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표면개질에 의한 혈액적합성 폴리우레탄의 제조

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Preparation of blood-compatible polyurethanes by surface modification

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Abstract

To develop better blood compatibility of commercial polyurethane(PU), PU surface was chemically modified with a hydrophobic perfluorocarbon or a hydrophilic polyethylene oxide(PEO) and/or sulfonated groups, respectively. The water contact angle of modified PUs varied from 110° to 0°. All the modified PUs were more blood compatible than untreated PU. In particular, PEO-sulfonate grafted PUs showed a very enhanced antithrombogenicity due to the synergistic effect of PEO and SO_3 groups. Therefore more hydrophobic and hydrophilic PU surfaces are promising for improving the blood compatibility.

I. Introduction

In order to prepare blood-compatible polymeric surfaces many researches have been carried out on the basis of several hypotheses such as negative surface charge, surface or interfacial free energy, pharmacologically active surface, and surface motion [1].

It was reported that polymers grafted with hydrophilic PEO [2,3] showed less protein adsorption and platelet adhesion to improve the antithrombogenicity significantly. Many polymers containing negative charges, especially sulfonate groups, have also received much attention. Recently some workers [4,5] reported the enhanced blood compatibility of sulfonated polyurethanes(PUs). On the other hands, hydrophobic fluorinated polymers [6] having low surface free energy and therefore inertness were found to be blood compatible.

From these points of view, we modified the surface of the commercial PU by grafting a hydrophobic or hydrophilic compounds and/or negatively charged groups to investigate the relationship between more hydrophobic or more hydrophilic surface and the blood compatibility.

II. Materials and Methods

Figure 1 illustrates the reaction scheme of modification onto PU surfaces.

The methanol extracted PU (Pellethane) was treated with hexamethylene diisocyanate(HMDI) to introduce free isocyanate groups(PU-HMDI). PU-HMDI was further reacted with aqueous Na_2CO_3 solution to produce PU-NH_2. PU-HMDI was also grafted with perfluorodecanoic acid(PFDA), dodecanediol(DDO), or PEO(molecular weight, MW=200 and 2000) to have more hydrophobic or hydrophilic surface(PU-PFDA, PU-DDO, or PU-PEO, respectively).

Sulfonations were employed by three different methods. Propane sultone(PST) was coupled directly to the free -NH_2 groups attached onto PU-NH_2(PU-SO_3). PST was also reacted with the hydroxyl end groups of PU-DDO and PU-PEO surfaces(PU-DDO-SO_3 and PU-PEO-SO_3, respectively).

Surface structure and characteristics of each modified PU were examined by performing surface analyses such as ATR-FTIR, ESCA, SEM, and dynamic contact angle [7]. The blood compatibility was evaluated by in vitro platelet adhesion test, APTT, PT, and also by ex vivo rabbit A-A shunt [3].

III. Results and Discussion

The characteristic peaks of -NCO, C-F, -OH, and -SO_3 of various modified PUs were confirmed by ATR-FTIR. A sharp peak of -NCO group was observed at 2250cm^{-1} for PU-HMDI and C-F group was confirmed at 1184cm^{-1} for PU-PFDA. Also, a little broad -OH band was appeared in the region of 3300-3600cm^{-1} for PU-PEO and PU-DDO, and a SO_2 symmetric stretching peak of sulfonated PUs was confirmed around 1030cm^{-1}.

As shown in Table 1, ESCA data were well corresponded to IR results, as higher F atomic % for PFDA grafted PU, more O atomic % for PEO grafted PU, and higher S and Na atomic % for sulfonated PUs were determined.

At SEM observation untreated PU surface was relatively smooth, while PU-PFDA surface was somewhat rough. The surface of PU-PEO was fairly smooth and all the sulfonated PU surfaces were very smooth.

The contact angles were measured by Wilhelmy plate method. As shown in Table 1, the water contact angle of modified PUs varied from 110° (fluorinated surface) to 0° (sulfonated surfaces).

Meanwhile, from platelet adhesion test, the PFDA, PEO grafted or sulfonated PUs displayed less adhesion and shape change of platelet than untreated PU. Table 2 shows the thromboresistance of various modified PUs. The APTT and PT, particularly APTT, of PFDA grafted or sulfonated PUs were extended, whereas those of PU-PEO and PU-DDO were not.

