

Biodegradable Blend Nanoparticles of Amphiphilic Diblock Copolymers Prepared by Nano-Precipitation Method

Wichuda Nanthakasri, Mangkorn Srisa-Ard, Yodthong Baimark*

Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Mahasarakham University, Mahasarakham, Thailand.

E-mail: *yodthong.b@msu.ac.th, *yodthongb@gmail.com

Received September 30th, 2011; revised November 15th, 2011; accepted November 26th, 2011.

ABSTRACT

Nanoparticles of biodegradable methoxy poly(ethylene glycol)-*b*-polyester amphiphilic diblock copolymers have widely investigated for use as controlled release drug delivery carriers. In this work, blend nanoparticles of methoxy poly(ethylene glycol)-*b*-poly(D,L-lactide) (MPEG-*b*-PDLL) and methoxy poly(ethylene glycol)-*b*-poly(ϵ -caprolactone) (MPEG-*b*-PCL) were prepared by nano-precipitation method without any surfactants. ¹H-NMR spectra showed significant difference in integral peak areas, suggesting the nanoparticles with different MPEG-*b*-PDLL/MPEG-*b*-PCL blend ratios can be prepared. Transmission electron microscope revealed the blend nanoparticles had nearly spherical in shape with smooth surface. Average size of the blend nanoparticles obtained from light-scattering analysis slightly decreased with increase in blend ratio of MPEG-*b*-PCL. The MPEG-*b*-PDLL and MPEG-*b*-PCL were amorphous and semi-crystalline, respectively. Thermal transition properties of the blend nanoparticles were studied with differential scanning calorimetry (DSC). The DSC results showed that glass transition temperatures of the blend nanoparticles decreased and heats of melting steadily increased, while the melting temperature did not change as the MPEG-*b*-PCL blend ratio increased. This indicates the miscibility of MPEG-*b*-PDLL and MPEG-*b*-PCL in the amorphous phase of the blend nanoparticles. Thermogravimetric analysis showed that the blend nanoparticles clearly exhibited two thermal decomposition steps due to MPEG-*b*-PDLL decomposition followed with MPEG-*b*-PCL. The blend nanoparticles had two temperatures of maximum decomposition rate ($T_{d,max}$) accorded to each blend component. The $T_{d,max}$ of MPEG-*b*-PDLL phase significantly decreased, while $T_{d,max}$ of MPEG-*b*-PCL phase did not change as the MPEG-*b*-PCL blend ratio increased. These results suggested that the desired thermal properties of blend nanoparticles can be tailored by varying the blend ratio.

Keywords: D,L-Lactide, ϵ -Caprolactone, Diblock Copolymers, Blend Nanoparticles, Nano-Precipitation

1. Introduction

Amphiphilic diblock copolymer nanoparticles of methoxy poly(ethylene glycol)-*b*-poly(D,L-lactide) (MPEG-*b*-PDLL) and methoxy poly(ethylene glycol)-*b*-poly(ϵ -caprolactone) (MPEG-*b*-PCL) have attracted much attention in drug delivery applications in the human body due to their biocompatibility and biodegradability [1-4]. The hydrophilic MPEG layer coated on the nanoparticle surfaces can increase blood circulation time of these nanoparticles [5,6]. Their thermal, biodegradation and drug release properties can be controlled through several approaches including block length adjustment [7-10] and copolymerization [11]. The physical blending is an al-

ternative method that has been widely used to adjust the properties of polymers such as crystallinity, mechanical properties and biodegradation properties [12-15]. These properties strongly affected the drug release behaviors.

In addition, the MPEG segments attached to polyester segments can improve miscibility between PDLL and PCL blends to reduce the phase separation [12]. Thus, unique properties of polymer blends quite different from their origin polymers were obtained. However, the preparation of blend nanoparticles of the amphiphilic diblock copolymers has been scarcely published.

The present work describes the preparation of blend nanoparticles of amorphous MPEG-*b*-PDLL and semi-

crystalline MPEG-*b*-PCL. The blend nanoparticle were prepared by nano-precipitation method, which were then investigated by transmission electron microscopy (TEM) for particle morphology, ¹H-NMR spectroscopy for chemical composition and light-scattering analysis for particle size and size distribution. Thermal properties of the blend nanoparticles were also determined by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA).

