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Improved Membranes for Hemodialysis

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SUMMARY

Asymmetric membranes of cellulose acetate and cellulose acetate modified with pendant amino groups have been evaluated for ultrafiltration and dialysis properties. Ultrafiltration rates from 4 to 30 times that of Cuprophan were obtained. During the ultrafiltration test, up to 89% of inulin in the test solution permeated with the ultrafiltrate in contrast to the 14% permeation of inulin through a Cuprophan membrane. In spite of the apparently facile permeation of high molecular weight species (e.g., inulin) through the experimental membranes, human albumin was quantitatively reflected. Dialysis tests indicate that cellulose acetate membranes 38 μ or less in thickness should surpass 23-μ-thick (wet) Cuprophan in purely diffusional transport of blood solutes of low molecular weight.

In addition to their promising ultrafiltration and dialysis properties, membranes made from a blend of cellulose acetate and N,N-diethylaminoethylcellulose acetate were found to sorb heparin strongly. The clotting time of rabbit blood in contact with the heparinized membranes was extended, in some cases indefinitely.

INTRODUCTION

The literature concerning membrane technology has greatly expanded over the past 10 years, largely as a result of the development of membranes for the desalination of salt-laden water by reverse osmosis [1]. Practical hydraulic permeabilities for this purpose have been achieved by the development of "asymmetric membranes" consisting of a very thin "active layer" surmounting a relatively thick (50 to 100 μ) porous substructure. By regulation of processing variables, the hydraulic and solute permeability of the active layer may be varied over a wide range. This suggested that asymmetric membranes might be prepared which are superior in transport properties to the membranes currently employed for hemodialysis. The desired improvements were increased ultrafiltration rate, increased rate of transport of blood solutes (particularly metabolites of relatively high molecular weight), and nonthrombogenic properties.

Cellulose acetate and slightly modified cellulose acetate were chosen for investigation as polymers for hemodialysis membranes on the basis of the broad experience and success in preparing asymmetric membranes from cellulose esters. Scanning electron photomicrographs of an experimental cellulose acetate hemodialysis membrane at two magnifications are shown in Fig. 1 to illustrate the asymmetric structure. Although the pores in the substructure are clearly shown to be about 0.2 to 1.0 μ in diameter in the cross sections, the thickness of the active layer is not resolved. It may be seen, however, that the surface of the active layer does not contain pores of the size present in the substructure, but is relatively smooth and dense. It is believed that the ultrafiltration rate of asymmetric membranes and the transport of large molecules is controlled to a great extent by the thickness and homogeneity of the active layer. On the other hand, the rate of transport of low molecular weight solutes by diffusion is less dependent on the active layer and increases as the gross thickness of the membrane is reduced.

In addition to improved transport properties, asymmetric membranes were also sought which would strongly sorb heparin and thereby become nonthrombogenic. Following the general process successfully used by Gott [2] and Merrill [3] for heparin binding, cellulose acetates containing amino groups were prepared on the assumption that the amino groups would form ionic bonds with sulfate groups in heparin and thus immobilize it. For this phase of the work, the preparation of membranes from N,N-diethylaminoethylcellulose acetate was investigated. The progress with

