Synthesis and Microphase Separation of Biodegradable Poly(ε-caprolactone)-Poly(ethylene glycol)-Poly(ε-caprolactone) Multiblock Copolymer Films

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Abstract: Poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCL-PEG-PCL) multiblock copolymers at various hydrophobic-hydrophilic ratios were successfully synthesized by the chain extension of triblock copolymers through isocyanate (hexamethylene diisocyanate). Biodegradable films were prepared from the resulting multiblock copolymers using the casting method. The mechanical properties of the films were improved by chain extension of the triblock copolymers, whereas the films prepared by the triblock copolymers were weak and brittle. Atomic force microscopy (AFM) of the multiblock copolymer film showed that the hydrophilic PEG had segregated on the film surface. This is consistent with the observed contact angle of the films.

Keywords: poly(ε-caprolactone) (PCL), poly(ethylene glycol) (PEG), multiblock copolymers, film properties, microphase separation.

Introduction

Biodegradable polymers have attracted much attention in the recent decades for their role in biomedical applications such as drug delivery systems, surgery and tissue engineering.[1-3] Poly(ε-caprolactone) (PCL) is among the most important biodegradable polymers because of its biocompatibility, biodegradability, non-toxicity and good permeability to drugs.[4-8] This substantially hydrophobic, semicrystalline, and aliphatic polyester has a glass transition temperature of around -60 °C and a low melting point of 60 °C.[9] However, its slow degradation rate resulting from poor hydrophilicity and semicrystallinity limits its diverse applications in biomedical fields. Generally, molecular modification through copolymerization is necessary to obtain materials with desirable properties. Hence, many copolymers of ε-caprolactone (CL) and monomers such as lactide,[10,11] glycolide[12,13] and poly(ethylene glycol) (PEG)[14,15] were investigated in order to expand application fields. PEG is a highly biocompatible material that is used in diverse biomedical applications.[16] PEG is used mainly to enhance water permeability with favorable interactions with human tissues.[17-19] Amphiphilic block copolymers that consist of hydrophilic and hydrophobic segments exhibit a unique phase behavior and have potential applications like drug delivery systems.[20-22] In many case, these di- and tri-block copolymers have a relatively low mechanical strength and limited hydrophilicity. To improve mechanical property and control the hydrophilicity, multiblock copolymers is assumed to be more promising way than di- or triblock copolymers.[23-25] In addition, multiblock copolymers with flexible and crystalline segments allow the modification of physical and chemical properties.[26]

The aim of this work is to prepare of multiblock copolymer film with the comparable mechanical properties to PCL homopolymer film and to evaluate their surface characteristics by contact angle analysis and AFM.

Experimental

Materials. ε-Caprolactone (CL) was purchased from Aldrich (USA) and dried over calcium hydride for 48 h at room temperature. It was then distilled under reduced pressure prior to polymerization. Poly(ethylene glycol) (PEG, molecular weight 1, 2, and 4.6 k) was purchased from Aldrich (USA). It was dried in a vacuum prior to use. Stannous

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Table I. Recipes of PCL-PEG-PCL Triblock Copolymers

Triblock Copolymers[a]	Quantity		
	PEG (g)	ε-CL (mL)	SnOct₂ (mL)
tPCL2k-PEG1k-PCL2k	5	20	0.1
tPCL2k-PEG2k-PCL2k	8	16	0.1
tPCL4k-PEG2k-PCL4k	5	20	0.05
tPCL4.6k-PEG4.6k-PCL4.6k	8	16	0.05

[a]Reaction condition: 120 °C, 24 h.

octoate (tin(II) 2-ethylhexanoate) were purchased from Sigma (USA). Hexamethylene diisocyanate (HDI) was purchased from Aldrich (USA). Toluene (Ducksan) and methylene chloride (MC, Ducksan) were distilled before use. Isopropyl alcohol (IPA, Ducksan) and ethyl ether (Ducksan) were used as received. Distilled water was Milli-Q quality (Millipore, Bedford, MD, USA). All organic solvents were either HPLC grade or American Society analytical grade reagents.

