Properties of Crosslinked Blends of Pellethene and Multiblock Polyurethane Containing Poly(ethylene oxide) for Biomaterials

Hye-Jin Yoo, Han-Do Kim

Department of Textile Engineering, College of Engineering, Pusan National University, Busan 609-735, Korea

Received 17 March 2003; accepted 10 June 2003

ABSTRACT: A series of multiblock polyurethanes, containing various poly(ethylene oxide) (PEO; number-average molecular weight = 400–3400) contents (0–80 wt %) and prepared from hexamethylene diisocyanate/PEO/poly(dimethylsiloxane) diol/polybutadiene diol/1,4-butanediol, were used as modifying additives (30 wt %) to improve the properties of biomedical-grade Pellethene. Different molecular weights of PEO were used to keep poly(ethylene glycol) at a fixed molar content, if possible, although the PEO content, related to the PEO block length in the multiblock polyurethanes, was varied from 0 to 80 wt %. The hydrophilic PEO component was introduced through the addition of PEO-containing polyurethanes and dicumyl peroxide as a crosslinking agent in a Pellethene matrix. As the PEO content (PEO block length) increased, the hydrogen-bonding fraction of the crosslinked Pellethene/multiblock polyurethane blends increased, and this indicated an increase in the phase separation with an increase in the PEO content in the crosslinked Pellethene/multiblock polyurethane blends. According to electron spectroscopy for chemical analysis, the ratio of ether carbon to alkyl carbon in the crosslinked Pellethene/multiblock polyurethane blends increased remarkably with increasing PEO content. The water contact angle of the crosslinked Pellethene/multiblock polyurethane blend film surfaces decreased with increasing PEO content. The water absorption and mechanical properties (tensile modulus, strength, and elongation at break) of the crosslinked Pellethene/multiblock polyurethane blend films increased with increasing PEO content. The platelet adhesion on the crosslinked Pellethene/multiblock polyurethane blend film surfaces decreased significantly with increasing PEO content. These results suggest that crosslinked Pellethene/multiblock polyurethane blends containing the hydrophilic component PEO may have potential for biomaterials that come into direct contact with blood. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 91: 2348–2357, 2004

Key words: polyurethanes; biomaterials; polyethylene glycol

INTRODUCTION

Recently, segmented polyurethanes have been widely used for various commercial and experimental blood-contacting and tissue-contacting applications, such as vascular prostheses, blood pumps, heart valves, pacemaker lead wire insulation, catheters, artificial hearts, and cardiac-assist devices, because of their generally favorable physical and mechanical properties and fairly good biocompatibility and antithrombogenicity characteristics.[1–5] Although many successful results have been obtained with polyurethanes in different biomedical devices, the inherent thrombogenicity of segmented polyurethanes remains a problem.[6] Generally, blood coagulates and causes blood clotting when it encounters foreign solid surfaces. This phenomenon is assumed to begin with the initial adsorption of blood proteins, which is followed by platelet adhesion and activation of the coagulation pathway, leading to thrombus formation.[7] Thus, several strategies have been proposed to improve the blood compatibility of biomaterials, such as the incorporation of ionic groups onto the polymeric surface,[8] the alteration of the surface properties by grafting techniques,[9,10] the immobilization of heparin, functionalized dextrans, or biological compounds,[11,12] and the introduction of hydrophilic polymers.

Among hydrophilic polymers, a particularly effective polymer for the prevention of protein adsorption and platelet adhesion appears to be poly(ethylene oxide) (PEO).[7] The hydrophilicity and unique solubility properties of PEO produce surfaces that are in a liquid-like state, with the polymer chains exhibiting considerable flexibility or mobility.[13–16] It is well known that PEO surfaces in water with rapidly moving hydrated PEO chains and a large excluded volume tend to repel protein or platelet molecules that approach the surface.[17] The adsorption of PEO-containing block or graft copolymers is more stable than that of PEO homopolymers because the hydrophobic segments provide hydrophobic adsorption forces or anchors to the polymer substrate. PEO surfaces have been prepared by the physical adsorption of various PEO-containing amphiphilic block or graft copolymers onto

Correspondence to: H.-D. Kim (kimhd@pusan.ac.kr).

Journal of Applied Polymer Science, Vol. 91, 2348–2357 (2004)

TABLE I
Description of Multiblock Polyurethanes Containing PEO

Sample designation	Composition of multiblock polyurethanes (molar ratio)	PEO content (wt %)
A0	HDI/PDMS/PBD/BD (2/0/1.5/0.05/0.45)	0
A20	HDI/PEO(M_n = 400 g/mol)/PDMS/PBD/BD (2/0.9/0.6/0.05/0.45)	20
A40	HDI/PEO(M_n = 1000 g/mol)/PDMS/PBD/BD (2/0.9/0.6/0.05/0.45)	40
A60	HDI/PEO(M_n = 2000 g/mol)/PDMS/PBD/BD (2/1.0/0.5/0.05/0.45)	60
A80	HDI/PEO(M_n = 3400 g/mol)/PDMS/PBD/BD (2/1.1/0.4/0.05/0.45)	80

hydrophobic substrates.[2] However, one problem with these methods is the stability of the PEO additives entrapped in the substrates.

The more stable methods for preparing PEO surfaces include covalent coupling[18–23] and graft copolymerization[24–26] of PEO or PEO-containing materials to substrates, which create permanent PEO surfaces. PEO surfaces have been prepared by the addition of PEO-containing amphiphilic block copolymers (PEO–PPO–PEO) as surface-modifying additives and by the addition of dicumyl peroxide (DCP) as a crosslinking agent in segmented polyurethane.[7]

DCP has been widely used as a crosslinking agent for polyethers such as PEO and poly(propylene oxide) PPO.[27,28] Because the biomedical-grade polyurethane (Pellethene) used in this study contains about 50% polyether soft segments, DCP can be used to obtain random crosslinking of Pellethene and multiblock polyurethanes containing PEO. However, research on the influence of multiblock polyurethanes containing PEO on the properties of crosslinked Pellethene/multiblock polyurethane blends can hardly be found.