2. Materials and Methods

2.1. Materials

D,L-lactide (DLL) monomer was synthesized by thermal decomposition reaction of low molecular weight poly (D,L-lactic acid) (PDLLA) at 220°C under reduced pressure. The low molecular weight PDLLA was obtained from polycondensation of D,L-lactic acid solution (90%, Fluka) at 160°C. Crude DLL was purified by repeated re-crystallization from ethyl acetate and dried in vacuo at 50°C for 48 h before use. ε-Caprolactone (CL) monomer (99%, Acro, USA) was purified by drying with CaH₂ followed by distillation under reduced pressure before storage over molecular sieves in a refrigerator. Methoxy polyethylene glycol (MPEG) with a molecular weight of 5000 g/mol (Fluka) was used after it was dried in vacuo at 120°C for 4 h. Stannous octoate (Sn(Oct)₂, 95% Sigma) was used without further purification. All solvents in analytical grade were used.

2.2. Synthesis of Diblock Copolymers

Both MPEG-*b*-PDLL and MPEG-*b*-PCL diblock copolymers were synthesized by ring-opening polymerization in bulk under nitrogen atmosphere at 130°C for 24 h. Feed mole ratios of MPEG/DLL and MPEG/CL were 1/416 and 1/526, respectively. MPEG and Sn(Oct)₂ were used as the initiating system. Sn(Oct)₂ concentration was kept constant at 0.02 mol%. The diblock copolymers were dissolved in chloroform before precipitating in cool *n*-hexane for purification. They were then dried to constant weight in vacuo at room temperature. According to this procedure, the purified diblock copolymers were obtained with more than 95% yields.

2.3. Characterization of Diblock Copolymers

2.3.1. ¹H-NMR Spectrometry

Chemical compositions of the copolymers were measured by ¹H-NMR spectrometry using a Bruker Advance DPX 300 ¹H-NMR spectrometer at 25°C CDCl₃ was used as the solvent, and tetramethylsilane was used as the internal standard.

2.3.2. Gel Permeation Chromatography

The number-average molecular weight (M_n) and molecu-

lar weight distribution (MWD) of the copolymers were determined by gel permeation chromatography (GPC) using a Waters 717 plus Autosampler GPC equipped with an Ultrastaygel® column operating at 35°C and employing a refractive index detector. Tetrahydrofuran was used as the solvent at a flow rate of 1 mL/min.

2.3.3. Differential Scanning Calorimetry

Thermal transition properties of the copolymers were carried out by non-isothermal differential scanning calorimetry (DSC) using a Perkin-Elmer Pyris Diamond DSC. The sample (~10 mg) was heated at the rate of 10°C/min under helium flow.

2.4. Preparation of Blend Nanoparticles

Blend nanoparticles of diblock copolymers were prepared by the nano-precipitation method. Briefly, 60 mg mixed copolymer was dissolved in 6 mL acetone. The blend solution was added drop-wise into 60 mL distilled water in a 100 mL beaker with magnetic stirring at speed of 800 rpm. The nanoparticle colloid was obtained after evaporating acetone at room temperature for 6 h in a fume hood. The nanoparticle aggregates were removed by centrifugation at 5000 rpm at 4°C for 30 min. The blend nanoparticles with MPEG-*b*-PDLL/MPEG-*b*-PCL blend ratios of 4/0, 3/1, 2/2, 1/3 and 0/4 (w/w) were prepared. Dried nanoparticle sample was collected by centrifugation at 15,000 at 4°C for 2 h before freeze-drying for overnight.

2.5. Characterization of Blend Nanoparticles

2.5.1. Transmission Electron Microscopy

Morphology of the blend nanoparticles was determined by transmission electron microscopy (TEM) using a JEOL JEM 1230 TEM. For TEM analysis, a drop of nanoparticle suspension was placed on a formvar film coated on the copper grid. The specimen on the copper grid was not stained.