Preparation of PCL-PEG-PCL Triblock and Multiblock Copolymers. PCL-PEG-PCL triblock copolymers with different PCL/PEG ratios were synthesized by ring-opening polymerization of CL from the hydroxyl end groups of PEG after activation with stannous octoate. Predetermined quantities of PEG, CL, and stannous octoate were introduced into a Pyrex reactor (Table I). After degassing, the reactor was evacuated by vacuum pump, sealed by torch before reaction and then heated in an oil bath at 120 °C for 24 h. After the reaction was completed, the resulting polymers were precipitated into excess IPA followed by centrifugation and drying in a vacuum at room temperature for 24 h.

PCL-PEG-PCL multiblock copolymers were synthesized from triblock copolymers by chain extension. The reaction was performed using HDI as the chain extender. Synthesis of multiblock copolymers was also achieved in a vacuum. Briefly, 3 g of PCL-PEG-PCL triblock copolymers made in a previous reaction were dissolved in 15 g of anhydrous MC, followed by the addition to the reactor of predetermined amounts of HDI and stannous octoate (Table II). The reaction was completed after 12 h at 80 °C. The resulting polymers were precipitated into excess ethyl ether and dried

Table II. Recipes of PCL-PEG-PCL Multiblock Copolymers

Multiblock Copolymers[a]	Quantity		
	Triblock Copolymers (g)	HDI (mL)	SnOct₂ (mL)
mPCL2k-PEG1k-PCL2k	3	1.0	0.3
mPCL2k-PEG2k-PCL2k	3	0.8	0.2
mPCL4k-PEG2k-PCL4k	3	0.5	0.08
mPCL4.6k-PEG4.6k-PCL4.6k	3	0.4	0.06

[a]Reaction condition: 80 °C, 12 h.
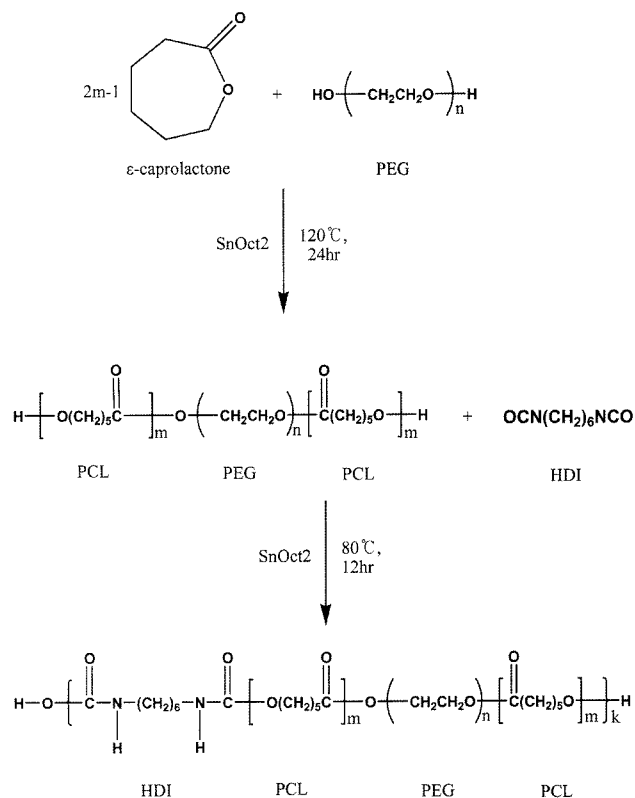
Figure 1. Synthetic procedure of PCL-PEG-PCL multiblock copolymers.

in a vacuum at room temperature. The synthetic procedure of PCL-PEG-PCL multiblock copolymers is shown in Figure 1.