In this study, a series of multiblock polyurethanes containing various PEO contents (0–80 wt %; surface-modifying additives) were synthesized from hexamethylene diisocyanate (HDI)/PEO/poly(dimethylsiloxane) diol (PDMS)/polybutadiene diol (PBD)/1,4-butanediol (BD). The PEO surfaces were prepared by the addition of multiblock polyurethanes containing various PEO contents to Pellethene, which was followed by their crosslinking for enhanced blood compatibility. The chemical structure of multiblock polyurethanes containing PEO was examined with ^{1}H-NMR and Fourier transform infrared (FTIR) spectroscopy. The surface properties of the crosslinked Pellethene/multiblock polyurethane blends were investigated with electron spectroscopy for chemical analysis (ESCA) and measurements of the water contact angles. The water absorption and tensile properties of crosslinked Pellethene/multiblock polyurethane blends were also investigated. The blood compatibility of crosslinked Pellethene/multiblock polyurethane blends was evaluated with platelet-rich-plasma (PRP) contact experiments, and the results were observed with scanning electron microscopy (SEM).

EXPERIMENTAL

Materials

A segmented biomedical-grade polyurethane pellet (Pellethene 2363-80AE, Dow Chemical Co., Midland, MI) was used after being washed with methanol for 3 days and being dried in a vacuum oven overnight at 60°C. PEO [number-average molecular weight (M_n) = 400, 1000, 2000, or 3400 g mol^{-1}; Aldrich, Milwaukee, WI] and hydroxy-terminated PDMS (M_n = 1454 g mol^{-1}, Shin-Etsu, Chiyoda-Ku, Tokyo, Japan) were dried for 24 h at 80°C *in vacuo* before use. HDI (Aldrich), PBD (Aldrich), and BD (Aldrich) were used after dehydration with 4-Å molecular sieves for 1 day. DCP (Aldrich) was used as provided.

Synthesis of multiblock polyurethanes (modifying additives)

The appropriate amount of dried PEO (M_n = 400, 1000, 2000, or 3400 g mol^{-1}) and three drops of dibutyltin dilaurate as a catalyst were dissolved in tetrahydrofuran (THF). HDI was slowly added to the solution for 30 min, and the reaction mixture was stirred for 6 h at room temperature. Then, PDMS, PBD, and BD were added separately to the reaction mixture and reacted for 5, 3, and 1 h, respectively. The obtained multiblock polyurethanes were precipitated in η-hexane, after being washed with an excess amount of distilled water for the removal of any unreacted components. They were dried for 2 days at 45°C *in vacuo*. The compositions of the multiblock polyurethanes prepared in this study are given in detail in Table I.

Preparation of crosslinked Pellethene/multiblock polyurethane blend films

Pellethene was dissolved in THF to form 15 wt % solutions. The multiblock polyurethanes (ca. 40 wt % with respect to the dry Pellethene pellet) and DCP (4 wt % with respect to the dry multiblock polyurethane containing PEO) as a crosslinking agent were added to the Pellethene solutions. The polymer blend solutions were agitated homogeneously. Films were prepared via solution casting from the polymer blend solutions. The solvent was slowly evaporated at room tempera-

ture for 2 days in a desiccator cabinet, and this was followed by vacuum drying overnight at 60°C. The crosslinking was performed by the heating of the film in a vacuum oven at 120°C for 3 h.[7]

Characterization

The chemical structures of the multiblock polyurethanes containing PEO that were synthesized in this study were analyzed with ^{1}H-NMR and FTIR spectroscopy. ^{1}H-NMR spectra were obtained on a 300-MHz Fourier transform NMR instrument, which was operated at 300 MHz with dimethyl sulfoxide as a solvent. IR spectra were obtained with a Nicolet Impact 400D computerized FTIR spectrometer. For each sample, two scans at a 2-cm^{-1} resolution were collected in the transmittance mode.

The changes in the chemical structure of crosslinked Pellethene/multiblock polyurethane blend film surfaces were analyzed by ESCA (ESCA 250). The ESCA instrument was equipped with an Al Kα radiation source at 1486.6 eV and 300 W at the anode. Survey scan and C1s core-level scan spectra were taken for an analysis of the film surfaces.

The surface properties of the crosslinked Pellethene/multiblock polyurethane blend films were determined by measurements of the water contact angles. The contact angles were noted from a goniometer (Erma Contact Angle Meter, Japan) by a water droplet (3 μL) being carefully placed on the surface. The angles were noted immediately after 3 min on both sides of each drop. The contact angle, a measure of the surface wettability, was used to determine the hydrophobicity and hydrophilicity.

The swelling property of the crosslinked Pellethene/multiblock polyurethane blend films was examined by the measurement of the water absorption content. The films were weighed after drying (W_{dry}) and being immersed in purified water. After 1 day and 7 days, the films were taken out of the water, wiped dry with tissue paper, and weighed again immediately (W_{wet}) after drying. The water absorption was determined as follows :

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

The stress–strain measurements were carried out in a sample extension on dumbbell specimens with a tensile tester (SSTM-1 United Data System, Instron, Japan) at a crosshead speed of 20 mm/min.

