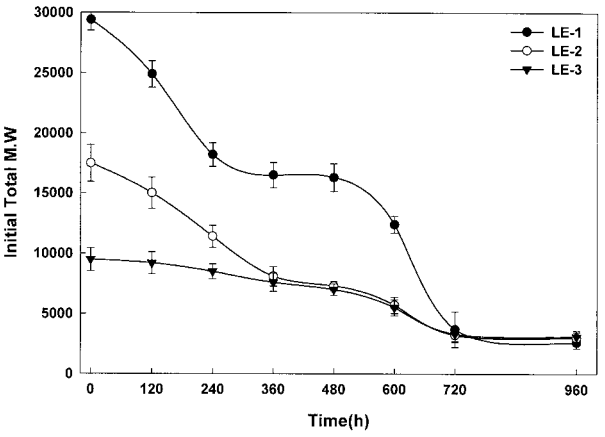
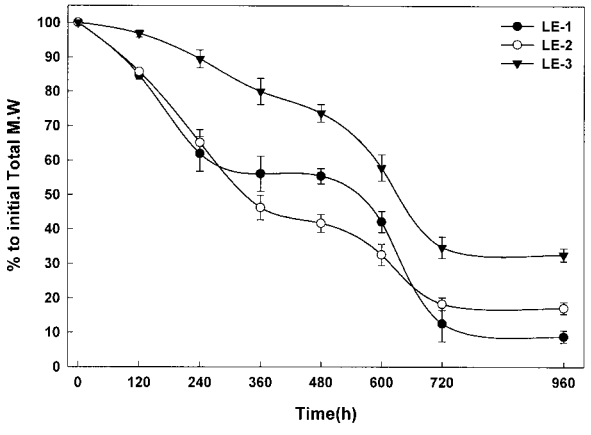


Figure 5 The effect of the drug loading contents on the lidocaine release from LE-2 core–shell type nanoparticles.



(a)



(b)

Figure 6 The degradation properties of core–shell type nanoparticles of LE diblock copolymers.

of the block copolymer had decreased. Core–shell type nanoparticles of LE diblock copolymers showed very complex degradation behavior and had three degradational phases. The molecular weights of LE-1, LE-2, and LE-3 block copolymers showed initial rapid decreases until 240, 360, and 240 h, respectively, and the stationary phase was shown between 360 and 480 h. However, the MW of all of the block copolymers again rapidly degraded until 720 h. The ratio of the MW decrease against the MW of the LE block copolymer was not significantly different between LE-1 and LE-2 but LE-3 showed a slower degradation than LE-1 and LE-2 as shown in Figure 6(b). After 720 h as shown in Figure 6(a) the MW of all of the LE block copolymer was similar, indicating almost all of the PLLA block was degraded and PEO only remained in the nondegradable block domain. These results showed that core–shell type nanoparticles of LE diblock copolymers were completely degraded in 720 h. Also, the time it took for complete degradation did not change significantly, even when the PLLA block length was increased. From these results it was suggested that the release kinetics of lidocaine from the LE core–shell type nanoparticles until 20 h were predominantly controlled by the diffusion mechanism rather than polymer degradation. It was thought that the release kinetics of lidocaine from LE core–shell type nanoparticles was controlled by both the degradation mechanism and the diffusion mechanism after 20 h. Moreover, Matsumoto et al.[26] reported that the degradation of LEL block copolymer does not contribute to drug release because only a slight MW loss was observed during the initial main release period.

CONCLUSION

Core–shell type nanoparticles of LE diblock copolymer were prepared by a dialysis technique. Their sizes were confirmed as 40–70 nm using PCS. ^{1}H-NMR confirmed formation of core–shell type nanoparticles and drug loading. The particle size, drug loading, and drug release rate of the LE nanoparticles were slightly changed by the initial solvents that were used. The drug release behavior of the LE core–shell type nanoparticles showed an initial burst during the first 12 h and then a sustained release until 100 h. The degradation behavior of LE block copolymer nanoparticles was divided into three phases: the initial rapid degradation phase, the stationary phase, and the rapid degradation phase until complete degradation. It was suggested that lidocaine release kinetics were predominantly governed by a diffusion mechanism at the initial burst phase and after that by both the diffusion and degradation mechanisms.

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