

Polyether-Segmented Nylon Hemodialysis Membranes. III. Preparation and Properties of New Polyether-Segmented Nylon

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ABSTRACT: In order to apply a blood-compatible polymer to hemodialysis membrane, a new polyether-segmented nylon which dissolved in common organic solvents was designed. The basic polyether-segmented nylon was synthesized by melt polycondensation from sebacic acid, *m*-xylenediamine, and α,ω -bisaminopropyl-poly(ethylene oxide). To improve the solubility, azelaic acid and hexamethylenediamine were copolycondensed with the basic copolymer. The solubility was correlated with the heat of fusion (ΔH_m) of the copolymer. When ΔH_m is < 30 mJ/mg, the polymer is soluble in dimethylsulfoxide and makes a stable solution. The nonthrombogenicity was investigated in the viewpoint of adhesion of platelet onto the copolymer surface. It is made clear that the surface of the block copolymer, having > 10 wt % of poly(ethylene oxide), suppresses the adhesion of platelet, and the composition of the nylon block has no effect on the adhesion of platelet. © 1997 John Wiley & Sons, Inc. *J Appl Polym Sci* **65**: 1723–1729, 1997

Key words: polyether-segmented nylon; preparation; solubility; DSC; platelet adhesion

INTRODUCTION

Recently, as hemodialysis membranes, synthetic membranes have been paid attention to because of their good blood compatibility and good permeability characteristics for rather large molecular weight substances. However, the materials of the membranes are polysulfone, ethylene-vinylalcohol copolymer, polymethylmethacrylate, and polyacrylonitrile, which are produced as industrial materials, and are not designed to improve the biocompatibility. On the other hand, many kinds of block copolymers have been investigated as biomedical materials. For instance, 2-hydroxyethyl methacrylate (HEMA)-styrene block copolymer, polyether-segmented nylon, and polyether-segmented polyure-

thane are mentioned. Especially, polyether-segmented nylon 610 (PE-Ny610) shows good nonthrombogenicity in terms of the suppression of the adhesion of platelet onto its surface.^{1–6} This polymer has been expected to be applied to medical equipment produced by means of melt compression and has recently been put to practical use as an intravenous catheter.⁷ As this polyether-segmented nylon has a linear aliphatic nylon block which is easy to crystallize, it does not dissolve in common organic solvents such as dimethylsulfoxide, dimethylformamide, and *N*-methylpyrrolidone, but dissolves special solvents such as formic acid, cresol, hexafluoroisopropanol, and methanol saturated with calcium chloride. In previous articles,^{8,9} we have reported on poly(propylene oxide) (PPO)-segmented nylon 610 (PPO-Ny610) and poly(ethylene oxide) (PEO)-segmented nylon 610 (PEO-Ny610) hemodialysis membranes prepared by the phase inversion method, and have concluded that these materials

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make a skin layer composed of crystallite at the top surface of the membrane because of liquid-solid phase separation at the top surface in the membrane formation process, and thus these membranes do not exhibit enough permeation characteristics. Therefore, it is important to prevent the top surface from having the skin layer composed of crystalline polygon plates. In order to apply the polyether-segmented nylon to hemodialysis, it is necessary to design the nylon block having lower crystallinity or stable amorphous state. We investigated the polyether-segmented nylon (random copolyamide) based on nylon M10. The synthesis, characterization, solubility, and nonthrombogenicity of the polyether-segmented nylon are reported.

EXPERIMENTAL

Materials

α,ω -Bisaminopropyl-poly(ethylene oxide) ($M_n = 2000$, PEO-amine), *m*-xylenediamine (*M*), hexamethylenediamine (6), azelaic acid (9), and sebacic acid (10) were purchased from Kawaken Fine Chemicals (Japan), Mitsubishi Gas Chemical (Japan), Toray (Japan), Wako Pure Chemistry (Japan), and Houkoku Corporation (Japan), respectively. These monomers were used without further purification.