Platelet adhesion

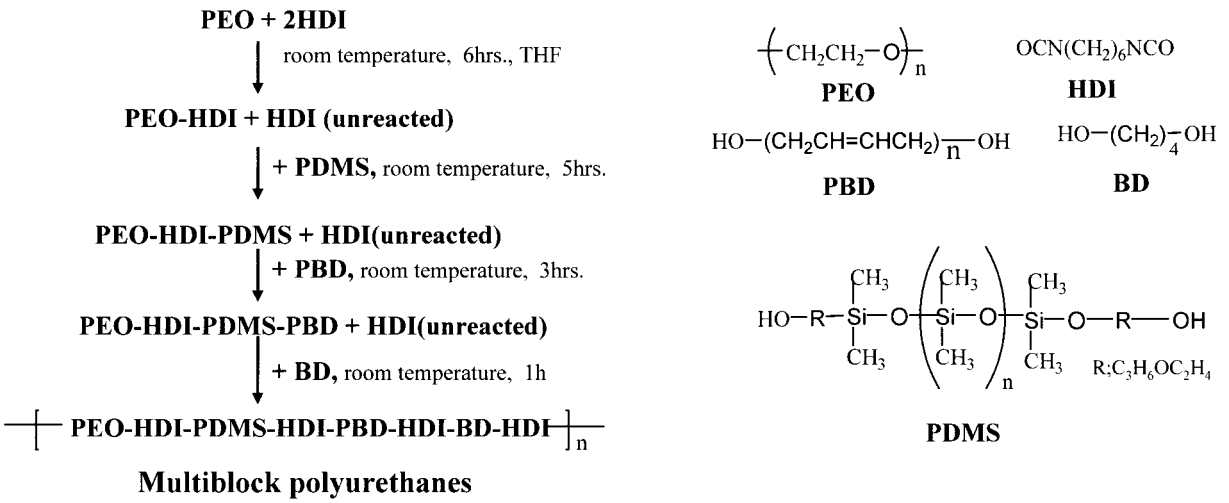
The test procedure for platelet adhesion was described previously.[27,28] Briefly, human whole blood was collected from healthy human donors in sodium citrate (3.8%), which was used as an anticoagulant. PRP was obtained by centrifugation of the blood at 1500 rpm for 20 min. The crosslinked Pellethene/multiblock polyurethane blend films were hydrated with a phosphate-buffered saline (PBS; pH 7.4) solution overnight. After the removal of the buffer solution, 1 mL of PRP, in which the platelet density was adjusted to 1.17 $\times$ 10^5/μL, was added, and the films were rotated for 3 h at 37°C in a shaking incubator. The number of platelets in the resulting PRP was countered immediately with a Coulter counter (blood cell calculator). PRP incubated without films was used as a reference. The platelet adhesion was determined from the percentage of the final number of platelets adhering to the film surface against the reference value. For the SEM observations, the adsorbed platelets were rinsed three times with PBS, and then they were fixed on the surfaces by the immersion of the films in 2.5 vol % glutaraldehyde at room temperature for 2 h. The platelets adhering to the surfaces were dehydrated after treatment with ethanol/distilled water mixtures (from 50 to 100% ethanol, in 10% increments, 10 min per step), and then they were dried at room temperature. The dried films were coated with evaporated gold, and the adherent platelets were observed with SEM (model 4200, Hitachi, Japan).

RESULTS AND DISCUSSION

Synthesis and characterization of multiblock polyurethanes

Multiblock polyurethanes with various PEO contents (0–80 wt %) were prepared from HDI/PEO/PDMS/PBD/BD, as shown in Scheme 1. So that the moles of poly(ethylene glycol) (PEG) remained constant, if possible, different molecular weights of PEO (M_n = 400–3400) were used in this study, although the PEG content in the multiblock polyurethane was varied from 0 to 80 wt % (Table I). Therefore, the increase in the PEG content was related to the increase in the PEG block length. Figure 1 shows the FTIR spectra of multiblock polyurethanes. The multiblock polyurethanes showed characteristic peaks of the Si—CH_3 stretching band at 1260 and 1095, the Si—O—Si stretching band at 1023 cm^{-1}, the N—H stretching band at 3310 cm^{-1}, the C═O stretching band at about 1700–1725 cm^{-1}, the —CH_2— stretching band at 1460 and 770 cm^{-1}, and the CH═ stretching band at about 1630–1690. The characteristic peaks of PEO at 1413, 1359, 1343, and 843 cm^{-1} increased with increasing PEO content. The structures of the multiblock polyurethanes synthesized in this study were identified from these characteristic peaks.

The ^{1}H-NMR spectrum of a typical multiblock polyurethane (MP-A40) is presented in Figure 2. The characteristic peaks corresponding to the methylene group in the PEO block at 3.63 ppm, the methyl group in



Scheme 1 Synthetic procedure for multiblock polyurethanes.

PDMS at 0 and 1.2 ppm, and CH═ and CH_2 of PBD at 2.4 and 5.8 ppm can be observed, confirming the structures (compositions) of the crosslinked Pellethene/multiblock polyurethane blends. The methylene group peak of PEO at 3.63 ppm was increased with increasing PEO content in the crosslinked Pellethene/multiblock polyurethane blends.

The sample designations, PEO contents, hydrogen-bonding fractions (X_B's), ESCA results, and mechanical properties of the crosslinked Pellethene/multiblock polyurethane blend films are shown in Table II. The PEO content of the crosslinked Pellethene/multiblock polyurethane blend films was varied from 0 to 80 wt % at a fixed blending ratio (30 wt %) of the multiblock polyurethanes. Figure 3 shows the decomposition of C═O and N—H stretching bands of the IR spectrum for a control Pellethene film. X_B was calculated from the total peak area (C_T) and the peak area of hydrogen-bonding C═O or N—H groups (C_B) as follows: $X_B = C_B/C_T$, where C_T is equal to $a + b + c$ for C═O and $a + b$ for N—H and C_B is equal to $b + c$ for C═O and b for N—H. The X_B values for all the samples prepared in this study are shown in Table II. The $X_{B\ C=O}$ and $X_{B\ N-H}$ values of the crosslinked Pellethene/multiblock polyurethane blend films increased with increasing PEO content (or PEO block length). As the amount of PEO incorporated into Pellethene was increased, X_B of the crosslinked Pellethene/multiblock polyurethane blends increased, and this suggested an increase in the phase separation with an increase in the PEO content in the crosslinked Pellethene/multiblock polyurethane blends. This increase may be attributed to the increase in the PEG block length. X_B values are known to be related to the phase separation and mechanical properties of polyurethane.[29]

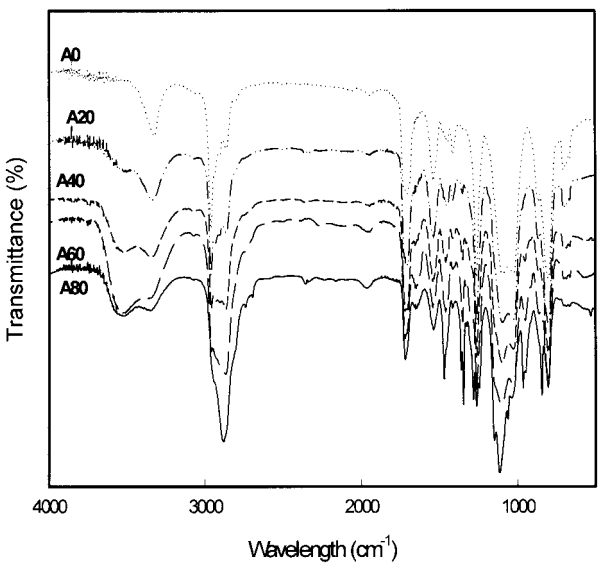


Figure 1 IR spectra of multiblock polyurethanes.