Characterization of Block Copolymers. The resulting block copolymers were characterized by gel permeation chromatography (GPC, Waters Breeze System, Waters Co., USA) and nuclear magnetic resonance (^{1}H-NMR, JEOL, Japan). The average molecular weights of block copolymers were obtained from GPC, relative to polystyrene standards with M_w 2,800~700,000 gmol^{-1}. The GPC column was a series of μStyragel® columns (HR5, HR4, HR1, and HR5E), and tetrahydrofurane (THF) was used as an eluent at a flow rate of 1 mL/min and 1×10³ Pa pressure. The identity of block copolymers was determined by ^{1}H-NMR. Three hundred MHz ^{1}H-NMR spectra were measured in CDCl₃ containing 0.05% v/v of tetramethylsilane (TMS) as the internal reference.

Characterization of Copolymer Films. The mechanical strength of PCL-PEG-PCL multiblock copolymers films (15 mm × 35 mm × 0.15 mm) was examined by a universal testing machine (UTM, LR10K, Lloyd Instruments, Ltd., UK) with a crosshead speed of 10 mm/min. The tensile strength and Young's modulus were calculated. At least three specimens were tested from each sample and their average values were determined. The contact angles of copolymer films were measured using contact angle & surface tension analysis (Model Phoenix 300, SEO) equipped with an image

analysis attachment (IAA). The IAA used a digital video camera in combination with a personal computer to scan an image of the drop and automatically calculated both the left and right angles and drop dimension parameters from the digitized image. Contact angles were measured as a function of time.

Atomic Force Microscopy of Multiblock Copolymer Films. The multiblock copolymer films were prepared by a spin coater (Midas System Co., SPIN2100D). The polymers were dissolved in MC at 1 wt% and cast onto a glass slide at 2,500 rpm for 150 sec. To visualize the microphase separation, atomic force microscopy (AFM) images were taken in tapping mode on a Multimode Nanoscope IV (Digital Instrument, Veeco Metrology Group, Santa Barbara, CA) using etched silicon probes. Images were recorded in height mode, and Nanoscope IV software was used for data processing. Images of a different composition of each sample were recorded. All the images were collected with the maximum available number of pixels (512) in each direction. Nanoscope image processing software was used for image analysis.

Results and Discussion

Synthesis of PCL-PEG-PCL Block Copolymers. PCL-PEG-PCL triblock copolymers were synthesized by the ring-opening polymerization of CL in the presence of PEG as an initiator. Two terminal hydroxyl groups of PEG activated with stannous octoate served as initiating groups to synthesize block copolymers. The molecular weights and polydispersity of the triblock copolymer are shown in Table III. PCL-PEG-PCL triblock copolymers with a narrow molecular weight distribution were obtained. The composition of the copolymers was determined from the intensity ratio of peaks in the ^{1}H-NMR spectrum in CDCl$_3$: 4.1 ppm (a, CH$_2$ for PCL backbone), 1.65 ppm (b & d, two CH$_2$ for PCL backbone), 1.4 ppm (c, CH$_2$ for PCL backbone), 2.32 ppm (e, CH$_2$ for PCL backbone) and 3.65 ppm (f, CH$_2$CH$_2$O for PEG) (Figure 2). The analysis of GPC and NMR confirms that the triblock copolymers were successfully synthesized.

High molecular weight and superior mechanical properties are often required in biomedical fields,[27] especially in
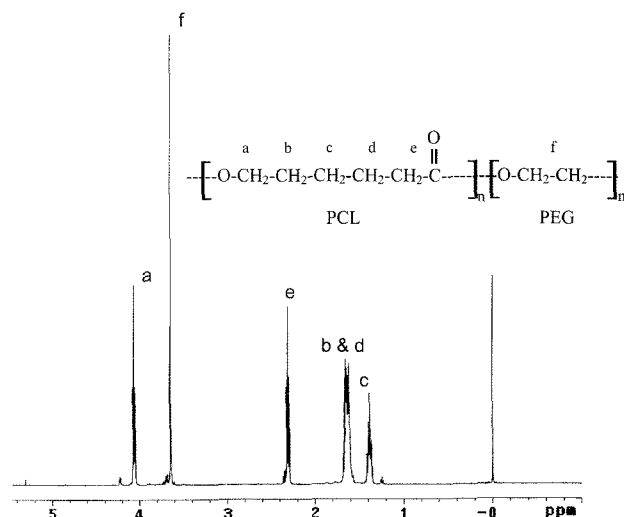
Figure 2. Representative ^{1}H-NMR spectrum in CDCl$_3$ of triblock copolymer (tPCL2k-PEG1k-PCL2k).