2.5.2. Light-Scattering Particle Size Analysis

Particle size and size distribution of the blend nanoparticles were measured from the nanoparticle colloids by light-scattering analysis using a Coulter LS230 particle size analyzer at 25°C.

2.5.3. ¹H-NMR Spectrometry

Chemical functional groups of the blend nanoparticles were studied by ¹H-NMR spectrometry using a Bruker Advance DPX 300 ¹H-NMR spectrometer at 25°C. CDCl₃ was used as the solvent, and tetramethylsilane was used as the internal standard.

2.5.4. Differential Scanning Calorimetry

Thermal transition properties of the blend nanoparticles were determined by non-isothermal differential scanning

calorimetry (DSC) as described above.

2.5.5. Thermogravimetric Analysis

The thermal decomposition behaviours of the blend nanoparticles were characterized by non-isothermal thermogravimetric (TG) analysis using a TA-Instrument SDT Q600 TG analyzer. For TG analysis, sample (~5 mg) was heated from 50°C to 800°C at the rate of 20°C/min under nitrogen atmosphere.

3. Results and Discussion

3.1. Characterization of Diblock Copolymers

Chemical compositions of diblock copolymers were determined from ¹H-NMR spectra. For this purpose, the ratio of integral peak areas was calculated corresponding to the ethylene oxide (EO, repeating units of MPEG) methylene protons at $\delta = 3.6 - 3.7$ ppm, the DLL methine protons at $\delta = 5.0 - 5.3$ ppm and the CL ϵ -methylene protons at $\delta = 4.0 - 4.2$ ppm. The chemical compositions of MPEG-*b*-PDLL and MPEG-*b*-PCL were measured as EO/DLL = 20/80 and EO/CL = 18/82 (mol%) corresponding to the MPEG/DLL and the MPEG/CL mole ratios of 1/452 and 1/515, respectively. These calculated copolymer compositions are similar to MPEG/monomer (DLL or CL) feed mole ratios (1/416 and 1/526 for MPEG-*b*-PDLL and MPEG-*b*-PCL, respectively). This suggests that the polymerization reactions were taken to near-quantitative conversion.

The M_n s of MPEG-*b*-PDLL and MPEG-*b*-PCL obtained from GPC curves were 49,000 and 47,000 g/mol, respectively. The MWD values were 1.8 and 1.6 for the MPEG-*b*-PDLL and the MPEG-*b*-PCL, respectively. The M_n s obtained from GPC results were less than to that calculated from the feed ratios (65,000 g/mol). The transesterification degradation side-reactions may occur during polymerization.

3.2. Characterization of Blend Nanoparticles

Figure 1 shows the TEM micrographs of various blend nanoparticles at different MPEG-*b*-PDLL/MPEG-*b*-PCL

blend ratios. It can be clearly seen that the blend nanoparticles had nearly spherical in shape with smooth surface. They had nanometer in size range. The blend ratio did not affect on the morphology of nanoparticles. Average particle sizes of the blend nanoparticles measured from light-scattering analysis are summarized in Table 1. The size of MPEG-*b*-PCL nanoparticles was the smallest. The average sizes of blend nanoparticles increased significantly as the MPEG-*b*-PDLL blend ratio increased. This may be due to the crystallisable PCL block enhanced more compact nanoparticles.

The chemical compositions of blend components in the nanoparticles can be investigated from the ¹H-NMR