Surface characterization of crosslinked Pellethene/multiblock polyurethane blend films

To prevent the platelet adhesion of Pellethene, we crosslinked Pellethene with a series of multiblock polyurethanes containing the hydrophilic component PEO and DCP as a crosslinking agent. In our preliminary study, we observed that the water contact angles of the crosslinked Pellethene/multiblock polyurethane blend film surfaces decreased with increasing multiblock polyurethane content up to 30 wt %, and no further significant increase in the contact angles was found at a higher PEO content. This indicated that surface saturation might have occurred at a multiblock polyurethane content of approximately 30 wt %. Therefore, we fixed the blending percentage of the

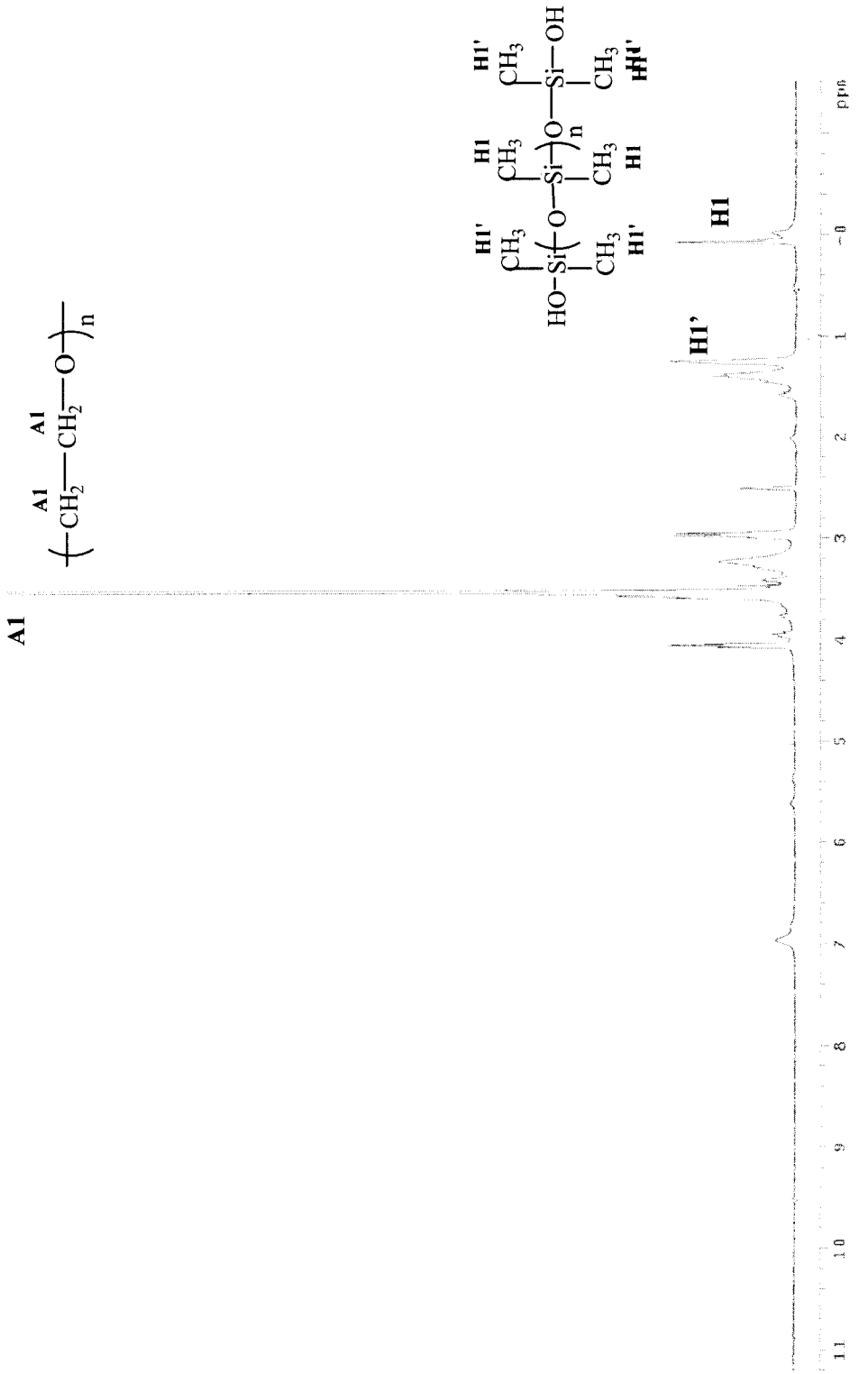


Figure 2 ^{1}H-NMR spectrum of a typical multiblock polyurethane (MP-A40).