An arterio-arterial (A-A) shunt test, a new ex vivo rabbit model, was conducted under the condition of low flow rate and low shear rate [8]. The flow rate was controlled to 2.5ml/min, and the occlusion time was defined as the time that the blood flow decreases to zero. The occlusion time of untreated PU was only 50 min, but that of PFDA grafted PU was prolonged to 130min, while that of PU-PEO was extended to 120min (MW200) and 145min (MW2000). In addition, the occlusion time of PU-SO_3 was 90 min, however that of PU-DDO-SO_3 and PU-PEO-SO_3 was 200min (DDO), 350 min (PEO 200), and 370 min (PEO 2000), respectively, indicating the synergistic effect of PEO and SO_3 groups as can be explained with a "negative cilia" model [5].

Such an enhanced blood compatibility of PFDA grafted PU may be explained by low surface free energy, inertness, and water-repellent of fluorinated surface. In the case of PEO grafted PUs it can be resulted from the repulsive forces and the flexible surface motion of grafted hydrophilic chains. Furthermore, the introduction of sulfonate groups at the end of grafted PEO chain (PU-PEO-SO_3) enhanced the antithrombogenicity enormously due to the synergistic effect of hydrophilic PEO and negatively charged SO_3 groups.

IV. Conclusions

The commercial PU surface was chemically modified by PFDA, DDO, PEO, and/or PST to have different hydrophobic, hydrophilic, and/or negative sulfonated surfaces. The water contact angle of modified PUs ranged from 110° (fluorinated surface) to 0° (sulfonated surfaces). All the modified PUs were more blood compatible than untreated PU. The ex vivo occlusion times were well coincided with in vitro evaluation results: the less the adhesion and shape change of platelets and the extender the clotting times, the longer ex vivo occlusion times. Therefore more hydrophobic, more hydrophilic and/or sulfonated PU surfaces are promising for improving the blood compatibility.

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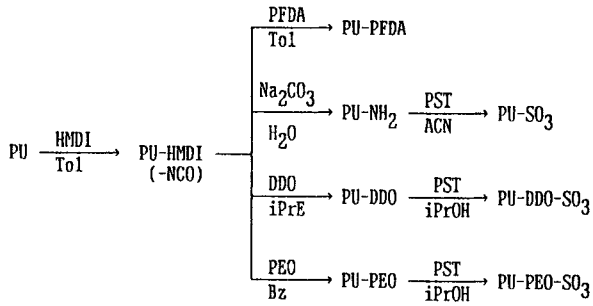

Figure 1. Modification scheme of PU surfaces.
HMDI = $OCN(CH_2)_6NCO$, PFDA = $CF_3(CF_2)_8COOH$
PST = $(CH_2)_3SO_3$, DDO = $HO(CH_2)_{12}OH$
PEO = $HO(CH_2CH_2O)_nH$

Table 1. Surface characteristics of modified PUs

Material	ESCA (atomic %) C	O	N	F	S	Na	Contact angle θadv	θrec
PU, MeOH ext.	76.9	21.5	1.5				86	41
PU-PFDA	36.1	8.3	6.8	48.8			110	50
PU-DDO	80.6	14.5	4.8				66	46
PU-PEO200	69.9	24.8	6.2				30	20
PU-PEO2000	59.9	38.9	1.2				49	14
$PU-SO_3$	69.2	18.0	11.1		1.8	-	58	wet
$PU-DDO-SO_3$	76.7	15.3	5.4		1.4	1.2	68	"
$PU-PEO200-SO_3$	65.6	24.3	3.9		3.1	3.1	39	"
$PU-PEO2000-SO_3$	58.3	37.9	1.2		1.5	1.2	51	"

Table 2. Thromboresistance data[a] of modified PUs

Material	In vitro(sec) APTT[b]	PT[c]	Ex vivo(min) occlusion time
PU	35.8 ± 0.2	13.3 ± 0.1	50 ± 5
PU-PFDA	40.2 ± 1.2**	13.6 ± 0.2*	130 ± 15***
PU-DDO	36.2 ± 1.0*	13.5 ± 0.2*	70 ± 10**
PU-PEO200	33.1 ± 0.5***	13.9 ± 0.2***	120 ± 15***
PU-PEO2000	35.5 ± 0.8*	14.9 ± 0.3***	145 ± 15***
$PU-SO_3$	41.9 ± 1.5***	14.4 ± 0.3**	90 ± 5***
$PU-DDO-SO_3$	40.5 ± 1.2***	14.2 ± 0.3***	200 ± 15***
$PU-PEO200-SO_3$	49.7 ± 2.5***	15.2 ± 0.6***	350 ± 30***
$PU-PEO2000-SO_3$	41.8 ± 1.4***	14.5 ± 0.4***	370 ± 30***

a. mean±S.D.(n=3); significance level using an unpaired Student's t-test when comparing modified PUs to PU (*$p>0.05$, **$p<0.01$, ***$p<0.005$).
b. APTT of pooled plasma was 36.0 sec.
c. PT of pooled plasma was 13.0 sec.