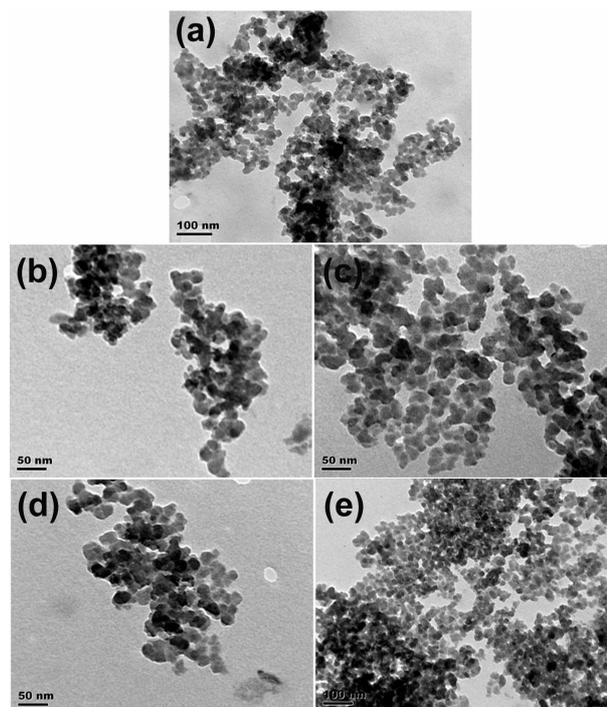


Figure 1. TEM micrographs of blend nanoparticles with MPEG-*b*-PDLL/MPEG-*b*-PCL blend ratios of (a) 4/0, (b) 3/1, (c) 2/2, (d) 1/3 and (e) 0/4 w/w. Bars = 100 nm for (a) and (e), and bars = 50 nm for (b)-(d).

Table 1. Average particle sizes and thermal properties of blend nanoparticles.

MPEG- <i>b</i> -PDLL/MPEG- <i>b</i> -PCL blend ratio (w/w)	Size (nm) ^a	T_g (°C) ^b	T_m (°C) ^c	ΔH_m (°C) ^d	$T_{d,max}$ (°C) ^e
4/0	348 ± 16	36	-	-	367
3/1	176 ± 16	34	48, 55	6.9, 2.9	334, 420
2/2	162 ± 16	29	54	23.4	329, 420
1/3	98 ± 15	25	55	56.9	319, 420
0/4	98 ± 18	-	55	94.2	420

^aAverage particle size measured by light-scattering analysis; ^bGlass transition temperature obtained from DSC thermograms; ^cMelting temperature obtained from DSC thermograms; ^dHeat of melting obtained from DSC thermograms; ^eTemperature of maximum decomposition rate measured from DTG thermograms.

spectra, as illustrated in **Figure 2**. It was found that the integral peak areas of DLL and CL units directly related to their blend ratios. The integral area of peak b (methine protons of DLL units) steadily decreased with decrease in the MPEG-*b*-PDLL blend ratio. Meanwhile the integral areas of peaks d and h (methylene protons of CL units) significantly increased as the MPEG-*b*-PCL blend ratio increased. This supported that the blend nanoparticles with different blend ratios can be prepared by nano-precipitation method of the blend solution.

The DSC thermograms of the MPEG-*b*-PDLL and MPEG-*b*-PCL showed that they were amorphous and semi-crystalline copolymers, respectively (DSC curves did not show). The MPEG-*b*-PDLL exhibited a single glass transition temperature (T_g) at 36°C. The melting temperature (T_m) and heat of melting (ΔH_m) of MPEG-*b*-PCL were 61°C and 86.0 J/g, respectively. The DSC thermograms of the blend nanoparticles are presented in **Figure 3** and the DSC results are also summarized in **Table 1**. The DSC thermograms of blend nanoparticles exhibited both T_g of MPEG-*b*-PDLL and T_m of MPEG-*b*-PCL. The T_g of MPEG-*b*-PDLL in blend nanoparticles significantly decreased as the MPEG-*b*-PCL blend ratio