TABLE II
Sample Designation, PEO Content, X_B, ESCA Results, and Mechanical Properties of Crosslinked Pellethene/Multiblock Polyurethane Blend Films

Sample designation	Component[a]	PEO content (%)	X_B (C═O)	X_B (N—H)	Atomic %[b] C	O	N	—C—O—/—C—C—[c]	Initial tensile modulus (MPa)	Tensile strength (MPa)	Elongation at break (%)
P (Pellethene)	Pellethene		0.627	0.510	74.7	21.6	3.7	0.16	85	55	788
MP-A0	P/A0	0	0.639	0.522					90	61	914
MP-A20	P/A20	5	0.640	0.535					129	67	950
MP-A40	P/A40	10	0.651	0.549	73.4	23.1	3.5	0.52	118	72	1066
MP-A60	P/A60	15	0.665	0.558					166	75	1057
MP-A80	P/A80	20	0.679	0.591	64.8	24.5	3.4	0.99	246	81	1348

X_B(C═O) = hydrogen-bonding fraction for FTIR C═O stretching band; X_B(N—H) = hydrogen-bonding fraction for FTIR N—H stretching band.
[a] Blending ratio (%) of multiblock polyurethanes (A0, A20, A40, A60, A80); 30 wt %.
[b] Analyzed from survey scan spectra (ESCA).
[c] Analyzed from C1s core-level scan spectra (ESCA).

multiblock polyurethanes with PEO of various molecular weights at 30 wt % in this study. The crosslinked Pellethene/multiblock polyurethane blend films after heating (120°C, 3 h) with DCP were insoluble in THF (a cosolvent for Pellethene and multiblock polyurethanes), whereas the Pellethene/multiblock polyurethane blend films were soluble in THF after the same treatment without DCP. This indicated that the heat treatment (120°C, 3 h) with DCP was an effective condition for the crosslinking of the multiblock polyurethanes and Pellethene matrix.

The chemical structure of the crosslinked Pellethene/multiblock polyurethane blend film surfaces was analyzed with ESCA. Figure 4 shows the ESCA C1s spectra of Pellethene MP-A40 and MP-A80 samples. These samples had alkyl carbon (—*C*—C—, binding energy ~ 285.0 eV), ether carbon (—C—O—, binding energy ~ 286.6 eV), and carboxylic carbon (O═*C*—O—, binding energy ~ 289.1 eV) peaks. However, the peak intensity of ether carbon increased with increasing PEO content (see Table II). The increase in the ether carbon peak was derived from the PEO component of the crosslinked Pellethene/multiblock polyurethane blend film surfaces because all the carbons in PEO were ether carbons. The oxygen content and the ether carbon/alkyl carbon ratio of the surfaces also increased as the PEO content increased.

Hydrophilicity of crosslinked Pellethene/multiblock polyurethane blend film surfaces

Because blood comes into contact with biomaterial surfaces, the hydrophilicity of biomaterials is very

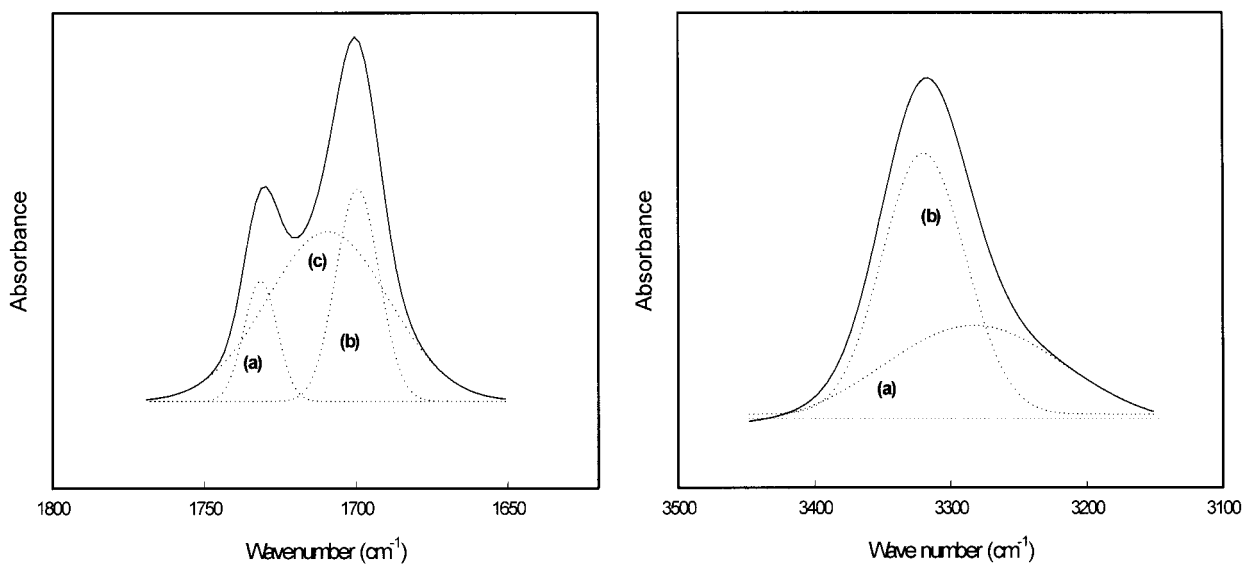


Figure 3 Decomposition of C═O and N—H stretching of Pellethene films.

