# Drug-Releasing Kinetics of MPEG/PLLA Block Copolymer Micelles with Different PLLA Block Lengths

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**ABSTRACT:** Copolymers of poly(L-lactic acid) and methoxy end-capped poly(ethylene glycol) were synthesized, and their structure and physical properties were characterized. Micellar structures were formed in aqueous media because of the amphiphilic nature of the copolymers, and their sizes were measured with both dynamic light scattering equipment and scanning electron microscopy. Indomethacin was loaded into the copolymer micelles, and its releasing behavior was monitored. The drug-releasing mechanism was determined from an investigation of the biodegradation kinetics of the copolymer micelles. The releasing mechanism was governed by diffusion rather than a biodegradation process. We adapted a model based on Fick's diffusion theory to describe the overall releasing behavior with the extraction of the diffusion coefficient. © 2001 John Wiley & Sons, Inc. J Appl Polym Sci 82: 2599–2605, 2001

**Key words:** polymeric micelles; diffusion; drug release; biodegradable

## INTRODUCTION

Polymeric micelles have been studied as novel types of drug-carrier systems, with a particular interest over the last decade in their potential applications for anticancer therapy.[1–5] Nanospheric drug-delivery systems guarantee a sustained release of a drug over a period of time. The stealth character of the system allows a sufficiently long half-life in the blood stream, and in addition, the encapsulation of the drug will most likely diminish the discomfort of the patients. Block copolymers composed of hydrophilic and hydrophobic segments can form micelle structures with hydrophobic inner cores and hydrophilic outer shells in aqueous media because of their amphiphilic nature. Because hydrophobic interactions are used effectively for the formation of micellar structures, the carrier systems for hydrophobic drugs can be constructed with polymeric micelles.

Biodegradable block copolymers consisting of poly(ethylene glycol) (PEG) and poly(lactic acid) (PLA) exhibit good potential for formulating drug-delivery systems. PLAs are well-known biodegradable polymers that have been used in a variety of biomedical applications because of their

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excellent biocompatibility and degradability. Also, PEG is one of the few water-soluble polymers that have been widely used for improving the biocompatibility of blood-contacting materials. A number of laboratories[6–14] have already studied the synthesis of PEG/PLA block copolymers with various block ratios, molecular weights, and structures with different synthetic methods; recently, the association behavior of these PEG/PLA block copolymer micelles and their usefulness as drug carriers have been studied.

Previously, we reported some results on the preparation, properties, and drug-releasing characteristics of methoxy end-capped PEG (MPEG)/poly(D,L-lactic acid) (PDLLA) diblock and MPEG/PDLLA/MPEG triblock copolymer micelles, focusing on the effect of the PEG block length.[15] In this work, a continued study of these polymer systems, the preparation and micellar characterization of MPEG/poly(L-lactic acid) (PLLA) block copolymers with different PLLA block lengths were examined. The releasing mechanism was determined on the basis of the biodegradation and diffusion kinetics. Simple models were provided for describing overall releasing characteristics with the extraction of the diffusion coefficient.

## EXPERIMENTAL

### Materials

All chemicals for the preparation of MPEG/PLLA block copolymers were purified before use. Acetone, hexane, ethyl acetate, and toluene were purified by distillation in the presence of calcium hydride. Poly(ethylene glycol) monomethyl ether (Aldrich Chemical Co., Milwaukee, WI) with a molecular weight of 2000 g/gmol was dissolved in acetone at 60°C and then reprecipitated by the addition of hexane at 5°C. (3S)-*cis*-3,6-Dimethyl-1,4-dioxane-2,5-dione (L-lactide) was purified by recrystallization in ethyl acetate before use. The residual solvents in L-lactide and MPEG were removed through drying *in vacuo* at 50°C for 2 days.

### Preparation of the MPEG/PLLA Block Copolymer Micelles

MPEG/PLLA block copolymers were synthesized through ring-opening polymerization as follows. Equivalent amounts of L-lactide and MPEG with 0.2 wt % stannous 2-ethyl-hexanoate (Sigma Chemicals, Milwaukee, WI) as a catalyst were put in a three-necked flask equipped with a reflux condenser. The polymerization reaction was conducted in toluene at 130°C for 18 h under a nitrogen atmosphere. After reaction, the products were precipitated in diethyl ether, producing MPEG/PLLA copolymers. The unreacted L-lactide monomer and homo-PLLA were removed by their dissolution in diethyl ether. Copolymer products were dried in a vacuum oven at 50°C for at least 1 day.