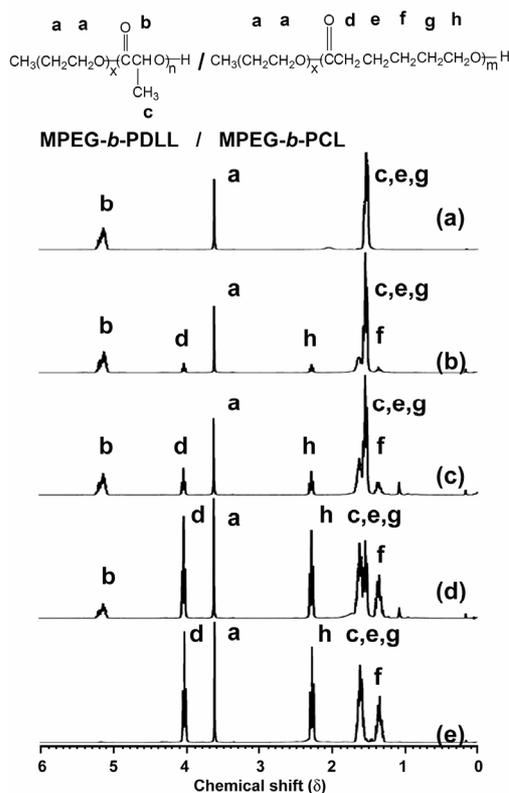


Figure 2. $^1\text{H-NMR}$ spectra of blend nanoparticles with MPEG-*b*-PDLL/MPEG-*b*-PCL blend ratios of (a) 4/0, (b) 3/1, (c) 2/2, (d) 1/3 and (e) 0/4 w/w (Peak-proton assignments as shown).

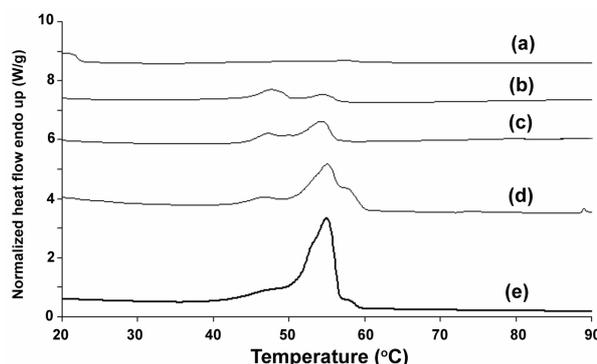


Figure 3. DSC thermograms of blend nanoparticles with MPEG-*b*-PDLL/MPEG-*b*-PCL blend ratios of (a) 4/0, (b) 3/1, (c) 2/2, (d) 1/3 and (e) 0/4 w/w (heating rate = 10°C under helium flow).

increased, suggesting that the MPEG-*b*-PDLL and MPEG-*b*-PCL exhibited miscible blended in the amorphous phase to reduce the T_g of MPEG-*b*-PDLL. The T_m of MPEG-*b*-PCL in blend nanoparticles did not change. It should be noted that the ΔH_m values of the blend nanoparticles decreased steadily as increasing the MPEG-*b*-PDLL blend ratio. This may be explained that the MPEG-*b*-PDLL interrupted crystallisability of MPEG-*b*-PCL in the blend nanoparticles.

The blend nanoparticles with controllable thermal transition properties (T_g and ΔH_m) might be of interest for controlled release drug delivery applications. Two main mechanisms of drug releasing from polymer matrix consisted of drug diffusion due to matrix swelling and drug release due to erosion of polymer matrix. The swelling and erosion rates of polymeric matrix strongly depended upon the T_g and ΔH_m , respectively. Thus drug release may be adjusted by varying the T_g and ΔH_m of the polymeric matrix.

Thermal stability of the blend nanoparticles was determined from the TG thermograms, as shown in **Figure 4**. The weight losses of MPEG-*b*-PDLL and MPEG-*b*-PCL started at approximate 300°C and 350°C, respectively. The MPEG-*b*-PCL exhibited higher thermal stability than that of MPEG-*b*-PDLL. The thermal decompositions completely finished at approximate 400°C and 450°C for the MPEG-*b*-PDLL and the MPEG-*b*-PCL, respectively. The blend nanoparticles showed two thermal decomposition stages with the first MPEG-*b*-PDLL decomposition following with the weight loss of MPEG-*b*-PCL component. The weight loss behaviors of the blend nanoparticles directly related to the blend ratio. The weight remaining of the first decomposition step decreased steadily with the MPEG-*b*-PDLL blend ratio. The 2/2 (w/w) MPEG-*b*-PDLL/MPEG-*b*-PCL blend nanoparticles showed remaining weight at approximately