Polymerization

In this study, the series of the PEO-segmented nylons (PEO-Ny) and homo nylon were synthesized by melt polycondensation of diamines and dicarbonic acids. The typical synthetic method of poly(ethylene oxide) segmented nylon, PEO-(10%)-Ny69/M10(1 : 9) is described briefly, where the abbreviation, PEO(10%)-Ny69/M10-(1 : 9) means that PEO content is 10 wt % and the feed ratio of nylon 69 salt to nylon M10 salts is 10 : 90 wt/wt. First, the aqueous solution of the nylon salts composed of dibasic acids and diamines was prepared. Namely, 2.25 g of nylon 69 salt, 20.25 g of nylon M10 salt, and 2.5 g of PEO-amine were added to 40 g of distilled water in a 100-mL glass tube. The molar balance between the diamines and dicarbonic acids was adjusted by adding small amounts of sebacic acid to the solution to have pH = 7.1 when the solution was diluted to 1 wt %. After the glass tube was set in an autoclave, the melt condensation was performed by two steps. In the first step, the polycon-

densation was carried out under the pressure of 8 kg/cm² at 240°C for 4 h after concentrating nylon salt solution by the distillation of water under the pressure of 8–10 kg/m². The second step was reduced pressure reaction under the conditions of 200 mmHg at 240°C for 2 h. Then the polymer was obtained.

Characterization

Specific viscosities of polymers were determined at 1.0 g/dL concentration in *m*-cresol at 30°C using an Ubbelohde viscometer. The specific viscosity is defined as follows.

$$\eta_{sp} = (\eta - \eta_o)/\eta_o$$

where η is a viscosity of polymer solution and η_o is a viscosity of a solvent.

¹H-NMR spectra were measured at 400 MHz (Varian Unity Plus 400, USA) by using dimethylsulfoxide (DMSO)-d₆ solution of the block copolymers at 80°C.

The glass transition point and melting point were studied using the differential scanning calorimeter (DSC-50, Shimadzu, Japan). The measurements were carried out on samples of ~ 5 mg under nitrogen atmosphere. The samples were heated, quenched by liquid nitrogen, and then heated in the DSC cell from -110°C to 220°C at the rate of 10°C/min.

Solubilities

The solubilities of the nylon and PEO-segmented nylon were investigated at 60, 80, and 100°C in dimethylsulfoxide (DMSO). The polymer (0.1 g) was suspended in 4.9 g of DMSO. After the mixture was stirred with a magnetic stirrer chip for 5 h at each temperature, the states of the polymers, unchanged, swelled, highly swelled, or solved, were observed.

In Vitro Evaluation of Nonthrombogenicity

As the detailed method was described previously,⁸ brief measurement methods are mentioned below. The polymer films used were prepared by casting 5 wt % polymer solution of hexafluoroisopropanol onto a petri dish and evaporating the solvent under atmosphere at room temperature. Citrated platelet-rich human plasmas (PRP) were placed on the polymer films at room temperature under

static conditions. After the fixation of the cell on the film surface, the samples were observed under the SEM at a magnification of 1,000 and five micrographs of the film surfaces were taken at random. Adhering platelets in each picture were counted and the numbers summed up for five pictures were the numbers of adhering platelets.

RESULTS AND DISCUSSION

In order to prepare a high-performance membrane in dialysis and ultrafiltration, the phase inversion method is very important. The method is that the polymer solution is immersed into the nonsolvent bath to coagulate the polymer. The polyether-segmented nylon known as the non-thrombogenic material is composed of a linear aliphatic nylon, Ny610, and polyether. We have already reported that this polymer is dissolved in only special solvents, such as formic acid, hexafluoroisopropanol, and methanol saturated with calcium chloride because of its high crystallinity.⁸ It has been reported by Cheng, Dwan, and Gryte¹⁰ that linear aliphatic nylons such as nylon 66 have a tendency to give liquid-solid phase separation at the top surface of the membrane in the phase inversion process. This liquid-solid phase separation is known to be induced strongly by the high crystallinity of the polymer. As such membranes have large spherulites, the high permeability is not expected. To avoid liquid-solid phase separation, it is important to change the linear nylon block to a nylon block having low crystallinity or stable amorphous state. This modification will also bring about the improvement of the polymer solubility for common organic solvents such as DMSO, dimethylformamide, dimethylacetamide, and *N*-methylpyrrolidone.