film applications. To improve the mechanical properties, PCL-PEG-PCL multiblock copolymers were synthesized from the chain extension of triblock copolymers. The two terminal hydroxyl groups of triblock copolymers were reacted with HDI through a urethane reaction between isocyanate and the hydroxyl group. The resulting PCL-PEG-PCL multiblock copolymers with various PCL and PEG ratios were characterized (Table III). The molecular weights of multiblock copolymers are controlled at about 120,000 to minimize the effect of the molecular weight on their mechanical properties.

Mechanical Property and Contact Angle Analysis of PCL-PEG-PCL Multiblock Copolymer Films. Tensile strength and Young's modulus of the multiblock copolymer films were determined by UTM (Figure 3). In our experimental scope, the films prepared by triblock copolymers were so brittle that their mechanical strength can not be measured due to their low molecular weight. This is the reason for the employment of the chain extension step using isocyanate. It was found that the mechanical properties of multiblock copolymer films were improved by the chain reaction of triblock copolymers, which were comparable to that of the PCL homopolymer film. The tensile strength and

Table III. Characterization of PCL-PEG-PCL Triblock and Multiblock Copolymers

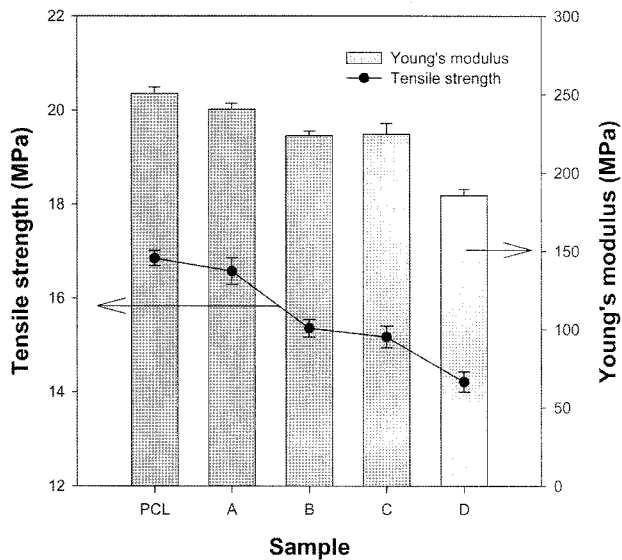|	Triblock Copolymer				Multiblock Copolymer		
	PCL/PEG ratio (wt)[a]	M_w	M_n	PDI	M_w	M_n	PDI
PCL2k-PEG1k-PCL2k	4.5	6,119	5,513	1.11	123,239	72,923	1.69
PCL2k-PEG2k-PCL2k	2.6	8,186	7,119	1.15	140,341	91,131	1.54
PCL4k-PEG2k-PCL4k	5.0	15,412	12,136	1.27	109,501	70,646	1.55
PCL4.6k-PEG4.6k-PCL4.6k	2.3	18,492	15,410	1.20	126,094	89,429	1.41

[a]PCL/PEG ratios were determined from NMR.

Figure 3. Mechanical properties of PCL-PEG-PCL multiblock copolymer films with varying composition (A: mPCL2k-PEG1k-PCL2k, B: mPCL2k-PEG2k-PCL2k, C: mPCL4k-PEG2k-PCL4k, D: mPCL4.6k-PEG4.6k-PCL4.6k), M_w of synthesized PCL homopolymer is 389,439 (PDI 2.36)).