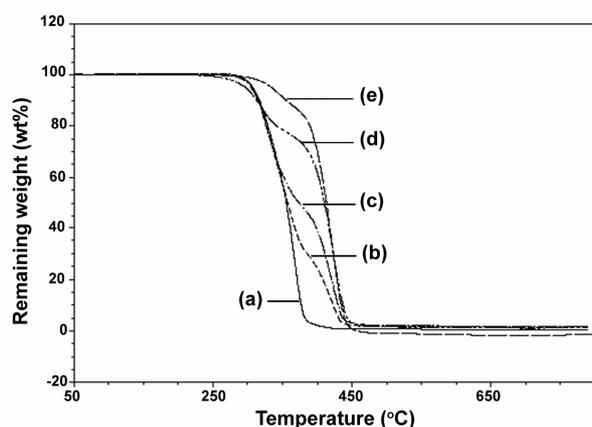


Figure 4. TG thermograms of blend nanoparticles with MPEG-*b*-PDLL/MPEG-*b*-PCL blend ratios of (a) 4/0, (b) 3/1, (c) 2/2, (d) 1/3 and (e) 0/4 w/w (heating rate = 20 °C under nitrogen flow).

50% by weight after MPEG-*b*-PDLL decomposition. This indicates that the weight ratio of MPEG-*b*-PDLL/MPEG-*b*-PCL was about 50/50 by weight, corresponding to the feed blend ratio (1/1 by weight). The TG results supported that the blend nanoparticles with different blend ratios can be prepared according to the ¹H-NMR analysis, as described above.

Thermal stability results can be clearly determined from the derivative TG (DTG) thermograms, as shown in **Figure 5**. The peak of the DTG thermogram indicates a temperature of maximum decomposition rate ($T_{d, \max}$). The resulting $T_{d, \max}$ values are also reported in **Table 1**. The $T_{d, \max}$ values of MPEG-*b*-PDLL and MPEG-*b*-PCL were 367 and 420 °C, respectively, supporting the higher thermal stability of MPEG-*b*-PCL than that of MPEG-*b*-PDLL. The DTG thermograms of blend nanoparticles exhibited two peaks (two $T_{d, \max}$) of MPEG-*b*-PDLL and MPEG-*b*-PCL. It should be noted that the peak areas of the DTG thermograms depended on the blend ratios. The peak area of the first peak of MPEG-*b*-PDLL decomposition steadily decreased as the MPEG-*b*-PDLL blend ratio decreased. The $T_{d, \max}$ of MPEG-*b*-PCL in the blend nanoparticles did not change. While, the $T_{d, \max}$ of MPEG-*b*-PDLL in the blend nanoparticles decreased slightly with the MPEG-*b*-PDLL blend ratio. The DTG results also supported that the blend nanoparticles with different blend ratios exhibited differences in thermal decomposition behaviors.

4. Conclusions

The MPEG-*b*-PDLL/MPEG-*b*-PCL blend nanoparticles with spherical shape and smooth surface were successfully prepared by nano-precipitation method. Blend ratios of MPEG-*b*-PDLL/MPEG-*b*-PCL affect the average

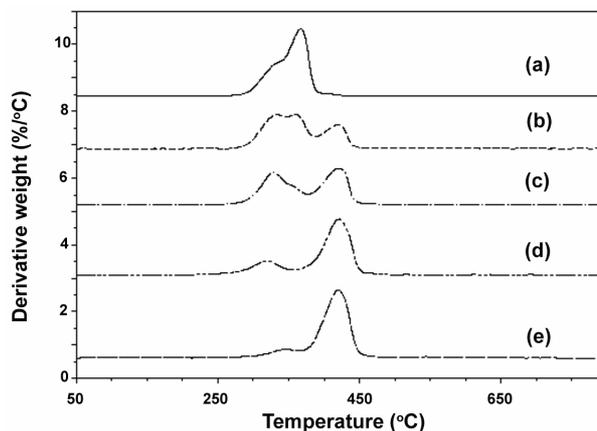


Figure 5. DTG thermograms of blend nanoparticles with MPEG-*b*-PDLL/MPEG-*b*-PCL blend ratios of (a) 4/0, (b) 3/1, (c) 2/2, (d) 1/3 and (e) 0/4 w/w (heating rate = 10 °C under nitrogen flow).