In order to disturb the crystallinity of nylon block of PEO-Ny610, the replacement of a part of the diamine component (hexamethylenediamine) in the Ny610 segment with *m*-xylenediamine was

investigated. In isomorphous copolymers, the increase of the comonomer brings about the decrease of the crystallinity and melting point, and they reach the minimum point when the substitution of the diamine is ~ 50 mol %. *m*-Xylenediamine can introduce the bending part in the nylon main chain, and therefore the decrease of its crystallinity will be expected. The solubility and the thermal behavior of PEO-Ny610, PEO-NyM10, and PEO-Ny610/M10, whose feed ratio of nylon 610 salt to nylon M10 salt was 50 : 50 (wt/wt), were investigated. The results are listed in Table I. The incorporation of *m*-xylenediamine into Ny610 block reduced its melting point (T_m) from 220 to 184.9°C. This temperature is lower than that of PEO-NyM10, but the heat of fusion (ΔH) for PEO-Ny610/M10 is significantly larger than PEO-NyM10, and is close to the one for PEO-Ny610. This result indicates that PEO-NyM10/610 has high crystallinity, like PEO-Ny610. That is, the incorporation of only *m*-xylenediamine into Ny610 block is inadequate to decrease the crystallinity of the nylon block. Indeed, PEO-NyM10/610 is insoluble in DMSO in 100°C, although PEO-NyM10 dissolves in DMSO under the same condition. From these results, it is concluded that co-nylons based on NyM10 have a high possibility to dissolve in common organic solvents.

It is well known that the incorporation of odd (even) number monomers to even (odd) number nylons induces a drastic decrease of the crystallinity because of the obstruction of intermolecular hydrogen bonding between amide groups. Therefore, the incorporation of azelaic acid and hexamethylenediamine, having an odd carbon number, 9, and even carbon number, 6, respectively, to the nylon block was investigated. The melt polycondensations of PEO-diamine and nylon salts composed of low molecular weight diamines and dicarboxylic acids were carried out at 240°C. The feed ratios of each nylon salt, the abbreviation of polyether-segmented nylons, and the result of the polycondensations are listed in Table II. As

Table I Effect of Copolymerization on Thermal Behaviors and Solubility

Polymer	T_m (°C)	ΔH (mJ/mg)	Solubility ^a
PEO(10%)-Ny610	220.0	55	insoluble
PEO(10%)-Ny610/M10(5 : 5 ^b)	184.9	49	insoluble
PEO(10%)-NyM10	188.6	30	soluble

^a Solubility in DMSO at 100°C.

^b Feed ratio of nylon 610 salt to nylon M10 salt (wt/wt).

Table II Feed Ratio of Comonomer and Polymerization Results

Polymer (Abbreviation)	PEO (wt %)	Feed Ratio of Nylon 69 Salt to Nylon M10 Salt (wt/wt)	Specific Viscosity
PEO(5%)-NyM10	5	0 : 100	1.09
PEO(10%)-NyM10	10	0 : 100	1.74
PEO(20%)-NyM10	20	0 : 100	1.60
PEO(40%)-NyM10	40	0 : 100	1.12
PEO(10%)-Ny69/M10(1 : 9)	10	10 : 90	1.15
PEO(20%)-Ny69/M10(1 : 9)	20	10 : 90	2.03
PEO(10%)-Ny69/M10(3 : 7)	10	30 : 70	2.58
PEO(10%)-Ny69/M10(5 : 5)	10	50 : 50	2.29
PEO(10%)-Ny69/M10(7 : 3)	10	70 : 30	1.42
PEO(10%)-Ny69/M10(9 : 1)	10	90 : 10	1.68
PEO(10%)-Ny69	10	100 : 0	1.55