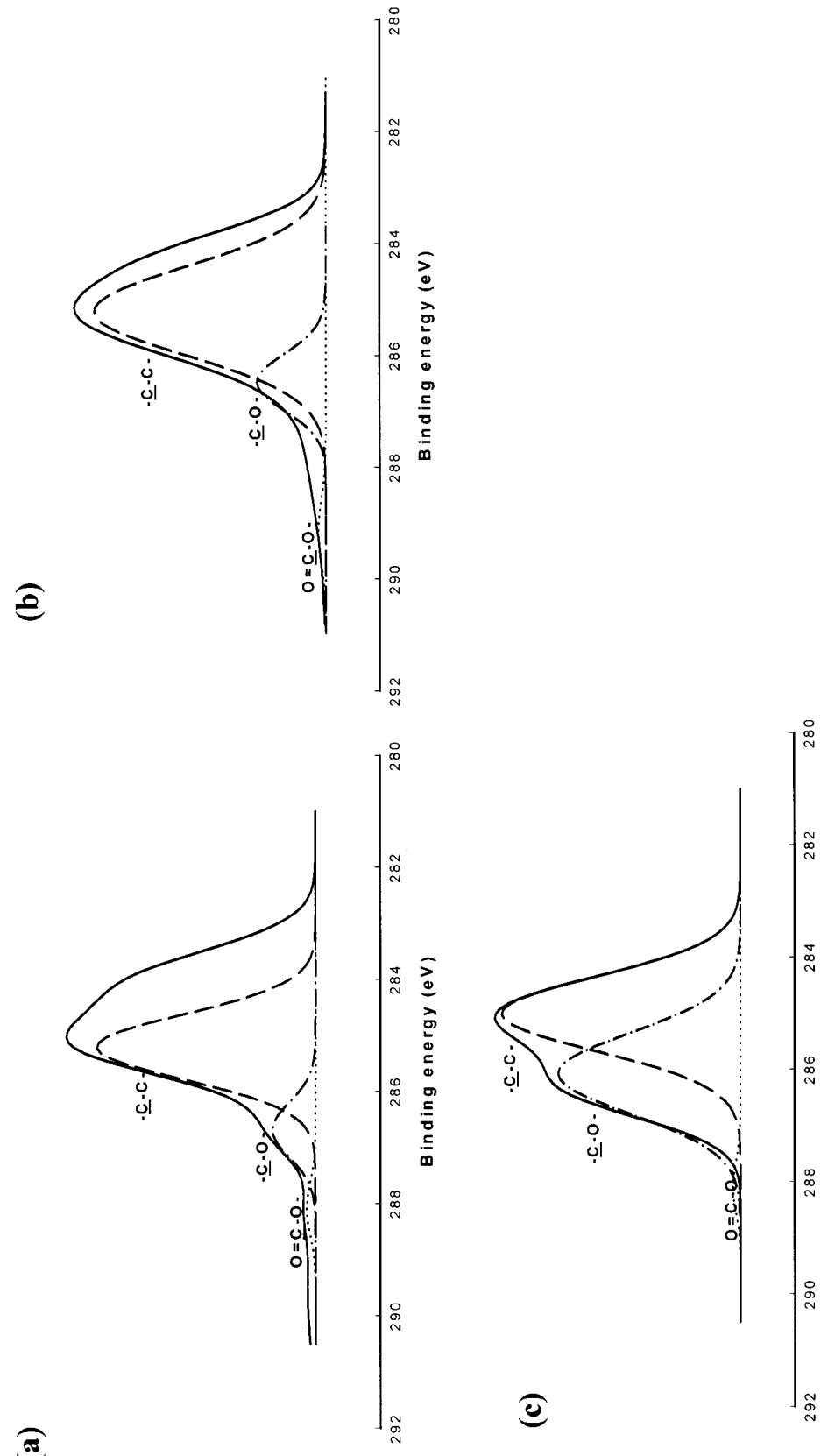


Figure 4 ESCA C1s core-level scan spectra of Pellethene and crosslinked Pellethene/multiblock polyurethane blend film surfaces: (a) Pellethene, (b) MP-A40, and (c) MP-A80.

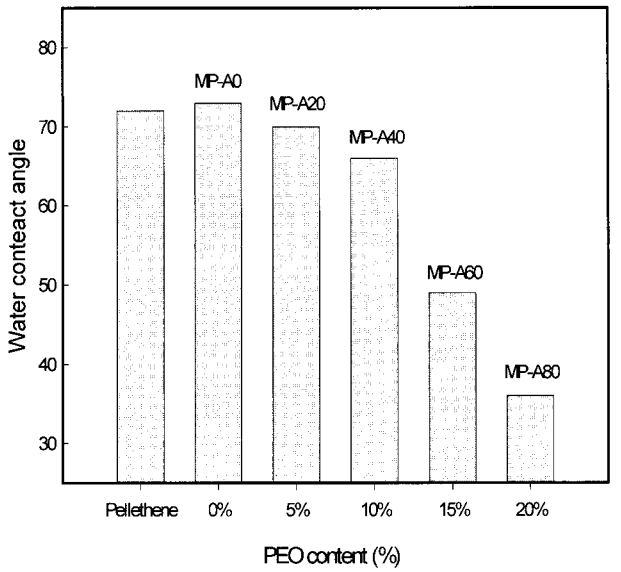


Figure 5 Water contact angles of crosslinked Pellethene/multiblock polyurethane blend films.

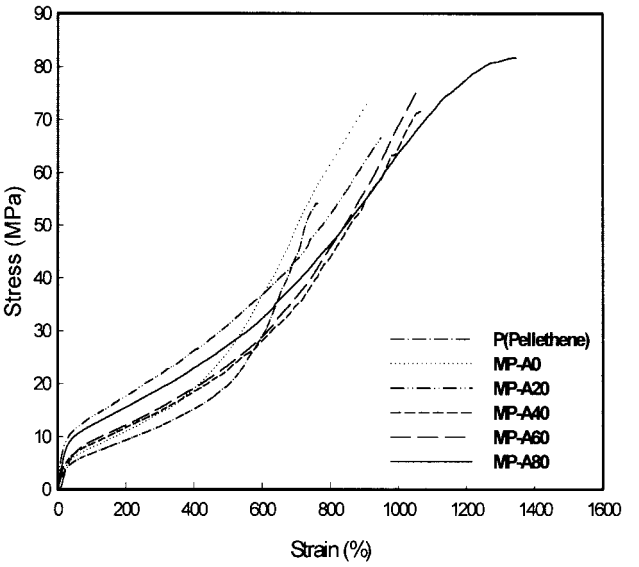


Figure 7 Stress–strain curves of crosslinked Pellethene/multiblock polyurethane blend films.

important for biocompatibility. The water contact angles of crosslinked Pellethene/multiblock polyurethane blend film surfaces are shown in Figure 5. The water contact angles on the surfaces decreased with increasing PEO content. The hydrophilicity of the samples was proportional to the PEO content of the crosslinked Pellethene/multiblock polyurethane blends. This phenomenon may be due to the hydrophilic PEO chains extended into the water phase.

Figure 6 shows the relationship between the water absorption (immersion time = 24 or 48 h) and the PEO content in crosslinked Pellethene/multiblock polyurethane blend films. Generally, the interfacial free energy with water (or blood) is related to the hydrophilicity of a biomaterial, and its value decreases with increasing hydrophilicity. Thus, the swelling property of biomaterial films may be an important parameter in many applications. The swelling property of crosslinked Pellethene/multiblock polyurethane blend films was examined by the measurement of the water absorption after immersion in purified water for 24 or 48 h. The water absorption of the crosslinked Pellethene/multiblock polyurethane blend films increased remarkably with increasing PEO content. This was attributed to the hydrophilic PEO component in the crosslinked Pellethene/multiblock polyurethane blend films.

