Effect of Drug-linkers on the Antibacterial Function of the Modified Polyurethane Surface

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INTRODUCTION

Polyurethane (PU) has been used for biomedical application with its biocompatibility and mechanical properties [1]. To inhibit the microbial growth on the PU surface for the application as a biomedical device, coating with heparin [2] or phospholipid [3] and drug in-corporation [4] were tried.

We focused on the drug immobilization of the PU surface by using chemical linkage [5], and found that the carbamate linkage resulted from the reaction of isocyanate in 1,6-Diisocyanatohexane (HMDI) and hydroxyl group in rifampin is unstable in bacterial suspension and can be cleaved by the enzymes of *S. aureus* . and *S. pneumonia* .

We used 1,3-Phenylene diisocyanate (PDI), 4-Methyl-1,3-diisocyanate (TDI), 1,12-Diisocyanato-dodecane (DDI) as new drug-linkers when rifampin was immobilized on the PU surface and then investigated their antibacterial function against *S. aureus* . in comparison to HMDI.

MATERIALS AND METHODS

Preparation of the surface modified PU beads.

PDI, TDI, HMDI and DDI were used as drug-linkers between PU surface and antibiotics, rifampin. (Fig.1) PU beads without surface treatment were used as a control. PU was pre-swelled in anhydrous toluene for 1 hr. The pre-swelling PU beads were reacted with drug-linker in anhydrous toluene at 40 °C under N_2 for 1 hr. (Fig. 2) We washed the modified PU bead to rule out the possible effect of residual rifampin by two kinds of washing methods. One method was that the modified PU was washed in methylene chloride for 5 days and successively in ethanol for 3 days. The other was that in distilled water for 8 days. After sterilized with ethylene oxide and dried in vacuum for 1 day, we performed the antibacterial evaluation using the modified PU.

Microorganism and culture condition

Staphylococcus aureus. (American Type Culture Collection 27735 Taniuchi strain Foggie, coagulase-negative, riphampin-sensitive) was used to test the inhibitory activity of the rifampin-immobilized PU bead.

Log phase culture was prepared by inoculating one colony from the nutrient-agar plate into 3 ml amount of nutrient broth at 37 °C for 3 hrs.

Antibacterial evaluation

Antibacterial activity was performed by inoculating 100 μl aliquot of $1.29*10^6$ colony forming unit of *S. aureus* . into 3 ml fresh nutrient broth containing with 2 g of the modified and control PU beads at 37 °C for 22 hrs.

To assess the antibacterial effect of the modified PU beads on the *S. aureus.*, we measured the absorbance of bacterial cultured broth at 595 nm.

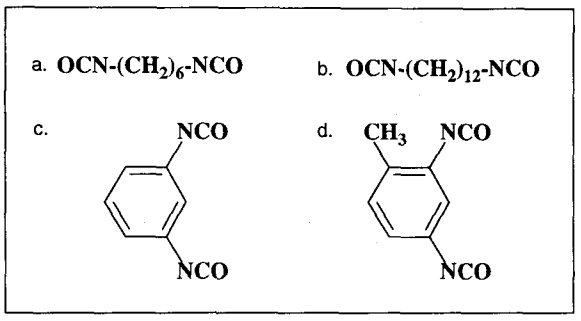

Fig.1 Chemical structures of drug-linkers
a. 1,6-Diisocyanatohexane (HMDI)
b. 1,12-Diisocuanatododecane (DDI)
c. 1,3-phenylene diisocyanate (PDI)
d. 4-methyl-1,3-phenylene diisocyanate (TDI)

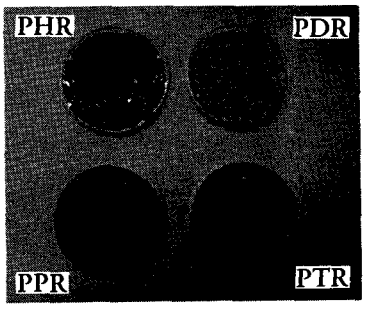

Fig.2 The PU beads modified with rifampin by using the chemical linkage of PHR (PU-HMDI-Rif.), PDR (PU-DDI-Rif.), PPR (PU-PDI-Rif.) and PTR (PU-TDI-Rif.).

RESULTS AND DISCUSSION

Antibacterial activity against S. aureus . : The effect of modified PU beads

The antibacterial function has been shown in the cases of PDI and HMDI. (Fig. 3)

However, carbamate linkages formed by TDI and DDI did not release rifampin enough to show the antibacterial effect. The carbamate linkage by using the TDI might be too strong to release rifampin due to the stable carbamate linkage between methyl group in bezene ring of TDI and rifampin. On the other hand, DDI that has longer carbon chain between two isocyanate groups than HMDI might be make the labile carbamate linkage.

In conclusion, we found the concentration of rifampin depends on the stability of carbamate linkage formed between drug-linker and rifampin. The PDI could be considered as one of the most efficient drug-linkers.

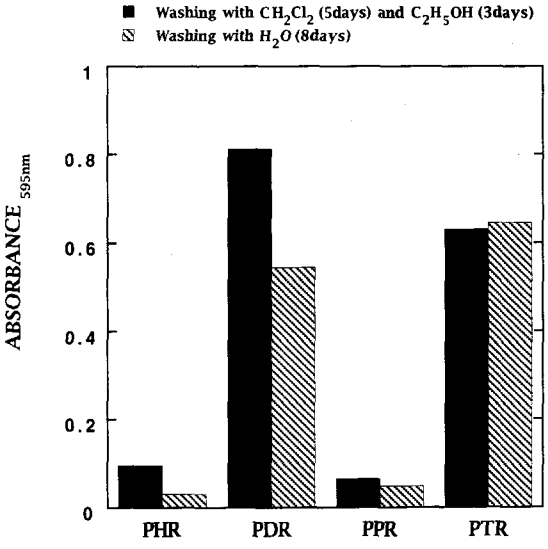

Fig.3 The antibacterial function of the modified PU beads against *S. aureus*.
PHR : PU-HMDI-Rif., PDR : PU-DDI-Rif.,
PPR : PU-PDI-Rif., PTR : PU-PTR-Rif.

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