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PCL/PCL-*g*-PEG 생분해성 블렌드에서 그래프트 공중합체의 조성에 따른 상용성의 영향

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Effect of Graft Copolymer Composition on the Compatibility of Biodegradable PCL/PCL-*g*-PEG Blend

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초록: 의료용으로 적용될 수 있는 새로운 재료를 제조하기 위하여 폴리카프로락톤(PCL)과 양친성 구조를 갖는 폴리(에틸렌 글리콜)(PEG)이 그래프트된 PCL을 이용하여 생분해성 블렌드를 제조하였다. 제조된 블렌드는 PCL을 기본으로 하고 여기에 그래프트 공중합체의 함량을 변화시키며 열적 그리고 결정화 특성을 관찰하였다. 그래프트 공중합체의 함량 변화에 따라 결정화 온도의 변화 및 결정화 속도가 변화하였고 이를 통해 그래프트 공중합체가 PCL의 결정화 거동에 영향을 미침을 확인하였다. 이는 광학현미경을 통한 결정의 교대 소광 밴드의 관찰을 통하여서도 확인할 수 있었다. 약물방출시스템과 같은 의료용 응용을 고려하여 블렌드 필름의 흡수거동과 단백질 흡착에 대한 특성도 평가하였다.

Abstract: Blend films based on the poly(ε-caprolactone) (PCL) and amphiphilic biodegradable polymer, poly(ethylene glycol) grafted poly(ε-caprolactone) (PCL-*g*-PEG), were prepared with different blend ratios in order to develop new biomedical material. PCL was the main component in the blend. The miscibility and characteristics of the blends were investigated. The crystallization temperature of the blend shifted to high temperatures with an increase of the graft copolymer contents when the homopolymer PCL was the main component of the blend. The PEG side chain in the blend affected the crystallization rate of the PCL crystals in the blend and alternating extinction bands were observed by optical microscopy. The protein adhesion behavior of the film was influenced by the water uptake of the film.

Keywords: blend, poly(ε-caprolactone), poly(ethylene glycol), crystallization, protein adhesion.

Introduction

Poly(ε-caprolactone) (PCL) is a semi-crystalline polymer which undergoes biodegradation and absorption *in vivo*.[1,2] It shows high permeability, biocompatibility and good mechanical property for film preparation. Due to these properties, PCL has attracted much attention in biomedical application such as drug delivery matrix.[3-6] However, PCL degrades very slowly due to relatively hydrophobic character and high crystallinity.[7,8]

Work on the modification of biodegradable polymers that contain PCL[9,10] has been performed, and the result show that changes in the properties of PCL can be obtained by the modification of chemical structure of polymer. Among the modifications to PCL, the introduction of hydrophilic components such as poly(ethylene glycol) (PEG) is highlighted, owing to its own potential application to biomedical matrices.[11-13]

Recently, novel graft structure amphiphilic biodegradable

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copolymers using PCL and PEG were reported.[14,15] Compared to previously reported block copolymers of PCL and PEG,[16,17] PCL−*g*−PEG is structurally advantageous in some aspects. It demonstrates similar properties, such as amphiphilic character, high water uptake, and suppression of crystallinity with shorter PEG chains compared to those of block co−polymers. Using short side chain PEG is of importance in its complete renal excretion after degradation of the poly−ester block.[18,19] The graft copolymer showed somewhat different properties due to its high hydrophilic−lipophilic balance, which is resulted in interesting characteristics for biomedical applications. In other aspects, an increase in the amount of PEG can be a cause of poor mechanical property in terms of film preparation. It is expected that the blending of PCL and PCL−*g*−PEG will compensate the demerits of each component. Also, this system will be good comparison to previous block copolymer systems dealt with rather long PEG chain.

Thus, in this work, the basic characteristics of morphology and crystallization of novel PCL/PCL−*g*−PEG blends are discussed. Additionally, preliminary work on protein adsorption on the blend films was studied in order to investigate these important characteristics for biomedical application.