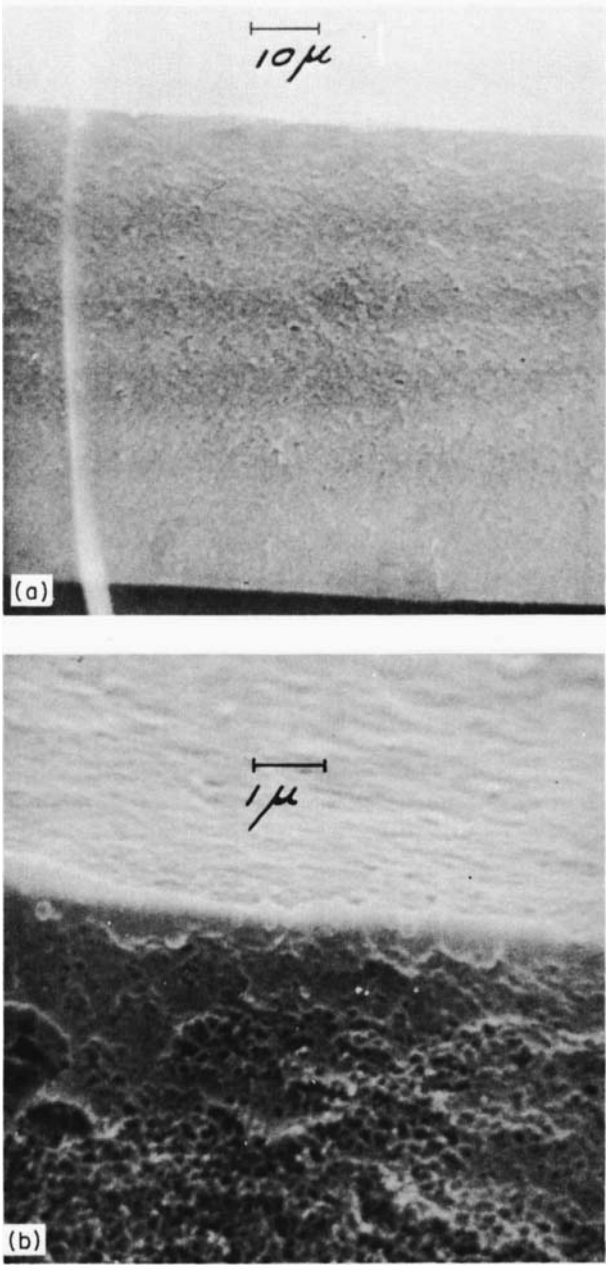

Fig. 1. Cross-sectional views of asymmetric membrane at two magnifications.

both the cellulose acetate and amine-modified cellulose acetate membranes is described here.

EXPERIMENTAL

Preparation of Membranes

The membranes were prepared by the general procedure used in the fabrication of asymmetric membranes from cellulosic polymer systems. A casting solution was first prepared containing a polymer, a polymer solvent, a polymer nonsolvent, and a membrane salt or swelling agent [4, 5]. A film of this solution was cast on a smooth surface, the solvents were partially evaporated, and it was then gelled in ice water. Variations in the casting solution formulation and casting techniques were used to control membrane transport characteristics [6]. The membrane fabrication parameters are presented in Table 1.

All cellulose acetates were obtained from Eastman Chemical Products, Inc. Type E-400-25 was used for the cellulose acetate membranes and Type E-394-60 was used in blend membranes prepared from cellulose acetate and N,N-diethylaminoethylcellulose acetate (DEAECA).

DEAECA was synthesized by the esterification of N,N-diethylaminoethylcellulose (Eastman Organic Products) by a modification of the procedure described by Malm [7] to an acetyl degree of substitution (ds) of 2.74. This was followed by partial hydrolysis according to the procedure described by Tanghe [8] to yield an acetone-soluble DEAECA of acetyl ds 2.29 and diethylaminoethyl ds of about 0.13.

Heparinized membranes for blood-clotting studies were prepared by soaking the membranes in 0.85% sodium heparin (159 units/mg) for 8 hr with frequent stirring. At the end of this period the membranes were removed from the heparin solution and transferred to a saline wash. The membranes were then transferred to fresh saline every half hour through ten washes, allowed to stand in saline overnight in the cold, and washed four more times before use. The rinse solutions were tested for heparin by decanting a sample from the membrane wash and adding a drop of the dye, Toluidine Blue (a precipitate forms in the presence of heparin). After about the fourth wash all tests for heparin in the wash solutions from the DEAECA-containing membranes were negative.

The membrane samples were prepared for scanning electron microscopy by a 48-hr immersion in dry carbon tetrachloride to remove the water, air-dried, then fractured by bending under liquid nitrogen to expose the porous substructure.