particle size, thermal transition properties and thermal decomposition behaviors. The average particle sizes and glass transition temperatures of the blend nanoparticles decreased and the heats of melting significantly increased as the blend ratio of MPEG-*b*-PCL increased. The blend ratio is an effective tool to modulate the particle size and thermal properties of the blend nanoparticles. The thermal property control suggested in this work may lead to rational manipulation of biodegradation and drug release rates of the blend nanoparticles. These blend nanoparticles might be interested in drug delivery applications.

5. Acknowledgements

The authors would like to acknowledge the financial support from the Mahasarakham University and the Research, Development and Engineering (RD&E) fund through The National Nanotechnology Center (NANO-TEC), The National Science and Technology Development Agency (NSTDA), Thailand (Project No. NN-B-22-EN4-30-52-11) to Mahasarakham University. We also gratefully acknowledge The Center of Excellence for Innovation in Chemistry (PERCH-CIC), Commission on Higher Education, Ministry of Education, Thailand for providing a scholarship for one of us (W. Nanthakasri).

REFERENCES

- [1] S. Y. Kim, Y. M. Lee and J. S. Kang, "Indomethacin-Loaded Methoxy Poly(Ethylene Glycol)/Poly(D,L-Lactide) Amphiphilic Diblock Copolymeric Nanospheres: Pharmacokinetic and Toxicity Studies in Rodents," *Journal of Biomedical Material Research*, Vol. 74A, No. 4, 2005, pp. 581-590. doi:10.1002/jbm.a.30342
- [2] E. Pierri and K. Avgoustakis, "Poly(Lactide)-Poly(Ethyl-