Experimental

Materials. PCL (M_w = 80000) was purchased from Union Carbide (Danbury, CT). Bovine serum albumin (BSA, Fraction V, lyophilized) and reagents for the preparation of saline phosphate buffers for adsorption experiments were purchased from Sigma (St Louis, MO). Dichloromethane were purchased from Merck (Darmstadt, Germany) and purified by usual distillation method.

The synthesis and characteristics of the PCL−*g*−PEG are described in our previous paper.[14] Briefly, ε−caprol−actone was bulk polymerized at 180 ℃ with epoxy terminated monomethoxy poly(ethylene glycol) (MPEG) using aluminum isopropoxide as a catalyst. The molecular weight of the starting MPEG was 350. The final product of graft copolymer has 10% graft efficiency, which was calculated from the ^{1}H−NMR spectrum.

Blend samples are prepared as follow; PCL and PCL−*g*−PEG were dissolved in dichloromethane to form 20% (w/v, 1.0 g/5 mL) solutions and cast onto flat Teflon plate. Solvent evaporation was performed and films were hooded for 12 h followed by vacuum drying for 2 day. The resulting film samples were pressed with a hot press at 70 ℃ to remove any pores generated by the solvent casting procedure. Blends are designated as xHyG, where x and y represents the weight ratio of PCL homopolymer and PCL−*g*−PEG graft polymer, respectively.

Measurements. The thermal transitions of the blends were measured in aluminum pans using a differential scanning calorimeter (DSC, TA instrument DSC2010) under a nitrogen atmosphere. Samples of 10−15 mg were used in the deter−mination of thermal properties. The samples were heated from −120 to 150 ℃ at a rate of 10 ℃/min. An indium standard was used to calibrate the temperature and the heat of fusion. The heat of fusion was determined by integrating the normalized area of melting endotherms. Crystallization temperature (T_c) of the blend was measured by cooling the samples at a rate of 5 ℃/min from 150 to −20 ℃.

The crystallization rate of the blends was measured with crystallization rate measurement instrument (MK−701, Kodaki, Japan). The instrument is composed of two tem−perature baths. The upper compartment dissolves polymer sample at predetermined temperature. The lower compart−ment is filled with silicone oil and set to the quenching tem−perature, which is generally slight higher than T_c of each blend measured from DSC thermogram. In the lower com−partment, polarized light source and detector are equipped to investigate the scattering of polarized light when the samples crystallize. A film having size of 1 cm×1cm is located between the two slide glass and fixed on the holder, which is located at the end of long stainless bar. The samples are melted in the upper compartment (fixed to 70 ℃) for 1 min. The repetition of melting over different time showed 1 min was enough for the complete melting of our films. The quenching procedure begins when the holder with melted sample drops into the silicon oil bath with the detection of polarized light simultaneously. The transmittance of the polarized light through the oil bath due to the scattering by crystalline phase formation was measured with time. Figure

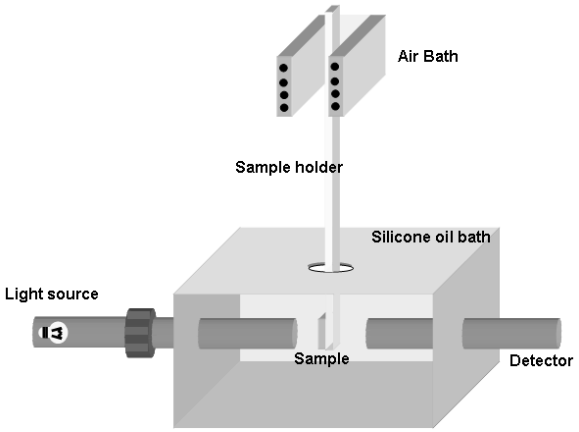

Figure 1. Schematic illustration of crystallization measure−ment apparatus.

1 shows the schematic illustration of the equipment.

Images of optical microscopy of the blend was observed by a polarized microscopy (Leica, Germany) equipped with an image analyzer connected to PC system. All of the samples were prepared using the solvent casting method with dichloromethane. Images were taken at 25 ℃ while the temperature was held constant by a temperature controller.