Table 1. Membrane Fabrication Parameters

Membrane No.	Casting solution		Casting conditions		
	Polymer[a]	Formulation[b]	Thickness (mils)	Temperature (°C)	Drying time (min)
7179-64C	CA	10/30/5/6	8	-10	0.8
7905-41A	CA	10/30/5/6	8	-11	1.2
7905-41D	CA	10/30/8/6	8	-11	1.2
7905-46B	CA	10/30/5/6	5	Room temp.	0.3
7905-46C	CA	10/30/6/6	5	Room temp.	0.3
7905-46D	CA	10/45/5/6	5	Room temp.	0.3
7905-75A	CA	10/30/5/5	5	-11	1.0
7233-10	DEAECA-CA	7/7/86/28/4	10	-10	3.0

[a]Symbols: CA, cellulose acetate; DEAECA, N,N-diethylaminoethylcellulose acetate.

[b]Formulation for the CA membranes (parts by weight): polymer/acetone/water/tartaric acid. Formulation for the DEAECA-CA membranes (parts by weight): CA/DEAECA/acetone/formamide/zinc chloride.

Membrane Transport Evaluation

An ultrafiltration cell developed in these laboratories [5] and the dialysis cell developed by the National Bureau of Standards [9] were used for the evaluation of the transport characteristics of the experimental membranes and of Cuprophan PT150 (obtained from Cobe Laboratories, Los Angeles, California).

The ultrafiltration cell was designed to permit a pressurized feed solution to be circulated across the active layer of an asymmetric membrane. The cell holds a membrane circle having a diameter of 7.6 cm and an effective membrane area of 29.4 cm^2. The distance between the membrane and the top of the cell is 0.025 cm. Tests were conducted at 25°C under a pressure of 1 atm in three cells connected in series. Flow through the unit was maintained at approximately 10 ml/min. This flow rate was arbitrarily selected to minimize 1) concentration polarization at the membrane surface, and 2) the increase in bulk solute concentration due to loss of water by ultrafiltration.

The ultrafiltration cells were used for the preliminary evaluation of all membranes. First, a feed of deionized water was passed across the membrane. The ultrafiltration rate was determined by the amount of water passing through the membrane per unit time. Next, feed which contained the solutes of interest in a solution of 8500 ppm sodium chloride in 0.01 M Na_2HPO_4-NaH_2PO_4 buffer of pH 7.2 to 7.4 was evaluated in a similar fashion. The solute permeation value of the individual solutes was calculated as the ratio of the solute concentration in the ultrafiltrate to the solute concentration in the feed solution. Membranes which allowed the transport of albumin were considered too permeable and were eliminated from further testing. The assumption was made that membranes which were impermeable to albumin when evaluated in the ultrafiltration cell would not transport albumin during dialysis.

Membrane permeability by dialysis was determined by the use of the test cell developed by the National Bureau of Standards. This cell was designed to hold a single membrane (a 51.6 cm^2 section) so that solutions can be circulated rapidly against both sides of the membrane. The "blood" solution contained the solutes of interest in a buffered saline solution of 5000 or 8500 ppm sodium chloride in 0.01 M Na_2HPO_4-NaH_2PO_4 buffer of pH 7.2 to 7.4. In all tests the "blood" solution was circulated against the active layer of the asymmetric membrane. The dialysate solution was either deionized water or the buffered saline solution and was circulated against the porous substructure of the membrane.

Dialysis tests were conducted at 25°C over periods of 1 to 5 hr, circulating both the "blood" and dialysate solutions across the respective membrane surfaces at 600 ml/min. Whenever feasible, the dialysis time was selected to permit the concentration gradient between the two solutions to decrease to approximately 40% of its original value. Membrane permeability was calculated from the rate at which a solute passed through the membrane; under the condition of zero transmembrane pressure it represents solute transport by diffusion.

Solute concentrations studied were 5000 and 8500 ppm NaCl, 500 ppm urea, 50 ppm creatinine, 50 ppm uric acid, 150 ppm inulin, 1000 ppm albumin (human, fraction IV) and a 0.01 M Na_2HPO_4 - NaH_2PO_4 buffer having a pH range of 7.2 to 7.4. (The inulin and albumin were obtained from Calbiochem.) The most satisfactory test solution for ultrafiltration was an inulin-albumin solution in buffered saline (8500 ppm NaCl in 0.01 M phosphate buffer). For dialysis, the most satisfactory combination of solutions was a single organic solute in buffered saline solution for the "blood" and buffered saline solution for the dialysate.