Micellar structures composed of inner PLLA cores and outer MPEG shells were formed by the dispersal of MPEG/PLLA block copolymers in distilled water at a concentration of 0.001 g/mL.

### Drug-Loading and -Releasing Experiments

MPEG/PLLA block copolymer and indomethacin were dissolved in methylene chloride. The solution was dispersed in distilled water to form an oil/water (O/W) emulsion with magnetic stirring. The drug-loaded particles were produced by the elimination of solvents and distilled water in a freeze drier at −35°C. The drug-loaded copolymers were placed in cellulose dialysis membranes (Cellu · Sep.H1, Aldrich) with a cutoff molecular weight of 1000 g/gmol. We performed the releasing experiments by locating the dialysis membranes in a phosphate buffer solution of pH 7.4 at 37°C. We kept the concentration of the buffer solution uniform by shaking the buffer solution bath during release experiments. The buffer solution (1 mL) was periodically sampled and placed in the vacuum oven to evaporate all the solvents. Drugs were separated from phosphate solids by the dissolution of the particles in 5 mL of chloroform. The drug content in the chloroform solution was measured with an ultraviolet (UV) spectrophotometer (Hitachi U-3210, Japan). The calibration curve relating the standard drug concentration and UV intensity was obtained before release experiments.

### Characterization

Fourier transform nuclear magnetic resonance spectroscopy (FT-NMR; Varian Unity Inova 500, Palo Alto, CA) was used for measuring the molecular weight of the MPEG/PLA block copolymers, and gel permeation chromatography (GPC; Waters Millennium 2.01, Milford, MA) was used for measuring the molecular weight distributions.

**Table I Characteristics of MPEG/PLLA Block Copolymers**

| MPEG/PLLA Block Copolymers | Molecular Weight of PLLA by NMR (g/gmol) | Polydispersity Index by GPC | Melting Temperature of MPEG (°C) | Heat of Fusion MPEG (J/g) |
|---|---|---|---|---|
| 2000/0 | — | — | 53.4 | 176.6 |
| 2000/400 | 420 | 1.06 | 49.8 | 127.8 |
| 2000/900 | 890 | 1.09 | 48.7 | 91.2 |
| 2000/1500 | 1510 | 1.09 | 46.7 | 65.8 |
| 2000/1900 | 1860 | 1.09 | 44.3 | 38.7 |

Fourier transform infrared spectroscopy (Unichem Mattson 1000, Madison, WI) and FT-NMR spectroscopy (Varian Unity Inova 500) were used for identifying the chemical structures of the synthesized copolymers.

Differential scanning calorimetry (DSC; PerkinElmer DSC7, Shelton, CT) was used for characterizing the thermal properties of the MPEG/PLLA block copolymers. In DSC experiments, the second heated thermograms were obtained from 25 to 200°C for determining the glass-transition temperature and melting temperature under a nitrogen flow. The ramping rate was 10°C/min.

Dynamic light scattering (DLS; Brookhaven BI-200SM, Holtsville, NY) was used for measuring micelle sizes. Before DLS experiments, foreign materials were screened with 0.45-$\mu$m porous filters.

Scanning electron microscopy (SEM) was used for photographing the micelle structure. The aqueous micelle solution was sampled with a micropipette and poured onto glass slides. The sample coated glass slides were freeze-dried for the removal of the solvents and then gold-coated for examination via SEM.

## RESULTS AND DISCUSSION

### Characterization of the MPEG/PLLA Block Copolymers

The MPEG/PLLA block copolymers produced in this work consisted of a PEG block of defined molecular weight (2000 Da) linked to the PLLA block. The size of the PLLA block was varied by the relative input amount of L-lactide monomer to the reaction mixture. Table I shows the characteristics of the prepared copolymers. Characterization by GPC resulted in polydispersity indices of 1.06–1.09, suggesting a very narrow distribution. The chemical composition of the copolymers was determined from the proton intensity ratio between methylene protons of PEG and methine protons of PLA, as measured by $^1$H-NMR. The molecular weights of the PLLA blocks determined were about 400, 900, 1500, and 1900 g/gmol.