- ene Glycol) Micelles as a Carrier for Griseofulvin," *Journal of Biomedical Material Research*, Vol. 75A, No. 3, 2005, pp. 639-647. [doi:10.1002/jbm.a.30490](https://doi.org/10.1002/jbm.a.30490)
- [3] H. M. Aliabadi, A. Mahmud, A. D. Sharifabadi and A. Lavasanifar, "Micelles of Methoxy Poly(Ethylene Oxide)-*b*-Poly(ϵ -Caprolactone) as Vehicles for the Solubilization and Controlled Delivery of Cyclosporine A," *Journal of Controlled Release*, Vol. 104, No. 2, 2005, pp. 301-311. [doi:10.1016/j.jconrel.2005.02.015](https://doi.org/10.1016/j.jconrel.2005.02.015)
- [4] X. W. Wei, C. Y. Gong, M. Gou, S. Z. Fu, Q. Guo, S. Shi, F. Luo, G. Guo, L. Y. Qiu and Z. Y. Qian, "Biodegradable Poly(ϵ -Caprolactone)-Poly(Ethylene Glycol) Copolymers as Drug Delivery System," *International Journal of Pharmaceutics*, Vol. 381, No. 2, 2009, pp. 1-18. [doi:10.1016/j.ijpharm.2009.07.033](https://doi.org/10.1016/j.ijpharm.2009.07.033)
- [5] R. Gref, Y. Minamitake, M. T. Peracchia, V. Trubetsky, V. Torchilin and R. Langer, "Biodegradable Long-Circulating Polymeric Nanospheres," *Science*, Vol. 263, No. 5153, 1994, pp. 1600-1603. [doi:10.1126/science.8128245](https://doi.org/10.1126/science.8128245)
- [6] S. Stolnik, L. Illum and S. S. Davis, "Long Circulating Microparticulate Drug Carriers," *Advanced Drug Delivery Review*, Vol. 16, No. 2, 1995, pp. 195-214. [doi:10.1016/0169-409X\(95\)00025-3](https://doi.org/10.1016/0169-409X(95)00025-3)
- [7] S. Y. Kim, I. L. Shin, Y. M. Lee, C. S. Cho and Y. K. Sung, "Methoxy Poly(Ethylene Glycol) and ϵ -Caprolactone Amphiphilic Block Copolymeric Micelle Containing Indomethacin. II. Micelle Formation and Drug Release Behaviours," *Journal of Controlled Release*, Vol. 51, No. 1, 1998, pp. 13-22.
- [8] A. Lucke, J. Tebmar, E. Schnell, G. Schmeer and A. Gopferich, "Biodegradable Poly(D,L-Lactic Acid)-Poly(Ethylene Glycol)-Monomethyl Ether Copolymers: Structures and Surface Properties Relevant to Their Use as Biomaterials," *Biomaterials*, Vol. 21, No. 23, 2000, pp. 2361-2370. [doi:10.1016/S0142-9612\(00\)00103-4](https://doi.org/10.1016/S0142-9612(00)00103-4)
- [9] C. He, J. Sun, C. Deng, T. Zhao, M. Deng, X. Chen and X. Jing, "Study of the Synthesis, Crystallization, and Morphology of Poly(Ethylene Glycol)-Poly(ϵ -Caprolactone) Diblock Copolymers," *Biomacromolecules*, Vol. 5, No. 5, 2004, pp. 2042-2047. [doi:10.1021/bm049720e](https://doi.org/10.1021/bm049720e)
- [10] H. Hyun, M. S. Kim, S. C. Jeong, Y. H. Kim, S. Y. Lee and H. B. Lee, "Preparation of Diblock Copolymers Consisting of Methoxy Poly(Ethylene Glycol) and Poly(ϵ -Caprolactone)/Poly(L-Lactide) and Their Degradation Property," *Polymer Engineering and Science*, Vol. 46, 2006, pp. 1242-1249. [doi:10.1002/pen.20581](https://doi.org/10.1002/pen.20581)
- [11] Y. Zhang, C. Wang, W. Yang, B. Shi and S. Fu, "Tri-Component Diblock Copolymers of Poly(Ethylene Glycol)-Poly(ϵ -Caprolactone-Co-Lactide): Synthesis, Characterization and Loading Camptothecin," *Colloid and Polymer Science*, Vol. 283, No. 11, 2005, pp. 1246-1252. [doi:10.1007/s00396-005-1306-5](https://doi.org/10.1007/s00396-005-1306-5)
- [12] Y. H. Na, Y. He, X. Shuai, Y. Kikkawa, Y. Doi and Y. Inoue, "Compatibilization Effect of Poly(ϵ -Caprolactone)-*b*-Poly(Ethylene Glycol) Block Copolymers and Phase Morphology Analysis in Immiscible Poly(Lactide)/Poly(ϵ -Caprolactone) Blends," *Biomacromolecules*, Vol. 3, No. 6, 2002, pp. 1179-1186. [doi:10.1021/bm020050r](https://doi.org/10.1021/bm020050r)
- [13] F. Ahmed and D. E. Discher, "Self-Porting Polymerosomes of PEG-PLA and PEG-PCL: Hydrolysis-Triggered Controlled Release Vesicles," *Journal of Controlled Release*, Vol. 96, No. 1, 2004, pp. 37-53. [doi:10.1016/j.jconrel.2003.12.021](https://doi.org/10.1016/j.jconrel.2003.12.021)
- [14] Y. Dong and S. S. Feng, "Nanoparticles of Poly(D,L-Lactide)/Methoxy Poly(Ethylene Glycol)-Poly(D,L-Lactide) Blends for Controlled Release of Paclitaxel," *Journal of Biomedical Material Research*, Vol. 78A, 2006, pp. 12-19. [doi:10.1002/jbm.a.30684](https://doi.org/10.1002/jbm.a.30684)
- [15] S. A. Casarin, S. M. Malmonge, M. Kobayashi and J. A. M. Agnelli, "Study on *in Vitro* Degradation of Bioabsorbable Polymers Poly(Hydroxybutyrate-Co-Valerate)-PHBV and Poly(Caprolactone)-PCL," *Journal of Biomaterials and Nanobiotechnology*, Vol. 2, 2011, pp. 207-215. [doi:10.4236/jbnb.2011.23026](https://doi.org/10.4236/jbnb.2011.23026)