Specific viscosity: 30°C, *m*-cresol, 1 g/dl.

sebacic acid and azelaic acid have carboxy groups in α - and ω -position without branch structure, the carboxy groups seem to have the same reactivity. In the same way, hexamethylenediamine and *m*-xylenediamine have the same aliphatic primary amino group, so the amino groups seem to have the same reactivity. Therefore, it will be concluded that nylon blocks have random structures. All the obtained polymers were transparent in melt state. The specific viscosities of the polyether segmented nylons in *m*-cresol were in the range

of 1.09–2.72, and these copolymers have enough molecular weight to prepare tough membranes.

The copolymers were characterized by $^1\text{H-NMR}$. The representative $^1\text{H-NMR}$ spectrum of PEO-segmented nylon, PEO(10%)-Ny69/M10(1 : 9), is shown in Figure 1. This copolymer has 10 wt % of PEO and 90 wt % of random copolyamide prepared by using M10 and 69 nylon salts whose feed ratio was 9 : 1 (wt/wt). The assignments of the signals are as follows. The broad singlet peak at 8.02 is the amide proton. The peaks at 7.05–

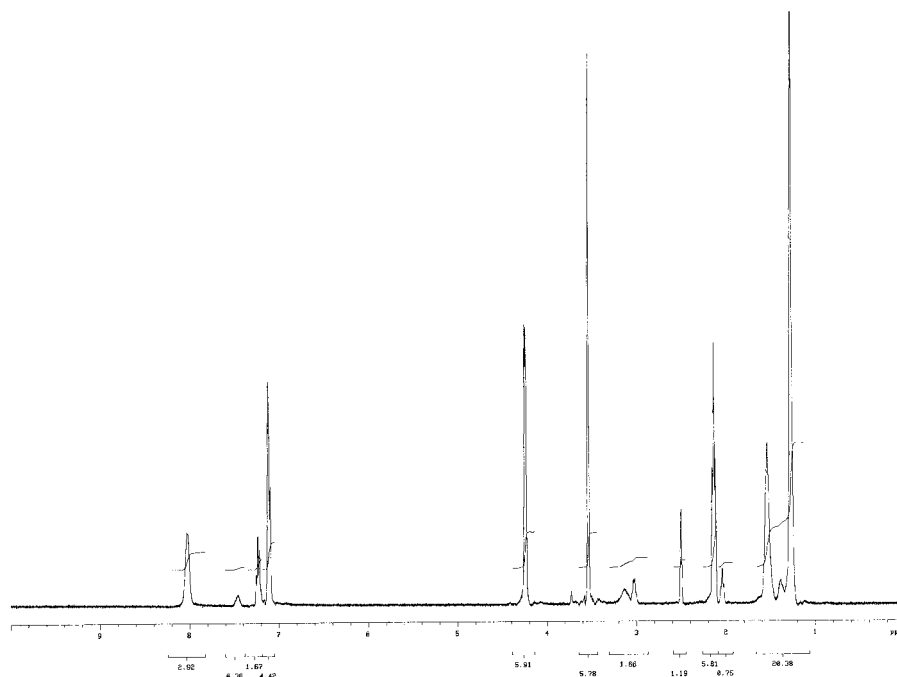


Figure 1. $^1\text{H-NMR}$ spectrum of PEO(10%)-Ny69/M10(1 : 9). Solvent: DMSO- d_6 , 80°C.

Table III Effect of PEO Content in PEO-NyM10 on Adhesion of Platelet

PEO Content (wt %)	The Counts of Platelet (A/B) ^a
5	515/602
10	26/0
20	59/1
40	0/0

^a A, B: the donor of the blood.

