Blood Compatible Materials and their Testing

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THE ROLE OF POLYMER PROPERTIES AND DESIGN IN THE BLOOD COMPATIBILITY OF CARDIOVASCULAR PROSTHESES

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Introduction

Hemocompatibility is not a characteristic depending only on chemical properties of polymers since it has been often observed that materials potentially hemocompatible with regards to their chemical structure, proved to be unsatisfactory for the fabrication of prostheses in contact with blood.

During the last few years we studied the synthesis and characterization of new potentially hemocompatible thermoplastic elastomers (TPE) and their use for the fabrication of both valvular and vascular prostheses.

The results so far obtained for the assessment of the role played by the physico-chemical properties of the polymers and by the design in determining the hemocompatibility of cardiovascular prostheses are presented.

Synthesis and characterization of new thermoplastic elastomers.

New three-block copolymers were synthesized in our laboratories through the "quasi living" cationic polymerization of styrene (or α-methylstyrene) and isobutylene (1). This result was achieved by the use of syncatalytic systems based on aluminium organic compounds and a catiogenic substance (Cl_2, t-butyl-chloride) in CH_3Cl or CH_2Cl_2 solution at low temperatures (1).

New comb-like TPE were synthesized by reacting styrene-isoprene two block living polymeric chains with both ethylene-maleic anhydride copolymer

(EMAC) and styrene-maleic anhydride copolymer (STYMAC)(2).

New polyurethanes or polyurethaneureas were synthesized by the use of new α,ω functional telechelic polymers.

α , ω - polyisobutylene diols were obtained by the polymerization of isobutylene with 2,5-dimethyl-2,5-dichlorohexane and $AlCl_3$ at low temperatures in CH_2Cl_2 solutions, or using Kennedy's INIFER techniques (3).

Through cationic polymerization processes some new α, ω - functional telechelic polymers were also prepared starting from oxygen containing cyclic or bicyclic monomers.

These oligomers were synthetized by the use of 7-oxabicyclo(2.2.1)heptane and some of its ring-substituted derivatives. The polymerization of these monomers and their copolymerization with ethylene or propylene oxide was carried out with $AlEt_3$ and H_2O as the catalytic system. Both cristalline and rubberlike materials were obtained depending on monomers and polymerization conditions.

All these diols were used for the production of new polyurethanes or polyurethaneureas by usual reaction with different diisocyanates followed by chain extension with various chain extenders such as low molecular weight diols or diammines (5).

The mechanical properties of the new TPE were varied over a wide range by modifying the ratio of the hard and soft segments.

The physico-chemical and biological characterization of the materials described above was carried out following the guidelines for the characterization of biomaterials gives in a publication of the U.S. National Institute of Health (5a). As far as the bulk properties were concerned, the following tests were carried out: IR and NMR spectra, solvent response, molecular weight and its distribution, extractability, thermal characterization (DSC) and stress-strain measurements.

As for the surface properties, we carried out: light microscope morphology and internal reflection infrared spectroscopy.Finally, we performed the following biological tests: the agar overlay tissue culture test on the material and agar overlay on material extracts. The results of all the physico-chemical tests performed confirm the expected thermoelastomeric nature of the polymers synthesized. Toxicity tests seem to exclude important toxic effects of leachable components possibly present in our polymers.

The blood-polymer interactions were investigated by means of some of the tests described in a second publication of the U.S. National Institutes of Health (5b), where guidelines for blood-material interactions are given. These tests are whole blood clotting time in tubes, sheets or films of test materials (the modified Lee-White clotting test), thrombin time, and platelet adhesion and aggregation. The results of these tests show that the new polyurethanes behave very similarly to other biomedical polyurethanes (Biomer, Avcothane 51), while graft copolymers on STYMAC or EMAC behave much better than other ionomers already described in the literature as biomedical polymers (6).

Cardiac valves

Some of the polymers described before were used for the fabrication of a new type of prosthetic leaflet heart valve (7).

The main problems so far encountered for the practical applications of prosthetic heart valves in cardiovascular surgery seem to be related to the short life exibited by biological valves (mainly due to calcification processes) and to the unsatisfactory hemodynamic behaviour shown by mechanical valves which induce thrombus formation unless anticoagulant drugs are used.

