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NEW POLYMETHYLMETHACRYLATE-POLYURETHANE (PMMA-PU) MEMBRANES FOR HEMODIALYSIS APPLICATIONS

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SUMMARY

PMMA has been introduced recently in dialysis procedures as a hollow fiber device. In order to improve efficiency, hemocompatibility and mechanical properties, new flat membranes have been made by spraying PMMA-PU mixtures over a cylindrical rotating mandrel using a combined spraying and phase inversion technique (4). Three different mixtures have been evaluated, namely: PMMA(70)-PU(30), PMMA(50)-PU(50), PMMA(20)-PU(80). Mechanical testing showed that adding PU results in a substantial toughness increase, especially for PU content above 20%. Hemocompatility characterization was carried out according to the protocol for blood material interaction proposed in an NIH-publication (6). No significant differences from the basal value for any performed test were found. Transport property measurements with water, NaCl, Vit.B12 were performed in a dialysis apparatus of new design. Such new membranes showed higher permeability to small solutes and middle molecules in comparison with Cuprophane® and polyacrylonitrile (PAN) particularly in convective diffusion. The resulting hydraulic permeability was about one order of magnitude higher than PAN. Our preliminary results show an improvement in mechanical behaviour, hemocompatibility, and in molecular sieving capacity with respect to PMMA. The high hydraulic permeability also makes these formulations interesting for hemofiltration.

INTRODUCTION

PMMA was selected as a material to be employed in membrane frabrication for hemodialysis applications because of its characteristics of good hemocompatibility (ref.1) and its extreme versatility (ref.2). In fact PMMA can be made in a variety of forms under a variety of conditions, and has been recently used by biomedical industries for manufacturing dialysis devices. A disadvantage of this material is its high brittleness which makes its use difficult in membrane dialyzer production. The machining of extruded membranes requires care, since their mechanical properties are very poor, fracture is more likely to occur. Therefore PMMA is preferentially shaped in hollow fiber form to

use in hollow fiber dialyzer production. In an attempt to enlarge its application we studied composite membranes composed of PMMA and an elastomeric PU.

As PU's to be employed as strengthening elements in the construction of the PMMA-PU membranes, we selected the segmented PU's. This class of materials, because of its excellent physical and mechanical behavior and relatively good hemocompatibility, has been found useful in the fabrication of various biomedical devices to be placed in contact with blood, such as artificial hearts, intra-aortic balloons, catheters, and blood conduits (ref.3).

MATERIALS and METHODS

Materials

As starting materials for our membrane fabrication we used the following commercial products: PMMA sheets (Perspex®, I.C.I. Ltd., England); poly(ether-urethane)(PEtU) pellets (Estane® 5707-F1, Goodrich Inc., U.S.A.); a 16% solution of PEtU (90%) - polydimethylsiloxane (PDMS) (10%) block copolymer in 2:1 Tetrahydrofuran (THF)-1,4 Dioxane (Cardiothane 51®, Kontron Cardiovascular Inc., Everett, Ma, U.S.A.).

Membrane fabrication technology

The fabrication of porous membranes was performed modifying a combined spraying and phase inversion technique previously employed for microporous small diameter vascular prostheses production (ref.4).

In order to obtain membranes with specific porosity requirements we treated the polymeric material using some principles similar to those employed for porous membrane frabrication in a process referred to by Kesting as phase inversion (ref.5). This process involves the conversion of homogeneous polymer solutions into a two-phase system with a solid, polymer-rich phase forming the rigid membrane structure, and a liquid, polymer poor-phase forming the membrane pores. In general, this phase separation can be achieved by adding a non-solvent to the polymeric solution. We achieved phase separation by using steam as non-solvent.

In practical terms fragmented PMMA sheets and the different segmented PU's (pellets or solution) were separately dissolved or diluted in the same solvent used for Cardiothane 51® copolymer.

The materials were solubilized in the 2:1 THF-1,4 Dioxane solvent mixture and stirred at 70 °C. Finally the solutions were kept just as or used to prepare mixtures of different PMMA-PU ratios. Moreover, because of the requirement of spray technology for low boiling point solvents, some solutions were diluted with acetone in order to drop their boiling point and to obtain solutions that were easier to spray. The preparative data for the working solutions are shown in Table 1:

TABLE 1
Materials and concentration of the solutions used for membrane preparation.