Figure 1 shows the $^1$H-NMR spectrum of an MPEG/PLLA block copolymer. As reported in the literature, the methylene protons of the PEG block and the methine protons of the PLA block appeared at 3.6 and 5.2 ppm, respectively. Also, the terminal methoxy protons of PEG appeared at 3.4 ppm.

Figure 2 shows the DSC thermograms of block copolymers with different compositions. The melting transition of the PEG block appeared at 45–53°C. As the PLLA block length increased, the melting transition shifted slightly to a lower temperature. Also, the enthalpy change of PEG fusion decreased gradually with increasing PLLA content, implying that the crystallization of the PEG block was prevented partly by phase mixing in the presence of PLLA. The crystallization and

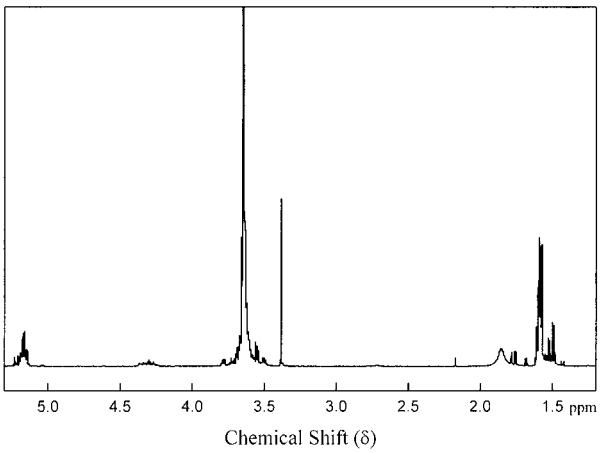


**Figure 1** $^1$H-NMR spectrum of an MPEG/PLLA (2000/1900) block copolymer.

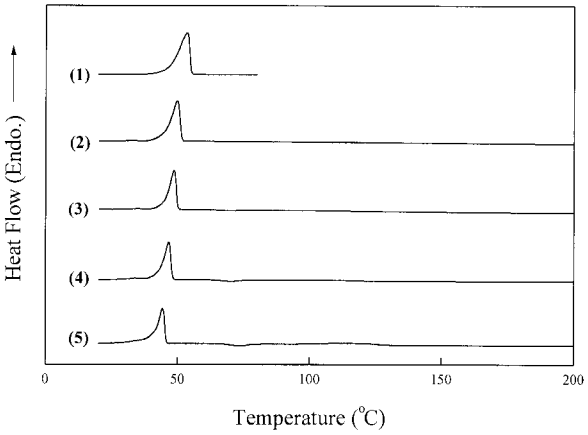


**Figure 2** DSC thermograms of MPEG/PLLA block copolymers with molecular weights of (1) 2000/0, (2) 2000/400, (3) 2000/900, (4) 2000/1500, and (5) 2000/1900.

melting transitions of PLLA were not clearly observed because of the shortness of the PLLA block length, but a slight exothermic peak appeared at around 70°C for the MPEG/PLLA (2000/900) system and slightly shifted to higher temperatures with increasing PLLA block length.

## Drug-Releasing Characteristics of the Block Copolymer Micelles

The preparation of the micelles was achieved by the simple dispersal of the block copolymers in distilled water, and the sizes of the resulting polymeric micelles were estimated with DLS measurements. Figure 3 shows a representative distribution profile of a micelle solution at a concentration of 0.001 g/mL. The micelles were 180–200 nm with narrow distributions.

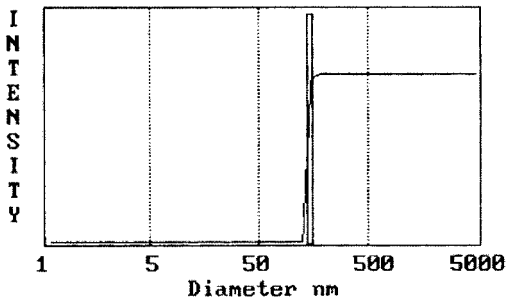


**Figure 3** Size distribution of MPEG/PLLA (2000/1900) block copolymer micelles in an aqueous solution at a concentration of 0.001 g/mL.