To investigate the swelling characteristics, blend films (30−50 μm in thickness) with a surface area of 1 cm×1 cm were immersed in double distilled water and incubated at 25 ℃. Duplicate film samples were incubated and characterized parallel. Samples were periodically recovered for water uptake determination. Surface water on films was removed with absorbent paper and the samples were weighed. Water uptake was calculated at each time point using the following equation:

$$\% \text{ Water Uptake} = 100 \times (W_{wet} - W_{dry}) / W_{dry}$$

where W_{wet} and W_{dry} are weights of wet and initial dry film samples. Values obtained for duplicate samples were averaged.

Protein Adsorption Test. Film samples with the same dimension as for the water uptake measurement were placed in the deionized water for 30 min at 37 ℃. Protein adhesion was performed by placing prehydrated samples in the 5 mL of BSA solution having a concentration of 0.2 mg/mL for 2 h at 37 ℃.[20,21] The films were washed with distilled water three times to remove physically adsorbed BSA on to the surface of the film. Adsorbed protein was redissolved from film by placing the film in 2.5 mL sodium dodecyl sample buffer (phosphate buffer saline, 1% SDS, pH 7.4) for 24 h at 37 ℃.

BSA adsorbed onto film was determined by measuring the initial and final concentrations of BSA in the medium by microBCA assay (Pierce, IL) method.

Results and Discussion

Thermal Properties and Morphology of the Blend. Blends of PCL homopolymer and PCL−*g*−PEG were prepared with different compositions (9H1G to 5H5G), and these compositions are shown in Table 1. To investigate the miscibility of PCL and PCL−*g*−PEG, the DSC thermograms of the blends were measured and all of the blends showed single T_g when blended with the graft copolymer, which indicates miscibility of the amorphous region between the two polymers. The melting peak of the blend shifted to lower temperatures with an increase of the PCL−*g*−PEG content in the blend, as shown in Figure 2. This supports the fact that PCL−*g*−PEG and PCL are miscible. The blending of semicrystalline polymers with other polymers showed a decrease in the melting temperature, which is indicative of the miscibility of the polymers in the amorphous phase.[22] In particular, a split of the melting peak was observed from the 8H2G to the 5H5G samples, and the peak area of the melting endotherm of the lower peak increased with an increase of graft copolymer composition. From this result, it is reasonable to expect that the PEG side chain has an effect on the PCL crystalline structure. The T_c was measured to investigate the role of the PEG on the PCL crystallization. Figure 3 shows the cooling curves of the blends with changes of the PCL−*g*−PEG composition and PEG graft frequency. The crystallization peak for PCL from the cooling curves shifted to higher temperatures with an increase of PCL−*g*−PEG, but after 7H3G, a further increase of the PCL−*g*−PEG content in the blend did not change the position of the crystallization peak. A shift of T_c to higher temperatures implies that the crystallization of PCL becomes progressively easier with increasing PCL−*g*−PEG content. Considering the onset temperature, pristine PCL starts crystallization at higher temperature. However with the increase of graft copolymer, shape of the peak gets sharp resulted in higher maximum T_c. This indicates that the

Table 1. Composition and Thermal Property of the PCL/PCL-*g*-PEG Blend

Notation	Blend Ratio (based on weight)		Water contact angle (°)	T_g (℃)	T_m (℃)	H_m (J/g)
	PCL	PCL−*g*−PEG				
PCL	100	0	74	−59.5	60.0	67.0
9H1G	90	10	67	−65.1	57.0	66.5
8H2G	80	20	59	−68.6	55.7	69.0
7H3G	70	30	54	−67.3	55.1	68.9
5H5G	50	50	38	−70.4	54.3	65.0

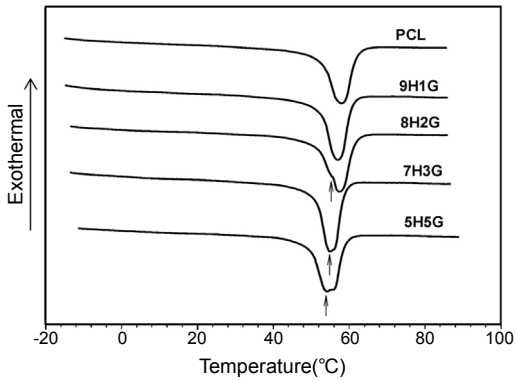

Figure 2. DSC thermograms of PCL/PCL−*g*−PEG blends with different blend ratio.