Young's modulus of PCL-PEG-PCL multiblock film with 1 k M_n of PEG were higher than that of the other copolymer films. Sample B and C with 2 k M_n of PEG exhibited similar mechanical properties despite the different molecular weight of the PCL segment. There was a clear trend of a decrease in mechanical properties with respect to introduction and increase in the molecular weight of PEG. It is assumed that
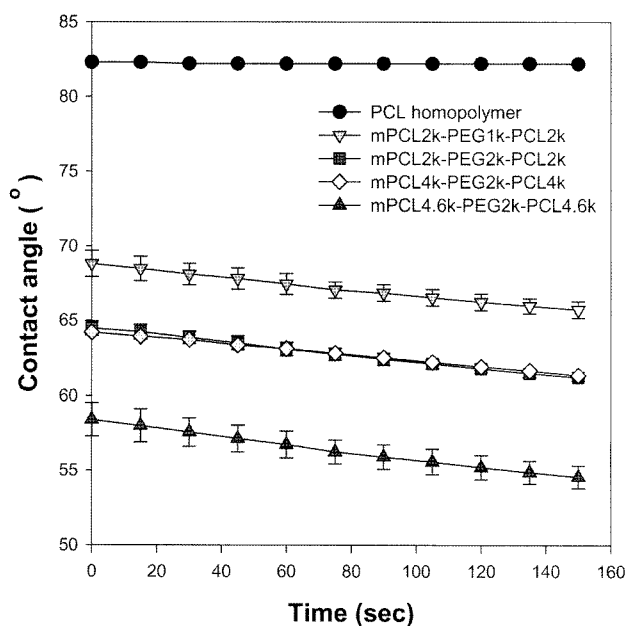

Figure 4. Contact angle of PCL-PEG-PCL multiblock copolymer films with varying composition.

PCL has strong ester bonds that are non-rotating, whereas PEG has an ether bond that is comparatively weak and rotating. PEG is considered as a weak material that behaves in a ductile and plastic manner.[28] Therefore, it was assumed that the variation of mechanical properties originated form the ratio and molecular weight of PEG. Although PEG is responsible for the decrease in mechanical strength, it has been often employed to control the hydrophilicity and flexibility of films in many application fields.
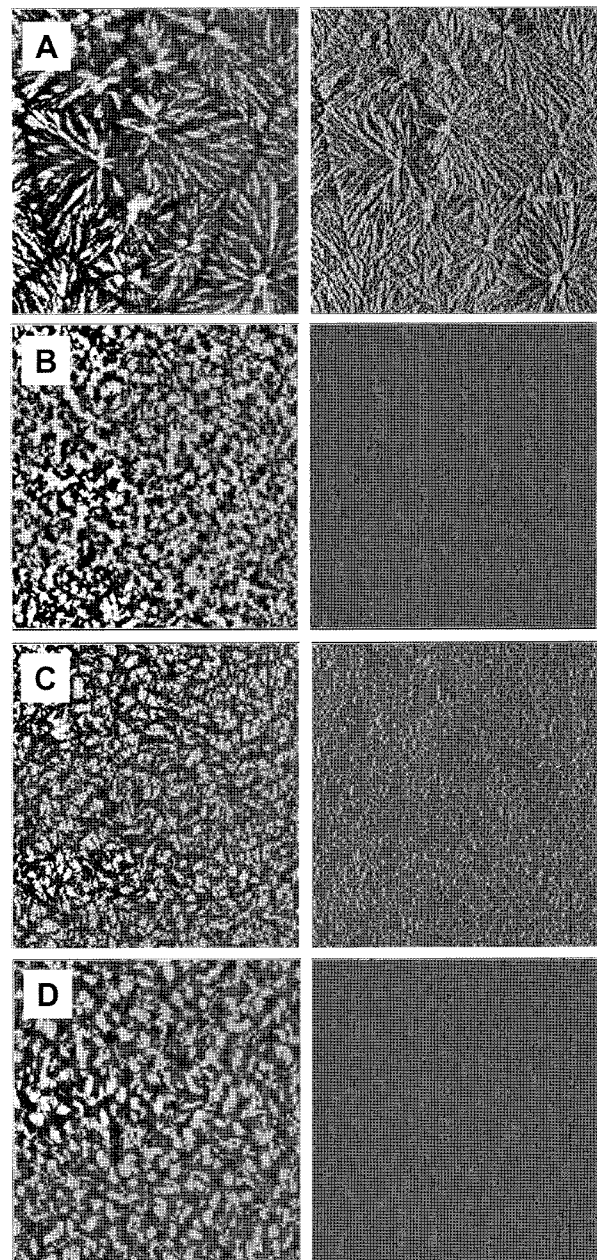