Modifications of established colorimetric procedures were used for all analyses. Sodium chloride concentrations were determined using mercuric chloroanilate as an exchange reactor for ionic chloride [10]. Urea was determined by reaction with p-dimethylaminobenzaldehyde [11], creatinine by the Jaffe reaction with alkaline picrate solution to form a red tautomer of creatinine picrate [10], uric acid by a modification of the method of Brown using sodium tungstate [12], inulin by reaction with anthrone [13], and albumin by the well-known biuret reaction [10] or by the turbidity produced by reaction with trichloroacetic acid [10]. Phosphorous was determined by reaction of the orthophosphate with an acidic molybdate solution followed by reduction of the hexavalent molybdenum in the resultant phosphomolybdic acid by 1,2,4-aminoaphtholsulfonic acid [14].

DISCUSSION

Calculation of Permeability for High Flux Membranes

The inherently high transport capabilities of asymmetric membranes necessitated some modification in the equation for permeability as presented by the developers of the dialysis test cell. Some difficulty in the proper evaluation of membranes for hemodialysis can result from the gain of solvent by osmosis and the loss of solution by ultrafiltration. This is a problem

of minor importance for membranes having low ultrafiltration rates, such as Cuprophan, but it is a problem of major importance for the very permeable membranes prepared in this study.

The problem is illustrated by the data in Table 2. In these runs the "blood" solution initially had a volume of 500 ml, contained 5000 ppm sodium chloride, had an osmotic pressure of about 60 psi, and was dialyzed against an initial volume of 500 ml of water. This gain in volume of the "blood" side indicated that an osmotic flow of water occurred at a transmembrane pressure of zero. When a transmembrane pressure was applied on the "blood" side, the loss of "blood" volume by ultrafiltration was countered by a volume gain by osmosis and the net change in volume was consequently the algebraic sum of the osmotic and ultrafiltration flows. Neither the changes in volume which are shown nor the changes in solute concentrations which may accompany these volume changes are accounted for by the equation suggested by the developers of the test cell; hence, spurious values may be obtained for mass transport data.

The equation given by the National Bureau of Standards for the calculation of membrane permeability [9] is

$$P = \frac{1}{At} \frac{V_b V_d}{V_b + V_d} \ln \frac{(C_b - C_d)_o}{(C_b - C_d)_t} \tag{1}$$

where P = permeability of the membrane, cm/min; A = the exposed area of the membrane, cm^2; t = the time interval between the initial and final reading, min; V_b = volume on the "blood" side, ml; V_d = volume on the "dialysate" side, ml; C_b = solute concentration on the "blood" side, ppm; and C_d = solute concentration on the "dialysate" side, ppm.

Application of this equation to the data presented in Table 2 for Runs 11A and 11B for a solute such as albumin, for which the permeability has been shown to be zero, gives the following permeability values.

Run 11A

$$P = \frac{1}{51.6\ cm^2\ 240\ min} \frac{(500\ ml)^2}{(500 + 500)\ ml} \ln \frac{527.8}{500}$$

$$= 11 \times 10^{-4}\ cm/min$$

Table 2. Volume Changes During Dialysis

Dialysis run No.	Membrane No.	Membrane polymer	Trans-membrane pressure (mm Hg)	Duration of run (hr)	Change in "blood" volume (ml)
13A	-	Cuprophan	0	4.0	+4.0
13C	-	Cuprophan	335	4.0	-10.2
14A	7905-46B	CA	0	4.0	+47.0
14B	7905-46B	CA	300	4.0	+21.4
11A	7233-10	DEAECA-CA	0	4.0	+27.8
11B	7233-10	DEAECA-CA	400	1.2	-198.4

Run 11B

$$P = \frac{1}{51.6\ \text{cm}^2\ 72\ \text{min}} \frac{(500\ \text{ml})^2}{(500 + 500)\ \text{ml}} \ln \frac{301.6}{500}$$

$$= -340 \times 10^{-4}\ \text{cm/min}$$

These values demonstrate that Eq. (1) is not satisfactory for the calculation of the permeability of membranes of very high water transport rates in the NBS cell. For membranes of low water transport rate, such as Cuprophan, this difficulty becomes minimal. A solution to the problem of volume changes due to osmosis and ultrafiltration is given below.