Material	Solution
1) Cardiothane 51	3 g of polym.; 2% solution in 2:1 THF-1,4 Dioxane
2) Estane 5707 F1	3 g of polym.; 2% solution in 2:1 THF-1,4 Dioxane
3) PMMA	
4) PMMA(20)-Card.(80)	
5) PMMA(30)-Card.(70)	3 g of polym.; 2% solution in 2:1 THF-1,4
6) PMMA(50)-Card.(50)	Dioxane carried at 1% with acetone.
7) PMMA(80)-Card.(20)	
8) PMMA(50)-Estane(50)	

The apparatus for the manufacture of membranes that we have developed in our laboratory is relatively simple. The polymer solution and the steam are simultaneously deposited through two separate identical ejectors (Letraset G1), onto a stainless steel rotating cylinder (Dia.68 mm). The ejectors are assembled onto a block which moves lengthwise bidirectionally with respect to the rotating cylinder. They are positioned at 45° to one another and alligned so that the jetstreams converge at one point on the cylinder (Fig. 1). Both the rotation of the cylinder and the longitudinal movement of the ejectors are driven by two separate motors provided with electronic variable speed controls. The cylinder was cleaned with a 0.5% solution of triton X-100 in

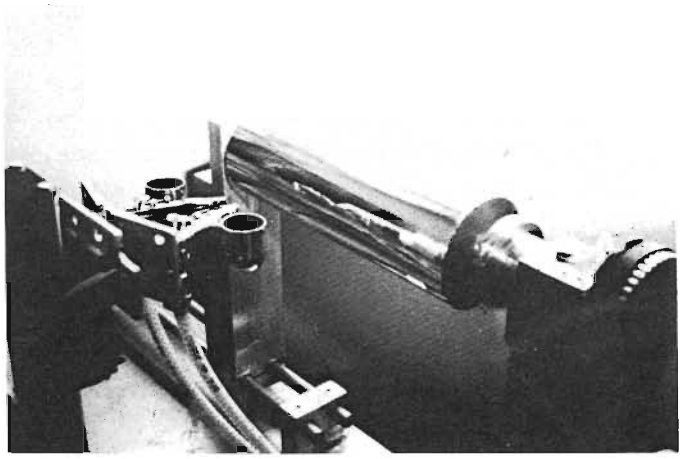

Fig.1. Machine for manufacture of the PMMA-PU membranes

water, rinsed with deionized water and absolute alcohol, and vacuum dryed before spraying on the polymer solutions. The solutions were sprayed using compressed air at 0.6 atm at room temperature, and with a distance of 8 cm between the ejector orifices and the rotating cylinder; the cylinder rotation speed and ejector movement speed were 600 rpm and 70 cm/min respectively. The polymer solution quickly converts into a white, opaque, swollen three-dimensional network when it comes in contact with the steam. The porous membrane resulted from local precipitation of polymer caused by the non-solvent. After 100 to 150 passes, membranes presenting a sponge-like structure, approximately 22 cm x 22 cm by 150-200 μm thick, were fabricated. In order to avoid inhalation of the solvents and possible contamination of the material, all processes were carried out in a laminar flow chemical hood.

At this point the stainless steel cylinder covered with the newly formed membrane was removed from the machine and immediately submerged in a bath of deionized water taking care to avoid dessication or compression. This step was performed in order to stabilize the delicate sponge-like structure of the membrane by allowing the solvents to gradually leave and the nonsolvent to enter the pores in the structure. The membrane was left in the bath overnight. Finally, the membranes were washed with deionized water and then placed to dry at room temperature between two sheet of absorbent paper.

Mechanical, morphological, and hemocompatibility characterization

The apparatus we used for mechanical testing was an Instron 1185 model. The tests were performed on samples of 100 mm in length, 15 mm wide, thickness variable between 10-60 μm, at room temperature, and at a deformation rate of 10 mm/min.

Scanning electron microscopy (SEM) was performed for estimation of the pore size and characterization of the surface morphology of the membranes. The apparatus we used was a JOEL T 300 SEM.

Hemocompatibility characterization was carried out according to the protocol for blood material interaction, primary and secondary evaluation tests, proposed in an NIH-publication (ref.6). The tests we performed as primary evaluation tests were: whole blood smear; platelet count; leukocyte count; erythrocyte count and morphology; PTT; plasma fibrinogen; plasma free hemoglobin. The test we performed as secondary evaluation test was: lactate dehydrogenase.