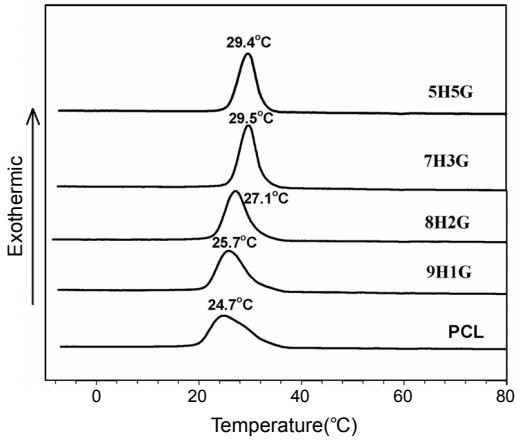

Figure 3. DSC cooling scans of the PCL/PCL−*g*−PEG blends with different blend ratio.

existence of the graft copolymer effect on the crystallization rate.

The effect of side chain PEG on PCL crystallization was also observed by measuring the crystallization rate of the blend samples. The overall crystallization rates under isothermal crystallization conditions were measured using the device shown in Figure 1. Molten blends are abruptly placed in the bath where the temperature is set to slightly higher than the measured T_c of the each sample.

The isothermal crystallization kinetics of the blend can be interpreted in terms of the Avrami equation

$$\alpha(t) = 1 - \exp(-kt^n) \quad (1)$$

where $\alpha(t)$ is the mass fraction of polymer transformed from melt to solid at time t, n is an exponent which contains contributions related to the crystal growth geometry and the time dependency of the nucleation rate, and k is an overall crystallization rate constant including contributions from crystal growth and nucleation.

Eq. (1) can be rewritten as eq. (2) if we define X_m as the maximum crystallization fraction and X_t as the crystallization fraction at time t. The crystallization rate can be obtained by the measuring the transmitted polarized light at the initial state, maximum state and time t, which is symbolized as I_0, I_∞ and I_t, respectively (eq. (3)).

$$\alpha(t) = 1 - (X_t/X_m) \quad (2)$$

$$1 - \alpha(t) = \frac{I_\infty - I_t}{I_\infty - I_0} \quad (3)$$

Generally, the bulk crystallization rate is expressed as the half time of crystallization, $\tau_{0.5}$, which is the time where

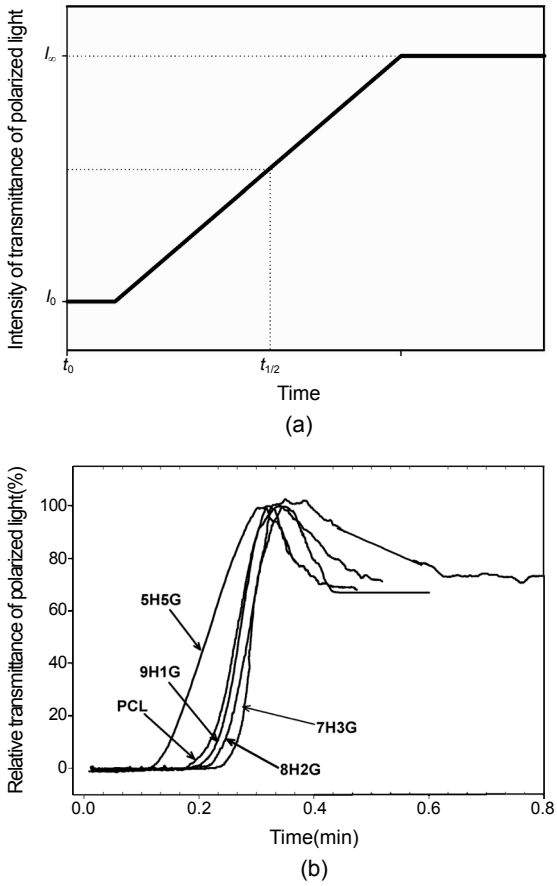

Figure 4. Measurement of transmitted polarized light with time: (a) General plot pattern; (b) result of the measurement with different blend ratios.

