NEW METHOD OF HEPARINZATION OF POLYMURETHANES (I)

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Polyurethanes are used in a number of blood-contacting devices, such as catheters, heart assist pumps, intra-aortic ballon pump, Pacemaker insulation heart valve, and hemodialysis unit. because of their physicological acceptability, relatively good blood tolerability, excellent mechanical properties, and their stability over long implant periods.

While mechanical limitation to the use of medical devices have for the most part been overcome, biomaterial thrombogenicity remains the single most important concern preventing even more widespread application of such devices.

Researchers have typically taken one of two approaches in attempts to eliminate this problem; the surface energetics approach, in which preexisting polymers are modified or new polymers synthesized with-surface properties deemed blood compatible, or the pharmaceutical approach, in which anti-coagulant and antiplatelet agents are employed along with the polymer.

In our approach, Heparin, the best known auticoagulant, was immobilized onto the surface of Polurethanes by a new noble method. This method involved the reaction of diiso cyanate such as HMDI via a covalent biuret and/or allophanate bonding with the Stannous octoate catalyst, and the followed coupling between functional groups of heparin and the free isocyanate group attached on the Polymer. The optimum conditions for both isocyanazation and heparination were discussed.

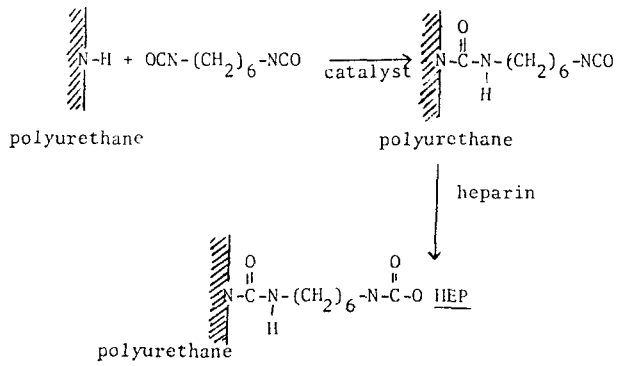
The surface concentration of covalently bonded heparin was investigated by toluidine blue method. (Biomer:1.38 ug/cm^2, Pellethane: 0.69 ug/cm^2) The amount of heparin eluting from the polymer surface into PBS and final heparin content of the surface were calculated using the toluidine blue assay.

This stability test showed that attached heparins onto the surface were very stable.

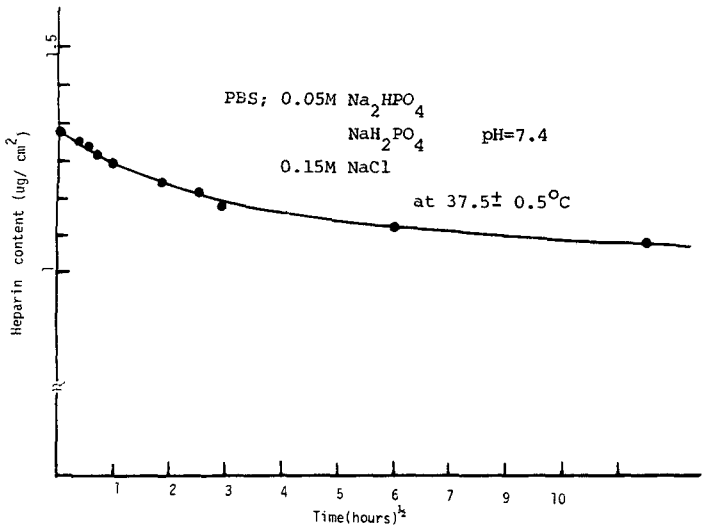
The resultant activities of attached heparins were examined in vitro. In vitro blood tests included a measure of Activated Partial Thromboplastin Time(APTT), Protrombin Time(PT), and Factor Xa assay. The heparinized surfaces were also studied by scanning electron microscopy after exposure to fresh whole blood.

These results showed that for Biomer, the yield of immobilized heparin was high enough to bring the improvement of antithrombogenicity.

Reaction Scheme of Heparinization on Polyurethane



Stability of Heparinized Polyurethane.



In-Vitro Clotting Tests

Materials	PT(sec)	PTT(sec)	FXa(sec) (% of control)
Biomer	10'8"	44	50(100)
HB - 1	10'9"	64	56(48)
HB - 2	10'9"	42	50(100)
HB - 3	12'7"	120	57(43)
Control	10'7"	33	51(100)

HB - 1 : Heparin concentration, 0.83 ug/cm^2

HB - 2 : " , 1.176 ug/cm^2

HB - 3 : " , 1.38 ug/cm^2

PT; Prothrombin Time, PTT; Partial Thromboplastin Tim.

Reaction Conditions for Heparinized Polyurethanes and their Heparin Concentrations

Polyurethanes		Reaction conditions	Heparin concentrations (ug/cm^2)
Biomer	solution	-NCO(0.542) + HEP[1]	3.450
	surface	-NCO(0.728) + HEP at 30°C 6hr, RT, 24hr	1.176
		" + HEP at 4°C 5hr, RT, 20hr	1.383
Pellethane	solution	-NCO(0.452) + HEP at 50°C 24hr	0.221
	surface	-NCO(0.644) + HEP at RT, 24hr	0.692
		-NCO(0.644) + HEP at 50°C 24hr	0.345
		-NCO(0.472) + HMDA + HEP at RT, 24hr	0.055
		-NCO(0.472) + HMDA / BC[2] + HEP at 70°C 2 days	0.083

1. HEP; Heparin
2. BC ; Benzyl chloride. quarternary ammonium salt.