7.15 ppm are derived from aromatic protons of the *m*-xylylene group. The doublet peak at 4.12 ppm is the methylene protons of the *m*-xylylene group. The singlet peak at 3.55 is methylene protons on PEO. The multiplet peaks at 2.15 ppm, 1.55 ppm, and singlet peak at 1.27 ppm are the α , β , and the other methylene protons of the sebacamide and/or the azeramide, respectively. The peaks at 3.02 and 2.25 ppm are derived from water and DMSO, respectively.

The evaluation of the nonthrombogenicity of PEO-NyM10 and PEO-Ny69/M10 was carried out to determine the effective PEO content in the polyether-segmented nylon for the suppression of platelet adhesion using solvent cast films of the copolymer. The results are shown in Table III. Here, in order to avoid the influence of the composition of the nylon block, the nylon block used was NyM10. This result indicates that the adhesion of platelet is suppressed and the counts are < 100 when the PEO content is > 10 wt %. Therefore, the new polyether segmented nylons having > 10 wt % of PEO offer good surfaces for platelet. The effect of the composition of nylon block in the PEO-segmented Ny69/M10 having 10% of PEO on the platelet adhesion was also investigated. The results shown in Table IV indicate that the adhesion of platelet is not affected by the composi-

Table IV Effect of Composition of Nylon Blocks in PEO(10%)-Ny 69M10 on Adhesion of Platelet

Composition of Nylon Block Ny69/M10 (wt/wt)	The Counts of Platelet (A/B) ^a
0 : 100	26/0
10 : 90	29/2
30 : 70	5/6
50 : 50	1/0

^a A, B: the donor of the blood.

Table V Solubilities of Nylons and Polyether-Segmented Nylons in Dimethylsulfoxide

Polymer	60°C	80°C	100°C
NyM10	××	△	○○
Ny69	××	××	××
PEO(10%)-NyM10	××	△	○○
PEO(10%)-Ny69/M10(1 : 9)	×	○	○○
PEO(20%)-Ny69/M10(1 : 9)	△	○○	○○
PEO(10%)-Ny69/M10(3 : 7)	○	○○	○○
PEO(10%)-Ny69/M10(5 : 5)	△	○○	○○
PEO(10%)-Ny69/M10(7 : 3)	×	×	○
PEO(10%)-Ny69/M10(9 : 1)	××	××	××

(×) swelled; (××) insoluble; (△) highly swelled; (○) gradually dissolved; (○○) rapidly dissolved.

tion ratio (the feed ratio of Ny69 to NyM10 salts) in the nylon block varied in the range from 0 : 100 to 50 : 50 (wt/wt), and is suppressed. Therefore, it is concluded that the adhesion of platelet is dependent on the PEO content, not on the composition of nylon.

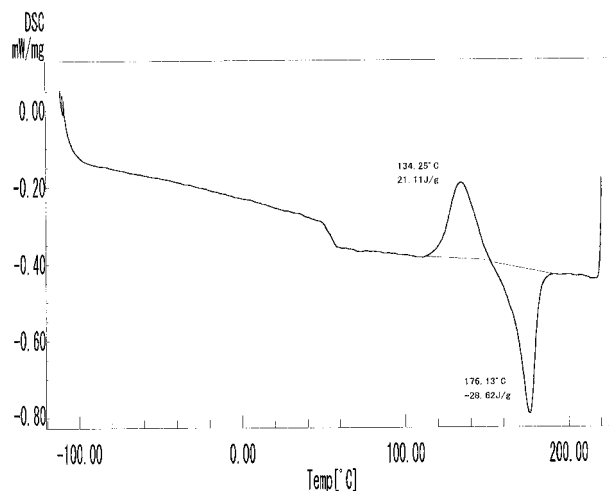
The effect of the incorporation of azelaic acid and hexamethylenediamine to the NyM10 block on the solubilities was evaluated, and the results are listed in Table V, where the PEO content in the block copolymer is > 10 wt %. PEO-NyM10 dissolved at > 100°C, as mentioned above, but the gelation occurs rapidly when the temperature falls. It is very important to obtain a stable polymer solution at low temperature, when membrane is prepared by using the phase inversion method. The random copolymerization in nylon block brings about the increase of solubility with an increase of the feed ratio of nylon 69 salt. The incorporation of nylon 69 salt in the range of 30–50 wt % causes good solubility. However, when the feed ratio of Ny69 salt is > 50 wt %, the solubility decreases because the crystallinity of the obtained copolymer seems to increase. The variation of the polyether content in the range from 10 to 20 wt % brings about the increase of the solubility. This will be the decrease of hydrogen bonding due to the increase of the PEO content. These results are supported by the results of the differential scanning calorimetry (DSC) as described below. Therefore, it is concluded that the polymer membranes are conveniently made from a DMSO solution of PEO-Ny69/M10, whose feed ratio of nylon salts (Ny69 : NyM10) is in the range from 10 : 90 to 50 : 50 (wt/wt).