α reaches a value of 0.5.

Figure 4 shows the traditional and measured bulk crystallization rate with the composition variation. Some decay of the peak was observed after the maximum peak intensity compared to that of the traditional pattern. This is due to the severe volume contraction of PCL, because the specific volumes of PCL in the amorphous state[23] (v_{sp}=0.9106+(6.013×10^{-4})×T) and perfect crystal state[24] (v_{sp}=0.833) are very different. The peak maximum was selected for the determination of I_∞. The lower crystallization rate of the PEG constituent compared to that of the PCL homopolymer is attributed to the mutual influence between the PEG constituent and the PCL crystal phase. Similar results were reported for a triblock copolymer composed of PCL and PEG.[16] However, this can be changed when the composition of PCL−*g*−PEG occupies 50% of the blend based on weight (5H5G).

The crystallization usually brings about the development of spherulite structure in the system. Optical microscopy of the spherulites is shown in Figure 5. Unlike PCL homo−

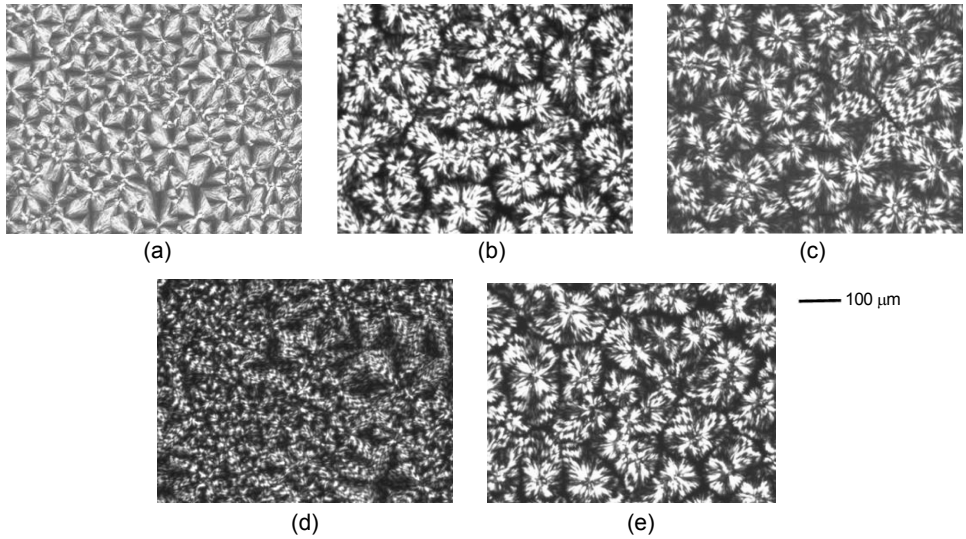

Figure 5. Optical microscope images of the PCL and blend samples(x100): (a) PCL; (b) 9H1G; (c) 8H2G; (d) 7H3G; (e) 5H5G.

polymer, the spherulite structure of the blend showed the alternating periods of the extinction rings in the PCL spherulite. Bands of extinction, or concentric rings, occur from the twisting of crystallographic orientation about the spherulite radii. This phenomenon was also observed for the compatible blend of PCL, poly(vinyl chloride)[25] and triblock copolymer, which has PCL and PEG block.[16] From 9H1G to 7H3G, the amount of extinction bands increased with an increase of graft copolymer composition. However, a decrease in extinction bands was observed for 5H5G compared to 7H3G. This is thought to be due to the increase of the band spacing. No shift in the T_c peak, an abrupt increase of crystallization rate, and a decrease of extinction bands for 5H5G shows that the influence of the PEG unit on the PCL crystal increases with an increase of the graft copolymer when the PCL homopolymer is the main component in the blend (over 50% by weight).