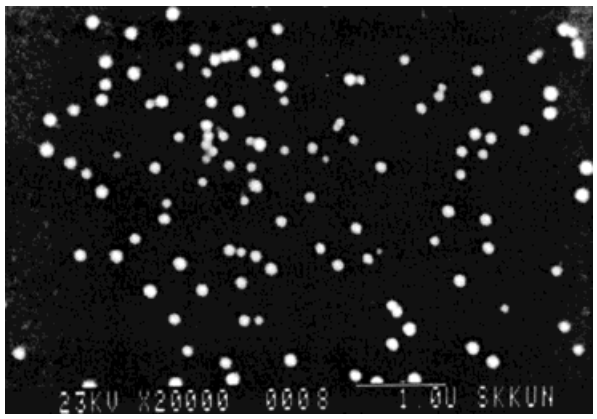


**Figure 4** SEM photographs of MPEG/PLLA (2000/1900) block copolymer micelles.

We used SEM to confirm the micelle sizes and uniformity, as the photographs show in Figure 4. In the microphotograph of the MPEG/PLLA (2000/1900) sample, the spherical and uniformly featured micelles are well illustrated. The particles were determined to be about 130–150 nm in size. The reduction in micelle sizes as measured by SEM was attributed to the aggregation of PEG blocks in a nonaqueous environment.

In Figures 5 and 6, the drug-releasing behavior of block copolymer micelles are illustrated. $M_{rel}/M_{eqm}$ indicates the mass fraction of the drug released from the total drug initially loaded in the polymer micelles, and $M_{rel}/M_p$ indicates the mass of drug released from the unit mass of block copolymer. From the equilibrium values of $M_{rel}/M_p$ in Figure 5, the drug-loading capacity could be estimated for each block copolymer micelle. As

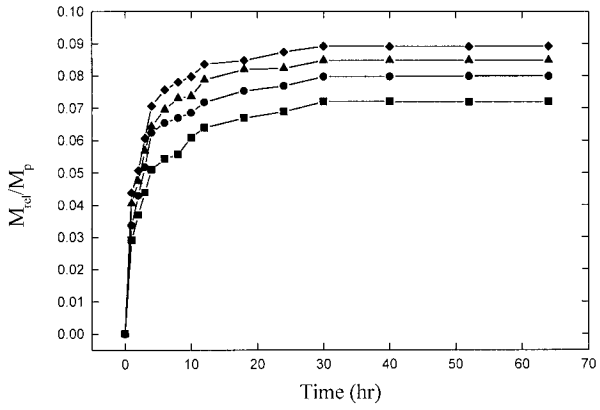


**Figure 5** Time dependence of the drug-releasing content from the unit mass of MPEG/PLLA block copolymer micelles with molecular weights of (■) 2000/400, (●) 2000/900, (▲) 2000/1500, and (♦)2000/1900.

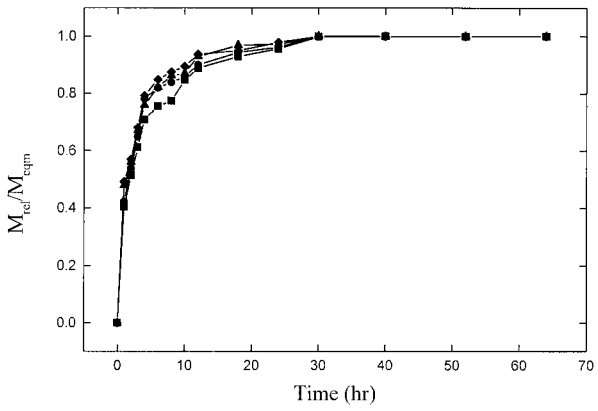


**Figure 6** Time dependence of the fractional drug release ($M_{rel}/M_{eqm}$) from MPEG/PLLA block copolymer micelles with molecular weights of (■) 2000/400, (●) 2000/900, (▲) 2000/1500, and (♦) 2000/1900.