The thermal properties of the polyether-segmented nylon were investigated by means of DSC

Table VI Thermal Properties of Polyether-Segmented Nylons

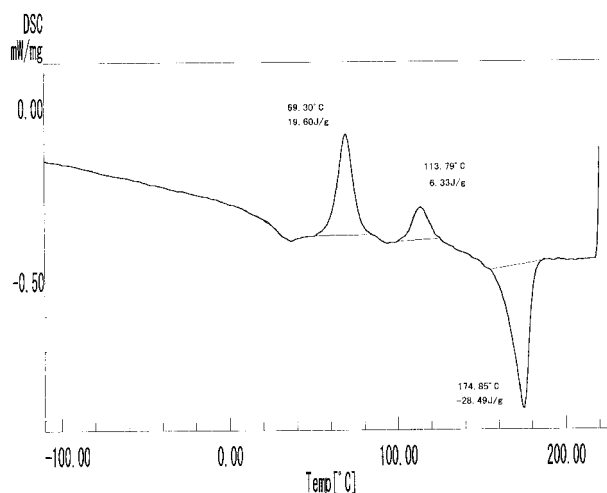
Polymer	T_m (°C)	ΔH_m (mJ/mg)
PEO(10%)-NyM10	188.6	30
PEO(10%)-Ny69/M10(1 : 9)	174.8	28
PEO(10%)-Ny69/M10(3 : 7)	149.1	19
PEO(10%)-Ny69/M10(5 : 5)	147	17
PEO(10%)-Ny69/M10(7 : 3)	172	31
PEO(10%)-Ny69/M10(9 : 1)	204	36

in order to be related with the solubility. The results are shown in Table VI. The copolycondensation of hexamethylenediamine and azelaic acid (Ny69 salt) with NyM10 salt in the range from 0 to 50 weight ratio induces the drop of melting point (T_m) of the polyether-segmented nylons from 188.6 to 147°C and ΔH from 30 to 17 mJ/mg. When the polycondensation of Ny69 with NyM10 is > 50 weight ratio, T_m and ΔH increase due to the increase of the strong hydrogen bonding derived from linear aliphatic polyamide parts. These results indicate that the copolycondensation of nylon 69 salt disturbs the intermolecular hydrogen bonding and decreases the crystallinity when the incorporation is < 50 weight ratio. These results coincide well with the result of the solubility to DMSO shown in Table V. Therefore, it is concluded that the polyether-segmented nylons having $\Delta H < 30$ mJ/mg give stable DMSO solutions. Considering the manufacturing process of the membrane, the higher T_m is desired because heat stability of the membrane is one of the important factors. These facts indicate that the most preferable composition ratio of the nylon block (69/M10) is 1 : 9. The effect of the PEO content in the block copolymer on T_m of nylon segment was investigated. The results are shown in Figures 2–4. The increase of the PEO content from 0 to 20 wt % brings about decrease of T_m from 176.8 (for 0 wt %) to 167.7°C (for 20 wt %). This suggests that the incorporation of PEO disturbs the crystallinity of the polymer weakly, that is, PEO segments are partially miscible with nylon segments. These results correspond to the results of the solubility shown in Table V. However, the endothermic peaks at 32°C due to the fusion of PEO segments are clearly observed in Figures 3 and 4. This result indicates that PEO segments are mainly immiscible with nylon segments. The glass transition point (T_g) of nylon segments is observed at 50.2°C only in the case of homo nylon