In attempt to alleviate these problems, studies were undertaken in order to design a new type of prosthetic three leaflets heart valves entirely manufactured in a composite polymeric materials.

The three leaflets of this valve consist of a layer of knitted Dacron fabric, to ensure mechanical resistance, coated with TPE, using different techniques, to increase the hemocompatibility; the leaflets were sewed with a braided polyester teflonized wire onto a Delrin stent.

An extensive in vitro evaluation of the proposed valve has been performed by means of different testing apparatus developed in our laboratory (8).

Flow patterns, visualized in steady flow conditions, exibit central flow without vortexes. In pulsatile flow tests the waveforms of both ventricular and aortic pressure and of flow rate are similar to the physiological ones, while high speed filmings show the substantial regularity of opening and closing movements of the valve.

The satisfactory behaviour of the proposed valve is confirmed by the successful implantation of the aortic prostheses in pigs, which remained alive several months, without anticoagulant drugs.

Vascular grafts

The second application of the previously described new TPE is the production of vascular grafts (9). The problem of substituting demaged natural vessels of large diameter (> 7 mm) has been satisfactorily solved by the use of vascular prostheses made of woven or knitted Teflon or Dacron fabrics. These grafts are purposely designed to avoid kinking by a technological process of circunferential heat crimping.

The reasons for the success of such prostheses has already been discussed in the relevant literature (6) and seem mainly due to the formation, inside the grafts, of a tissue which is structurally very similar to that of the natural artery. These artificial grafts, however, usually fail when used for the replacement of arteries smaller than 7 mm in internal diameter.

The reasons for this failure have also been discussed and seem to be related mainly to the crimped inner surface of the fabric graft which may give rise to turbulence of the blood and cause thrombosis.

One of the major advances in the construction of artificial arterial grafts has been the development of the expanded PTFE (polytetrafluorethylene) that needs no crimping and shows a grossly smooth internal line. These grafts show serious limitations, too, when used for the replacement of arteries smaller than 7 mm in internal diameter.

Quite recently, certain Authors (10,11) have suggested that the failure of small bore inelastic prostheses may be the result of the mismatch in the mechanical properties between the synthetic artery and the natural one to which the graft is attached.

These Authors have suggested that such problems may be solved by using elastomeric materials, such as polyurethane, purposely designed in order to possess mechanical characteristics similar to those of natural vessels.

As previously mentioned the new TPE described in this paper can be synthetized with a wide range of elastic properties, since these properties can be modified either changing the ratio of the hard and soft segments or by the use of different α,ω functional telechelic polymers for the synthesis of polyurethanes.

Using some of these TPE, chosen from among those which have shown the highest degree of hemocompatibility and good mechanical properties, a series of artificial compliant grafts with a diameter in the rang 2.5÷5 mm were fabricated.

Stress-strain and compliance tests performed on different tubes show the possibility of endowing the artificial grafts with an elastic behaviour which is very similar to that of natural arteries.

Some of these grafts were implanted in the femoral artery of medium-size dogs. Immediately after implantation a flowmeter was positioned at the distal end of the graft to measure the relative flow rate. At the same time, two pressure transducers were inserted two centimeters above the proximal anasthomosis and on the largest distal branch of the femoral artery in order to continuously record the pressure above and below the prosthesis.

The compliance of the grafts produces a visible pulsing which is supported by the shift in the pressure waveform, the pressure drop created by the prosthesis is very low, the flow through the prosthetic graft is normal.

Most of the grafts remained patent until the autopsy of the animal (45 days).

Concluding remarks

The new graft copolymers poly STYMAC (or EMAC)-g-isoprene-b-styrene show very high degree of hemocompatibility, from "in vitro" experiments, but their suitability for grafts fabrication has not jet been verified.

The new polyurethanes which appear to be of comparable blood compatibility to commercial materials offer a spectrum of mechanical properties based on segment sequence and the choice of chain extenders that permit the fabrication of both prosthetic grafts and cardiac valves with satisfactory performances. During short-term animal implantation, these grafts and valves did not cause any substantial troubles, presumably owing to their improved fluidodynamic design features. However the long-term mechanical properties and material-blood interaction characteristics should deserve further research efforts.

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