Protein Adsorption Behavior. Proteins adsorb to almost all surfaces during the first few minutes of blood exposure.[26] There has been a substantial amount of effort aimed at minimizing or eliminating protein adsorption, because surfaces which show minimal protein adsorption are important in many applications, including blood-contacting devices, membranes for separation processes, sensors, chromatographic supports, contact lenses, immunoassays, blood and protein storage applications, etc. An effective polymer for protein-resistant surfaces appears to be PEO, probably due to its low interfacial free energy with water and unique solution properties. In order to obtain a non-thrombogenic surface, it is desirable to reduce the adsorption of blood proteins.[27,28] The evaluation of protein adsorption onto the surface of PCL and different blend films was carried out with a BSA protein model, which is commonly used for assessing protein adsorption onto various polymer surfaces. Thus, we observed the adsorption of protein using BCA protein assay method using unlabeled BSA. Figure 6 shows the protein adsorption on the surface of various blend films prepared by blending PCL with PCL-*g*-PEG. As expected, the level of the protein adsorption decreased when the PEG component was introduced, except for 5H5G, which has a blend ratio of PCL/PCL-*g*-PEG of 50/50. In general, PEG is known to prevent protein adsorption. However, there are a few works examining the effect of PEG on protein adsorption on the surface of blend films. Park *et al.* have reported that diblock copolymers that consist of PLGA and PEG (M_w=5000) blend films show higher protein adsorption due to the matrix swelling effect. They insist that, owing to the facile hydration of PEG, incorporation of high molecular weight PEG results in swelling of the matrix. Therefore, they suggest that an optimum molecular weight of PEG

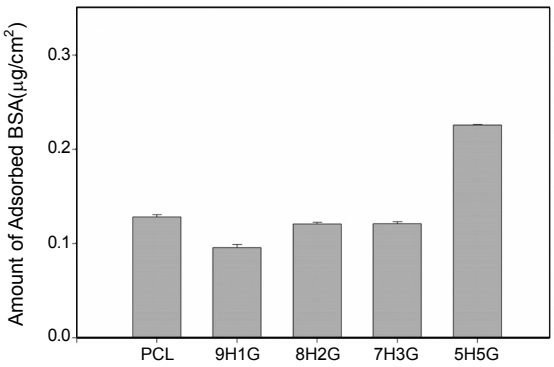

Figure 6. Amount of BSA adsorption on various blend films.

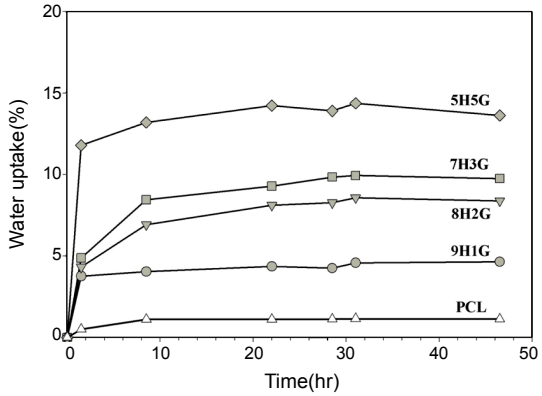

Figure 7. Water uptake of the blend films with the immersion time.

should be used for protein adsorption resistance.[29]

The water uptake profiles of the blend films were measured and shown in Figure 7. The amount of water uptake of the blend films increased with increasing PEG in the blend. The trend of water uptake was the same as that of the water contact angle of the films as shown in Table 1. Although short PEG compared to block copolymers of PCL and PEG were used, a swelling effect also occurred. From the protein adsorption and water uptake results, the amount of PEG in the bulk matrix is an important factor for facile hydration leading to protein diffusion into the matrix.

Conclusions

Novel blend systems based on PCL and PCL−*g*−PEG were prepared. The thermal properties and optical images showed that increasing graft copolymer content in the blend decreased the crystallization rate when PCL was the main component of the blend by weight. The spherulite morphology of PCL was influenced by short PEG chains in the graft copolymer, which resulted in extinction band formation. From the protein adsorption observation of the blend films showed that the composition of the blend effects on the amount of adsorbed protein.