**Figure 2.** DSC thermogram of homo Ny69/M10(1 : 9). Heating rate: 10°C/min.

(Fig. 2) but cannot be observed in Figures 3 and 4. The reason for the disappearance of T_g is that the incorporation of the polyether segment brings about the endothermic peak due to the fusion of PEO segments, and a new crystallization peak and these peaks seem to hide the T_g of the nylon segments. These thermal behaviors are observed in other PEO-Ny69/M10 and we cannot detect the T_g of the nylon segment of them by use of DSC.

Considering the solubility in DMSO, solution stability, thermal property, and platelet adhesion, it is concluded the preferable polyether-segmented nylon as a dialysis membrane material is PEO(10%)-Ny69/M10(1 : 9)

**Figure 3.** DSC thermogram of PEO(10%)-Ny69/M10(1 : 9). Heating rate: 10°C/min.

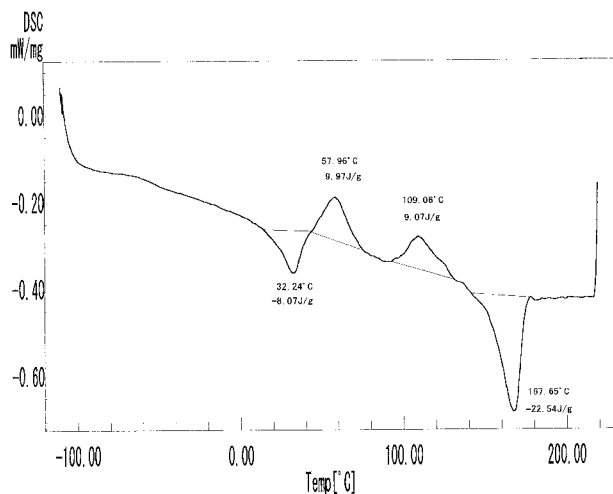


Figure 4. DSC thermogram of PEO(20%)-Ny69/M10(1 : 9). Heating rate: 10°C/min.

CONCLUSION

A new polyether-segmented nylon which dissolves in common organic solvents such as DMSO was designed to apply a blood-compatible hemodialysis membrane. The basic polyether-segmented nylon was synthesized by melt polycondensation from sebacic acid, *m*-xylenediamine, and α,ω -bisaminopropyl-poly(ethylene oxide). Moreover, to improve the solubility, azelaic acid and hexamethylenediamine were copolycondensed with the basic polymer NyM10. The polyether-segmented nylons whose feed ratios of nylon salts (Ny69 : NyM10) in polycondensation are in the range of 10 : 90–50 : 50 (wt/wt) dissolved in hot DMSO and give stable solutions. The solubility is correlated with the heat of fusion (ΔH_m) of the copolymer obtained by DSC. When ΔH_m is < 30 mJ/mg, the polymer is soluble. The copolycondensation of hexamethylenediamine and azelaic acid (nylon 69 salt) with nylon M10 salt in the range from 0 to 50 weight ratio induces the drop of T_m of the nylons from 188.6°C to 147°C, and ΔH from 30 mJ/mg to 17 mJ/mg. When the copolycondensation of Ny69 salt is > 50 wt %, T_m and ΔH increase. The non-thrombogenicity was investigated in terms of ad-

hesion of platelet onto the copolymer surface. It is shown that the surfaces of the block copolymers having > 10 wt % of PEO suppress the adhesion of platelet, and the composition of the nylon block has no effect on the adhesion. The results of the solubility, solution stability, thermal property, and platelet adhesion suggest that the preferable polyether-segmented nylon as dialysis membrane material is PEO(10%)-Ny69/M10(1 : 9).

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