Transport properties measurements

We studied the membrane transport properties with a dialysis apparatus consisting of two hydraulic circuits connected with cells separated by the testing membrane. Temperatures and pressures were monitored in each circuit and transmembrane pressures were balanced for liquid and solute permeability determinations. We used water as solvent and NaCl and Vitamin B12 as solute. For each kind of membrane, both commercial and produced by us, we plotted characteristic diagrams in which we reported the Lp, De*, Jv*.y values as a function of Δp. These parameters are normally used to describe the transport properties of homogeneous membranes and according to the theoretical considerations reported in literature (refs.7,8), their meaning is reported as follows:

Lp = Hydraulic permeability = Jy/Dp($cm^3/s.cm^2.mmHg$).
Jv = Volumetric flux (cm^3/s).
De*= Apparent effective diffusivity = Js.1/C1(cm^2/s),
Js = Solute flux (g/s).
C1 = Solute concentration (g/cm^3).
l = Membrane thickness (cm).
Jv*= Jv.l (cm^2/s).
y = Js/Jv.Cl (adimensional).

RESULTS and DISCUSSION

The results show that the combined spraying and phase inversion technique allows us to prepare composite membranes PMMA-PU which can not be obtained with the ordinary method used for membrane preparation (e.g. controlled evaporation or immersion precipitation). This is due to the inhomogeneous solution they form following their contemproary solubilization and to the resulting inhomogeneous cast membranes which show phase segregation following solvent evaporation. This technology may also facilitate the creation of membranes with mechanical, morphological, and transport property characteristics which vary over a wide range. In our approach, with the use of a liquid solvent-steam nonsolvent system sprayed onto a rotating cylinder we blocked in the solid phase the homogenous situation of the PMMA-PU mixtures (Tab.1), resulting in the local precipitation of the material to form a microporous structure (Fig.2).

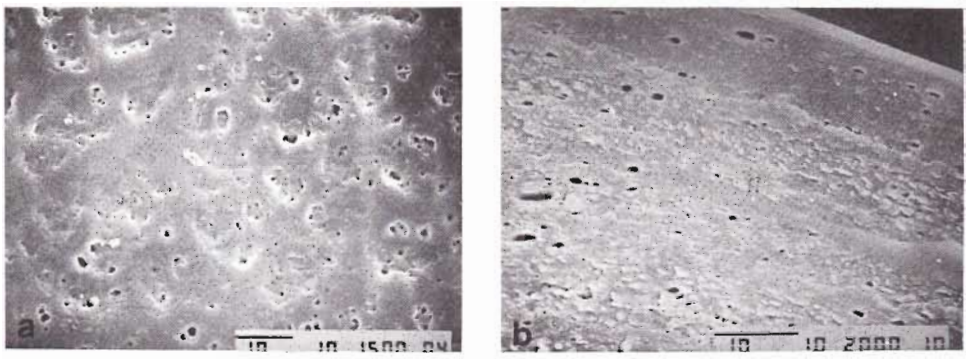

Fig.2. SEM's of the PMMA(30)-PU(70) membrane: a) Membrane surface at 1500x magnification showing pores of approximately 2-3 μm in diameter: b) Cross-sectional view at 2000x magnification. In this section the microporous sponge-like structure of the membrane is also noticeable.

The results of the mechanical testing relative to PMMA, PU and PMMA-PU membranes are illustrated in Fig.3.

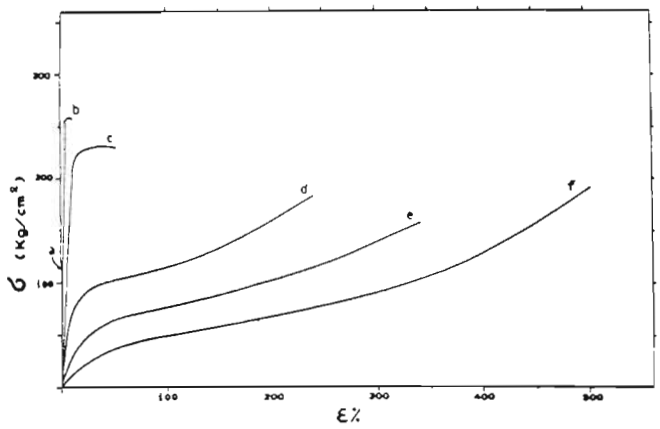

Fig.3. Stress-strain relationship curves of: a) PMMA 100%, b) PMMA 80%, c) PMMA 50%, d) PMMA 30%, e) PMMA 20%, f) PU 100%.