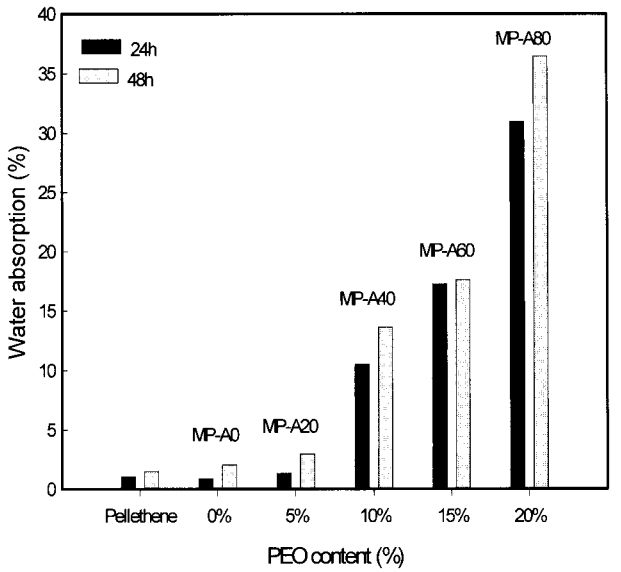


Figure 6 Water absorption of crosslinked Pellethene/multiblock polyurethane blend films after immersion in water for 24 and 48 h.

Mechanical properties of crosslinked Pellethene/multiblock polyurethane blend films

The stress–strain curves of crosslinked Pellethene/multiblock polyurethane blend films are shown in Figure 7. The mechanical properties (tensile modulus, strength, and elongation at break) of control Pellethene and crosslinked Pellethene/multiblock polyurethane blend films are compared in Table II. The Pellethene film had a tensile modulus of 85 MPa, a tensile strength of 54 MPa, and an elongation at break of 787.8%. These properties of the crosslinked Pellethene/multiblock polyurethane blend films were higher than those of the control Pellethene film and increased with increasing PEO content (or PEO chain length). The increase in these properties may have been due to the increase in X_B and the increase in the

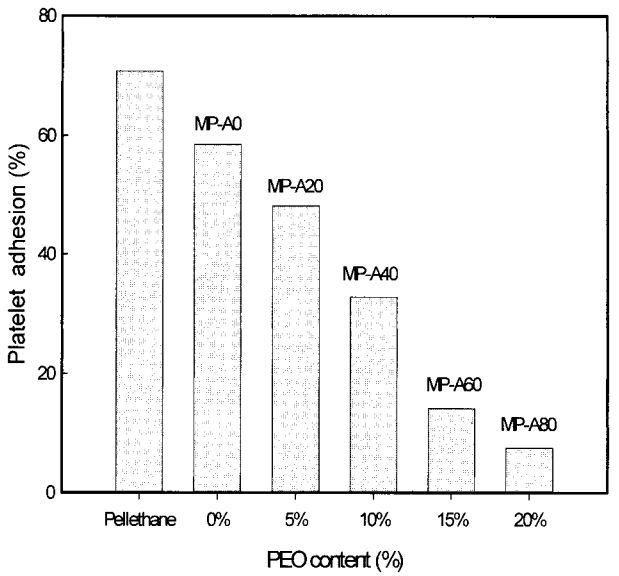


Figure 8 Platelet adhesion on crosslinked Pellethene/multiblock polyurethane blend film surfaces.

flexibility (or mobility) of PEO molecular chains with increasing PEO content (or PEO chain length) in the crosslinked Pellethene/multiblock polyurethane blend films.

Interaction of platelets with crosslinked Pellethene/multiblock polyurethane blend film surfaces

The platelet adhesion results for control Pellethene and crosslinked Pellethene/multiblock polyurethane blend films are shown in Figure 8. As expected, the highest adhesion was observed on the control Pellethene surface, and PEO component significantly affected platelet detachment. The platelet adhesion decreased markedly with increasing PEO content in the crosslinked Pellethene/multiblock polyurethane blend films. These results seem to be related to the hydrophilic surface properties of the crosslinked Pellethene/multiblock polyurethane blend films. Figure 9 shows SEM micrographs of samples. The number of adhered platelets significantly decreased when PEO was introduced into the crosslinked Pellethene/multiblock polyurethane blend films. From these results, it was found that the crosslinked Pellethene/multiblock polyurethane blend films containing the hydrophilic component PEO were much more resistant to platelet adhesion than the control Pellethene.

CONCLUSIONS

Multiblock polyurethanes with various PEO contents (0–80 wt %) were synthesized from HDI/PEO/PDMS/PBD/BD. For improved blood compatibility, crosslinked Pellethene containing the hydrophilic component PEO was prepared through a crosslinking reaction of Pellethene and multiblock polyurethanes with DCP as a crosslinking agent. As the PEO content increased, the contact angle of the crosslinked Pellethene/multiblock polyurethane blend films decreased, but water absorption increased remarkably. Also, the mechanical properties (tensile modulus, strength, and elongation at break) of the crosslinked