Figure 5. Height (left) and phase (right) AFM images of PCL-PEG-PCL multiblock copolymer films (A: mPCL2k-PEG1k-PCL2k, B: mPCL2k-PEG2k-PCL2k, C: mPCL4k-PEG2k-PCL4k, D: mPCL4.6k-PEG4.6k-PCL4.6k). The scan size of each image was 30 μm × 30 μm.

Table IV. Mean Surface Roughness of Multiblock Films

Multiblock Copolymers	Mean Surface Roughness (nm)[a]	
	Phase Image	Height Image
mPCL2k-PEG1k-PCL2k	182.87	122.63
mPCL2k-PEG2k-PCL2k	118.94	17.97
mPCL4k-PEG2k-PCL4k	111.41	74.96
mPCL4.6k-PEG4.6k-PCL4.6k	78.29	9.08

[a]Determined from AFM.

The variation in the contact angle was examined over time to evaluate the surface hydrophilicity of multiblock copolymer films (Figure 4). The contact angle of all multiblock copolymer films decreased steadily with time. The PCL film showed little water absorption even after 3 min because of its high hydrophobicity. It was revealed that the mPCL2k-PEG1k-PCL2k had more hydrophilic surface than the rest. The hydrophilic PEG segregated on the surface of the multiblock copolymer films help water to migrate into the film and provide a hydrogel-like nature to the film surface.

Microphase Separation of PCL-PEG-PCL Multiblock Copolymers. Figure 5 shows AFM images of various multiblock copolymer films. Their height variation and rough topography on the surface were believed to result from microphase separation. In all multiblock copolymer films, the structure of microphase separation was shown, but the patterns were different from the typical results of typical di- or triblock copolymer films, because PCL and PEG segments were linked with adjacent segments in the repeated block units.

A spherulitic structure clearly appeared on the surface of the mPCL2k-PEG1k-PCL2k copolymer (A images in Figure 5), which was due to the surface segregation of PEG with low molecular weight even if it was linked to PCL segment, and the crystallization property of PEG and PCL.[15,18] This result is corresponding to the analysis of contact angle. Mean surface roughness of the multiblock copolymer films was shown in Table IV. The multiblock copolymer films with a large PCL/PEG ratio had a rough surface, whereas the ductile PEG made the film surface smooth.

Conclusions

To improve the mechanical properties of PCL-PEG-PCL block copolymers, we prepared PCL-PEG-PCL multiblock copolymer by chain extension of triblock copolymer, which showed comparable mechanical strength to PCL homopolymer film. The surface hydrophilicity of the film can be tailored by controlling the copolymer composition and chain length. PEG was a critical factor affecting the contact angle and microphase separation. These AFM results were corresponding to the results of contact angle analysis.

References

(1) A. C. Albertsson and U. Edlund, *Adv. Drug Deliver. Rev.*, **55**, 585 (2003).

(2) J. C. Middleton and A. J. Tipton, *Biomaterials*, **21**, 2335 (2000).

(3) K. Woei, D. W. Hutmacher, J. T. Schantz, C. Seng, H. P. Too, T. Chye, T. T. Phan, and S. H. Teoh, *Tissue Eng.*, **7**, 441 (2001).