Curve a) represents PMMA alone. Its behaviour is typical of strong but brittle materials: high elastic modulus and small elongation at break. Curve f) represents the Cardiothane 51® alone. Its behaviour is typical of an elastomeric material: low elastic modulus, high deformation at low loads, and high elongation at break. Increasing the % of PMMA in the composite membrane (Curves e and d) results in less elastomeric behaviour, an increase of the initial elastic modulus, reduced elongation at low loads and an essential reduction of the elongation at break; ultimate tensile strength does not show significant variations. Passing from 30% to 50% in PMMA content in the membrane, we can note a marked variation of the material behaviour (Curves c and b). The trend of the curves are closer to the PMMA curve: the elogation at break is drastically reduced with remarkable increase in the elastic modulus and the ultimate tensile strength.

The results of the biological testing relative to PMMA-PU membranes samples are illustrated in Table 2. The values of the tests shown in Table 2, after 2 min of contact time between blood and different PMMA-PU preparations, do not alter significatively the basal value of the whole human blood.

TABLE 2
Values of the primary and secondary evaluation tests for blood material interaction.

Test	Basal Value	After contact (2 min at 37°C)
Primary Evaluation:		
1)Hb (%)	17.4 ± 2.1	17.6 ± 1.9
2)Platelet count (n°/ml)	175000±23000	170000±19500
3)Leukocyte count (n°/ml)	7400±800	6900±750
4)Erythrocyte count (n°/ml)	4890000±540000	4930000±600000
5)PTT (sec)	26 ± 4.2	25.8 ± 3.9
6)Plasma fibrinogen (mg%)	320 ± 60	305 ± 55
7)Plasma free haemoglobin	absent	absent
Secondary Evaluations:		
1)Lactate dehydrogenase (units)	45 ± 3	47 ± 2

The results of the transport properties measurements relative to our PMMA-PU membranes, compared with two commercial membranes (Cuprophane® and AN 69, po;yacrylonitrile (PAN)), are illustrated in Fig. 4.

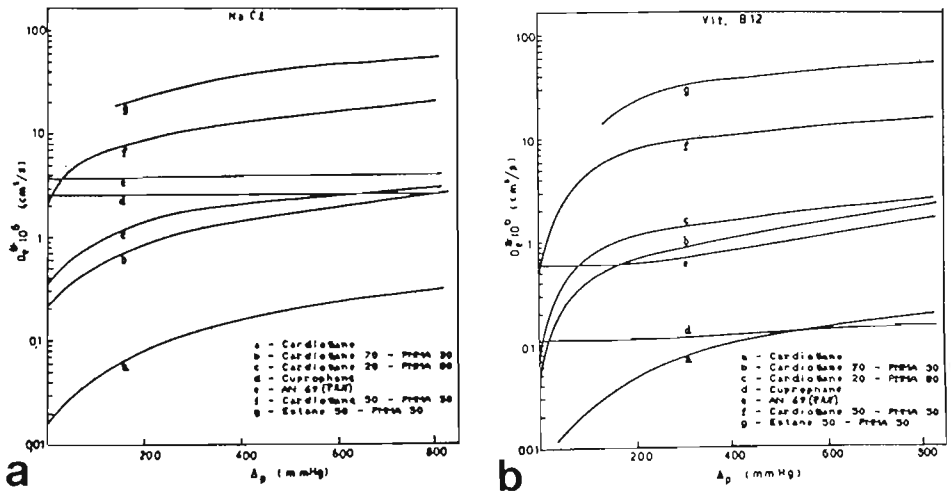

Fig. 4. Permeability measurements: a) with NaC1; b) with Vit.B12

Looking at these pictures it appears that the % composition of the membranes can markedly affect the membrane transport properties. Subsequently it is found that it is possible to modulate the value of De* in a wide range above and below the value of the commercial membranes. In addition, such new membranes can be formulated easily in order to present higher permeability to small solutes and middle molecules in comparison with Cuprophane® and AN69, particularly in convective diffusion.

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