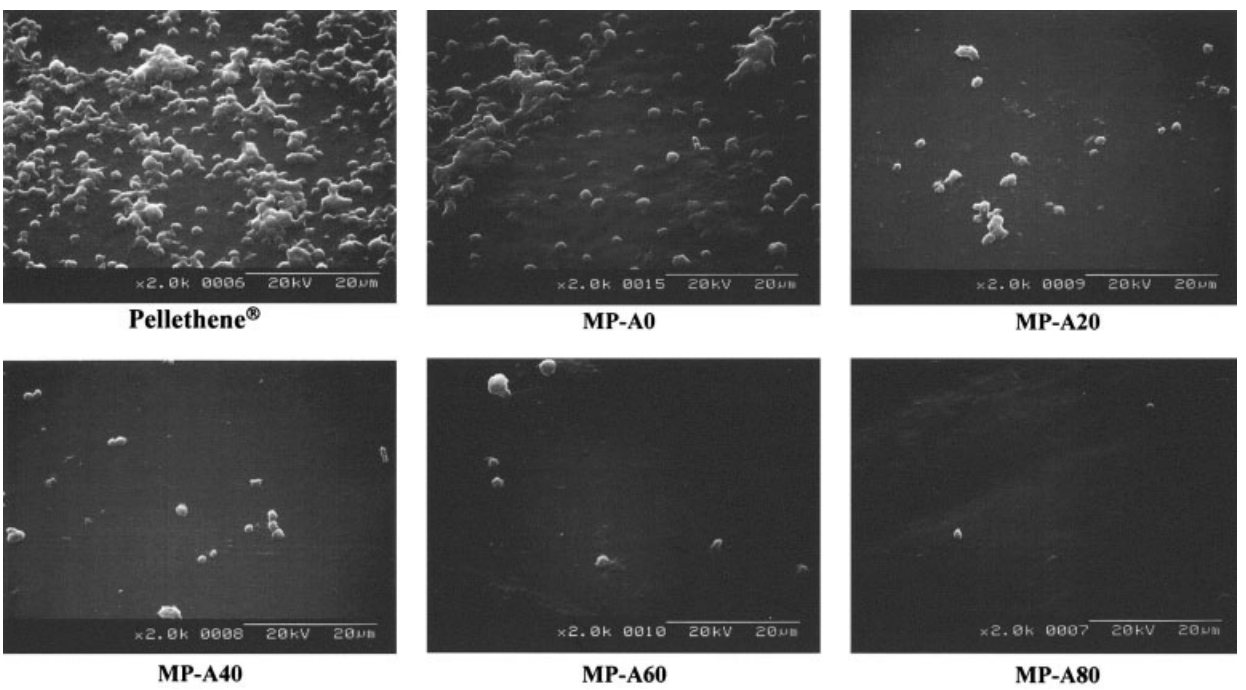


Figure 9 SEM micrographs of platelets adhering to crosslinked Pellethene/multiblock polyurethane blend film surfaces.

Pellethene/multiblock polyurethane blend films increased with increasing PEO content. By platelet adhesion testing, we observed that the platelet adhesion on the crosslinked Pellethene/multiblock polyurethane blend film surfaces decreased with increasing PEO content. These results indicated that the blood compatibility of the crosslinked Pellethene/multiblock polyurethane blends was generally better than that of the Pellethene film. These results suggest that crosslinked Pellethene/multiblock polyurethane blends containing the hydrophilic component PEO may have potential as new materials for biomedical applications that come into direct contact with blood.

References

1. Korematsu, A.; Takemoti, Y.; Nakaya, T.; Inoue, H. Biomaterials 2002, 23, 263.
2. Park, K. D.; Kim, Y. S.; Han, D. K.; Kim, Y. H.; Lee, E. H.; Suh, H.; Choi, K. S. Biomaterials 1998, 22, 851.
3. Cooper, S. L. J Biomater Sci Polym Ed 1999, 10, 679.
4. Lelah, M. D.; Cooper, S. L. Polyurethanes in Medicine; CRC: Boca Raton, FL, 1986; p 149.
5. Li, Y. J.; Nakaya, T.; Zhang, Z.; Kodama, M. J Biomater Appl 1997, 12, 167.
6. Abraham, G. A.; Roman, J. S. Biomaterials 2002, 23, 1625.
7. Lee, J. H.; Ju, Y. M.; Kim, D. M. Biomaterials 2000, 21, 683.
8. Han, D. K.; Park, K. D.; Kim, Y. H. J Biomater Sci Polym Ed 1998, 9, 163.
9. Ikada, Y. Biomaterials 1994, 15, 725.
10. Uyama, Y.; Kato, K.; Ikada, Y. Adv Polym Sci 1998, 137, 3.
11. Marconi, W.; Galloppa, A.; Mattinell, A.; Piozzi, A. Biomaterials 1995, 16, 449.
12. Logeart-Aviamoglou, D.; Jozefonvicz, J. J Biomed Mater Res Appl Biomater 1999, 48, 578.
13. Bailey, F. E.; Koleske, J. Y. Poly(ethylene oxide); Academic: New York, 1976; p 209.
14. Kjellander, R.; Florin, E. J Chem Soc Faraday Trans 1 1981, 77, 2053.
15. Merrill, E. W.; Salzman, E. W. Am Soc Artif Intern Org J 1983, 6, 60.
16. Andrade, J. D.; Nagaoka, S. S.; Okano, T.; Kim, S. W. Am Soc Artif Intern Org J 1987, 10, 75.
17. Lee, J. H.; Kim, S. H. Polymer (Korea) 1997, 21, 332.
18. Brinkaman, E.; van der Does, L.; Bantjes, A. Biomaterials 1990, 11, 200.
19. Horbett, T. A.; Ratner, B. D.; Schway, M. B.; Haque, Y. J Colloid Interface Sci 1993, 27, 1559.
20. Jansen, B.; Ellinghorst, G. J Biomed Mater Res 1985, 19, 1085.
21. Fujimoto, K.; Inoue, H.; Ikada, Y. J Biomed Mater Res 1993, 27, 1559.
22. Jeong, B. J.; Lee, H. J Colloid Interface Sci 1996, 178, 757.
23. Lee, J. H.; Jeong, B. J.; Lee, H. J Biomed Mater Res 1997, 34, 105.
24. Lee, J. H.; Kopecek, J.; Andrade, J. D. J Biomed Mater Res 1989, 23, 351.
25. Lee, J. H.; Kopeckova, P.; Andrade, J. D. Biomaterials 1990, 11, 455.
26. Amiji, M.; Park, K. Biomaterials 1992, 13, 682.
27. Park, J. H.; Park, K. D.; Bae, Y. H. Biomaterials 1999, 20, 943.
28. Li, Y. J.; Mattews, K. H.; Kodama, M.; Nakaaya, T. Macromol Chem Phys 1995,196, 143.
29. Yang, J. E.; Kong, J. S.; Park, S. W.; Lee, D. J.; Kim, H. D. J Appl Polym Sci 2002, 86, 2375.