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References

1. H. Sun, L. Mei, C. Song, X. Cui, and P. Wang, *Biomaterials*, **27**, 1735 (2006).
2. C. G. Pitt, F. I. Chasalow, Y. M. Hibionada, D. M. Klimas, and A. Schindler, *J. Appl. Polym. Sci.*, **26**, 3779 (1981).
3. D. R. Chen, J. Z. Bei, and S. G. Wang, *Polym. Degrad. Stabil.*, **67**, 455 (2000).
4. C. J. Goodwin, M. Braden, S. Downes, and N. J. Marshall, *J. Biomed. Mater. Res.*, **40**, 204 (1998).
5. H. Hyun, J. H. Lee, K. S. Seo, M. S. Kim, J. M. Rhee, H. B. Lee, and G. Kang, *Polymer(Korea)*, **29**, 468 (2005).
6. S. J. Park, K. S. Kim, B. G. Min, and S. K. Hong, *Polymer (Korea)*, **28**, 103 (2004).
7. R. Shogren, *J. Polym. Environ.*, **5**, 91 (1997).
8. C. X. Song, H. F. Sun, and X. D. Feng, *Polym. J.*, **19**, 485 (1987).
9. E. J. Choi, C. H. Kim, and J. K. Park, *Macromolecules*, **32**, 7402 (1999).
10. C. H. Kim, K. Y. Cho, and J. K. Park, *Polymer*, **42**, 5135 (2001).
11. J. M. Harris, *Poly(ethylene glycol) Chemistry: Biotechnical and Biomedical Applications*, Plenum Press, New York, 1992.
12. Y. Min, S. Lee, J. K. Park, K. Y. Cho, and S. J. Sung, *Macromol. Res.*, **16**, 231 (2008).
13. J. H. You, S. W. Choi, J. H. Kim, and Y. T. Kwak, *Macromol. Res.*, **16**, 609 (2008).
14. K. Y. Cho and J. K. Park, *Polym. Bull.*, **57**, 849 (2006).
15. J. Rieger, P. Dubois, R. Jerome, and C. Jerome, *Langmuir*, **22**, 7471 (2006).
16. B. Bogdanov, A. Vidts, E. Schacht, and H. Berghmans, *Macromolecules*, **32**, 726 (1999).
17. T. Shiomi, K. Imai, K. Takenaka, H. Takeshita, H. Hayashi, and Y. Tezuka, *Polymer*, **42**, 3233 (2001).
18. B. Ronneberger, W. J. Kao, J. M. Anderson, and T. Kissel, *J. Biomed. Mater. Res.*, **30**, 31 (1996).
19. T. P. Johnston and S. C. Miller, *J. Parenter. Sci. Technol.*, **43**, 279 (1989).
20. J. H. Lee, J. Kopecek, and J. D. Andrade, *J. Biomed. Mater. Res.*, **23**, 351 (1989).
21. J. H. Lee, Y. M. Ju, W. K. Lee, K. D. Park, and Y. H. Kim, *J. Biomed. Mater. Res.*, **40**, 314 (1998).
22. A. J. Nijenhuis, E. Colstee, D. W. Grijpma, and A. J. Pennings, *Polymer*, **37**, 5849 (1996).
23. V. Crescenzi, G. Manzini, G. Calzolari, and C. Borri, *Eur. Polym. J.*, **8**, 449 (1972).
24. Y. Chatani, Y. Okita, H. Tadokoro, and Y. Yamashita, *Polym. J.*, **1**, 555 (1970).
25. S. Nojima, K. Watanabe, Z. Zheng, and T. Ashida, *Polym. J.*, **20**, 823 (1988).
26. S. L. Copper and N. A. Peppas, *Biomaterials: Interfacial Phenomena and Applications*. ACS Press, Washington DC, 1982.
27. E. Ruckenstein and J. H. Chen, *J. Adhes. Sci. Technol.*, **6**, 611 (1992).
28. S. M. Butler, M. A. Tracy, and R. D. Tilton, *J. Control. Release*, **58**, 335 (1999).
29. J. H. Jeong, D. W. Lim, D. K. Han, and T. G. Park, *Colloid. Surface B*, **18**, 371 (2000).