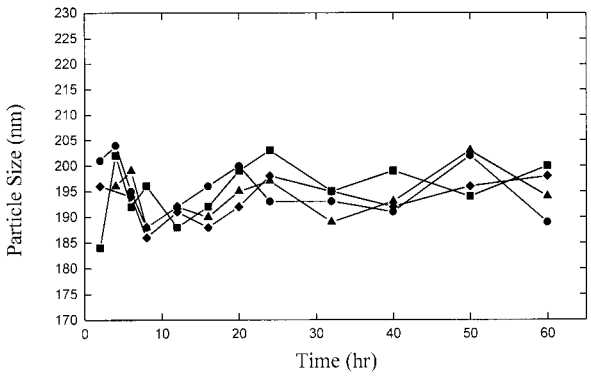


**Figure 7** Variation of the micelle sizes obtained by DLS measurements within 60 h for MPEG/PLLA block copolymer micelles with molecular weights of (■) 2000/400, (●) 2000/900, (▲) 2000/1500, and (♦) 2000/1900.

the PLLA chain length increased, the drug loading increased almost linearly from 7 to 9 wt % block copolymer; this probably resulted from the increase in the entanglement of hydrophobic micelle cores with longer PLLA chains. The release patterns of all samples appeared almost the same; that is, the fast release during the first few hours leveled off about 10 h later, and the entrapped drug seemed to be released completely within 30 h. This tendency is shown in a plot of $M_{rel}/M_{eqm}$ as a function of the elapsed time (Fig. 6).

## Drug-Releasing Mechanism and Model

In these biodegradable drug-carrying systems, the release of the drug could be triggered not only by a diffusion process but also by a biodegradation process of PLLA cores. We monitored the particle sizes over the release time to confirm the possibility of degradation during the release periods under an aqueous condition with a controlled pH. The results are shown in Figure 7, in which no noticeable changes in the sizes of the micelles are observed with DLS measurements within 60 h, implying no chemical degradation of the block copolymer micelles. Also, $^1$H-NMR spectra of the micelle samples were measured periodically during the releasing periods, and no appreciable changes in their spectral features or the calculated molecular weights were observed, as shown in Figure 8.

As this releasing mechanism was governed by a diffusion process, the following models were provided for describing its kinetics. A simple diffusion process for the spherical particles could be described by a Fickian model founded on Fick's classical theory.[16] In this theory, the diffusion process is driven by the local solute concentration difference throughout the spherical matrix. The diffusion process in this case could be described by eq. (1) with an initial condition of eq. (2) and two boundary conditions of eqs. (3) and (4):

$$\frac{\partial C}{\partial t} = D\,\frac{1}{r^2}\,\frac{\partial}{\partial r}\left(r^2\,\frac{\partial C}{\partial r}\right) \tag{1}$$

$$C(r,\,0) = C_0 \tag{2}$$

$$C(R,\,t) = 0 \tag{3}$$

$$\left.\frac{\partial C(r,\,t)}{\partial r}\right|_{r=0} = 0 \tag{4}$$

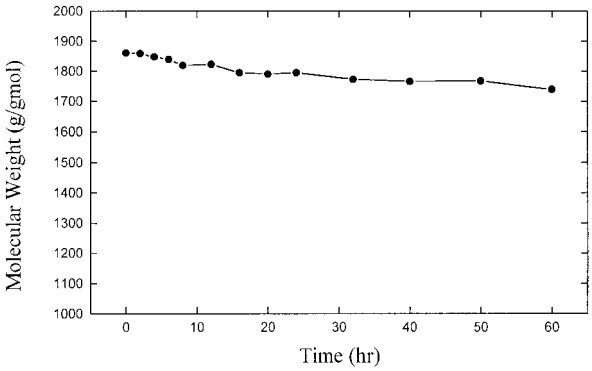


**Figure 8** Variation of the molecular weights of an MPEG/PLLA (2000/1900) block copolymer measured with $^1$H-NMR spectroscopy within 60 h.