(4) A. M. Le Ray, S. Chiffoleau, P. Iooss, G. Grimandi, A. Gouyette, G. Daculsi, and C. Merle, *Biomaterials*, **24**, 443 (2003).

(5) C. G. Pitt, A. R. Jeffcoat, R. A. Zweidinger, and A. Schindler, *J. Biomed. Mater. Res.*, **13**, 497 (1979).

(6) S. W. Hong, K. H. Kim, J. Huh, C. H. Ahn, and W. H. Jo, *Macromol. Res.*, **13**, 397 (2005).

(7) J. S. Yoo, M. S. Kim, D. S. Lee, B. S. Kim, and J. H. Kim, *Macromol. Res.*, **14**, 117 (2006).

(8) S. J. Im, Y. M. Choi, E. Subramanyam, K. M. Huh, and K. Park, *Macromol. Res.*, **15**, 363 (2007).

(9) W. Lin, *J. Biomed. Mater. Res.*, **47**, 420 (1999).

(10) W. P. Ye, F. S. Du, W. H. Jin, J. Y. Yang, and Y. Xu, *React. Funct. Polym.*, **32**, 161 (1997).

(11) H. Yavuz and C. Babac, *Polym. Degrad. Stabil.*, **75**, 431 (2002).

(12) I. Barakat, P. H. Dubois, C. H. Grandfils, and R. Jérôme, *J. Polym. Sci. Part A: Polym. Chem.*, **39**, 294 (2002).

(13) M. Bero, B. Czapla, P. Dobrzyński, H. Janeczek, and J. Kasperczyk, *Macromol. Chem. Phys.*, **200**, 911 (1999).

(14) H. X. Ge, Y. Hu, X. Q. Jiang, D. M. Cheng, Y. Y. Yuan, H. Bi, and C. Z. Yang, *J. Pharm. Sci.*, **91**, 1463 (2002).

(15) F. He, S. M. Li, M. Vert, and R. X. Zhuo, *Polymer*, **44**, 5145 (2003).

(16) J. M. Harris, *Topics in applied chemistry*, J. M. Harris, Ed., New York, Plenum Press, 1992, pp 1-14.

(17) R. Sbarbati del Guerra, C. Cristallini, N. Rizzi, R. Barsacchi, G. D. Guerra, M. Tricoli, and P. Cerrai, *J. Mater. Sci.; Mater. Med.*, **5**, 891 (1994).

(18) B. Bogdanov, A. Vidts, E. Schacht, and H. Berghmans, *Macromolecules*, **32**, 726 (1999).

(19) S. M. Li, X. M. Chen, R. A. Gross, and S. P. McCarthey, *J. Mater. Sci.; Mater. Med.*, **11**, 227 (2000).

(20) M. N. Kumar, N. Kumar, A. J. Domb, and M. Arora, *Adv. Polym. Sci.*, **160**, 45 (2002).

(21) J. Kreuter, *Colloidal drug delivery systems*, New York, Marcel Dekker, 1994, pp 219-342.

(22) H. Otsuka, Y. Nagasaki, and K. Kataoka, *Adv. Drug Deliver. Rev.*, **55**, 403 (2003).

(23) H. R. Kricheldorf and S. Rost, *Polymer*, **46**, 3248 (2005).

(24) D. Cohn and A. Hotovely-Salomon, *Polymer*, **46**, 2068 (2005).

(25) X. Chen, S. P. McCarthy, and R. A. Gross, *Macromolecules*, **30**, 4295 (1997).

(26) D. K. Gilding and A. M. Reed, *Polymer*, **20**, 1454 (1979).

(27) Z. Cheng and S. H. Teoh, *Biomaterials*, **25**, 1991 (2004).

(28) M. A. Al-Nasassrah, F. Podczeck, and J. M. Newton, *Eur. J. Pharm. Biopharm.*, **46**, 31 (1998).