Equation (2) represents that the drug concentration is uniform throughout all local positions at the initial stage. Equations (3) and (4) are represented under the reasonable assumptions that the solute concentration at the particle surface is the same as the solute concentration in the bulk solvent (~0) and that the solute concentration at the center position of the particle is finite, respectively. The application of these initial and boundary conditions to governing eq. (1) resulted in the time and position dependence of the solute concentration. The integration of the drug concentration over a total micelle volume led to the time dependence of the fractional drug release, as in eq. (5):

$$\frac{M_{\text{rel}}}{M_{\text{eqm}}} = 1 - \frac{6}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{n^2} \exp\left(-\frac{Dn^2\pi^2 t}{R^2}\right) \qquad (5)$$

An extreme case of non-Fickian transport process in polymeric systems is the relaxation governing process,[17] in which the solute transport in a polymer matrix is driven by macromolecular relaxation rather than the solute concentration gradient. In this transport process, the boundary between the solute-released region and solute-residual region is clearly distinguished, and it propagates into the center of the sphere at a constant velocity. In this case, the radius $R_B$, indicating this moving boundary position, decreases at a constant velocity $k$, as in eq. (6):

$$R_B = R - kt \qquad (6)$$

where $R$ is the radius of the micelle.

For this transport case, the amount of drug released from the spheres for a certain period time could be described by eq. (7), and the total (equilibrium) amount of drug released could be described by eq. (8):

$$M_{\text{rel}} = \frac{4}{3} C_0 N(R)(R_B^3 - R^3) \qquad (7)$$

$$M_{\text{eqm}} = \frac{4}{3} \pi C_0 N(R) R^3 \qquad (8)$$

The substitution of eq. (6) for $R_B$ in eq. (7) and the division of eq. (7) by eq. (8) resulted in the fractional drug release represented by eq. (9):

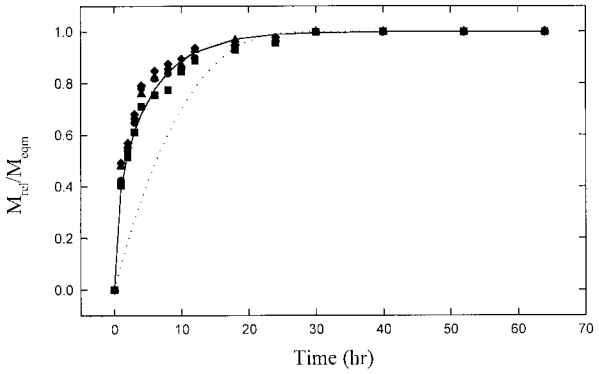


**Figure 9** Best fit of eqs. (5) (solid curve) and (9) (dashed curve) to the experimental drug-release data.

$$\frac{M_{\text{rel}}}{M_{\text{eqm}}} = 1 - \left(1 - \frac{kt}{R}\right)^3 \qquad (9)$$

Other non-Fickian transport processes usually take place between those two extreme processes. Now, the best fit of eq. (5) or (9) to the experimental data provides an appropriate diffusion model and characteristic coefficient. As shown in Figure 9, the experimental data were fitted well with a classical diffusion governing model, the Fickian model, rather than the relaxation governing model. This result was attributed to the fast relaxation of relatively short PLLA molecules consisting of micelle cores. The value of the diffusion coefficient extracted from the best fit of the model to the experimental data was $2.7 \times 10^{-16}$ cm$^2$/s.

## CONCLUSIONS

A series of MPEG/PLLA block copolymers with various PLLA block lengths were synthesized by the ring-opening polymerization of L-lactide with MPEG with a molecular weight of 2000 Da. Block copolymer micelles were prepared with a simple O/W emulsion method. The micelle sizes were estimated to be about 180–200 nm with DLS measurements, and the spherical and uniform features of the micelles were observed with SEM measurements. The loading and release behavior of the drug indomethacin were investigated. The loading level was 7–9 wt % block copolymer, increasing slightly with increasing hydrophobic PLLA block length. The rapid initial release in a few hours leveled off gradually and seemed to equilibrate after about 30 h. No material degradation within 60 h was observed from $^1$H-NMR

and DLS measurements. The releasing kinetics were well described with a typical Fickian diffusion model, and the value of the diffusion coefficient, $2.7 \times 10^{-16}$ $cm^2/s$, was extracted from the best fit of the theoretical model to the experimental data.

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