Consider a dialysis apparatus with fixed initial volumes of "blood" and dialysate solutions circulating rapidly past a membrane area. The overall mass transfer rate through the membrane may be expressed by either a loss of solute by the "blood" or a gain of solute by the dialysate, i.e.,

$$m_o = \frac{(V_b C_b)_i - (V_b C_b)_f}{t} \tag{2a}$$

or

$$m_o = \frac{(V_d C_d)_f - (V_d C_d)_i}{t} \tag{2b}$$

where m_o= overall mass transfer rate, g/min; V_b = blood volume, ml; V_d = dialysate volume, ml; C_b = solute concentration in the "blood", ppm; C_d = solute concentration in the dialysate, ppm; t = total time of run, min; i = initial values; and f = final values.

The overall mass transfer rate is also a function of the membrane permeability, membrane area, and the concentration gradient, i.e.,

$$m_o = PAC_m \tag{3}$$

where P = permeability, cm/min; A = membrane area, cm^2; and

C_m = log mean concentration difference, ppm

$$= \frac{(C_b - C_d)_i - (C_b - C_d)_f}{\ln \frac{(C_b - C_d)_i}{(C_b - C_d)_f}}$$

Equations (2a) and (3) may be combined to give Eq. (4).

$$\frac{(V_bC_b)_i - (V_bC_b)_f}{t} = PA \frac{(C_b - C_d)_i - (C_b - C_d)_f}{\ln \frac{(C_b - C_d)_i}{(C_b - C_d)_f}} \tag{4}$$

When rearranged, Eq. (4) gives Eq. (5) which takes into consideration the changes in volume that occur during the evaluation of a membrane in the calculation of membrane permeability:

$$P = \frac{1}{At} \frac{(V_bC_b)_i - (V_bC_b)_f}{(C_b - C_d)_i - (C_b - C_d)_f} \ln \frac{(C_b - C_d)_i}{(C_b - C_d)_f} \tag{5}$$

If no change in volume occurs during the dialysis and solute concentrations are expressed as mass per unit volume, i.e., m/V, then the term

$$\frac{(V_bC_b)_i - (V_bC_b)_f}{(C_b - C_d)_i - (C_b - C_d)_f}$$

in Eq. (5) may be expressed as

$$\frac{\frac{V_bm_{bi}}{V_b} - \frac{V_bm_{bf}}{V_b}}{\frac{m_{bi}}{V_b} - \frac{m_{di}}{V_d} - \frac{m_{bf}}{V_b} + \frac{m_{df}}{V_d}}$$

Rearrangement and simplification gives

$$\frac{m_{bi} - m_{bf}}{\frac{m_{bi} - m_{bf}}{V_b} + \frac{m_{df} - m_{di}}{V_d}}$$

Since the loss of mass by the blood becomes the gain in mass in the dialysate, this expression becomes:

$$\frac{1}{\frac{1}{V_b} + \frac{1}{V_d}}$$

or

$$\frac{V_b V_d}{V_b + V_d}$$

Therefore, if no change in volume occurs during the dialysis, Eq. (5) becomes equivalent to Eq. (1), the equation developed by the National Bureau of Standards.

Cellulose Acetate Membranes

Asymmetric membranes of cellulose acetate have been prepared with ultrafiltration rates from 4 to over 20 times that of Cuprophan (Table 3). Essentially quantitative solute permeation values for the low molecular weight solutes sodium chloride, phosphorus (as phosphate ion), urea, creatinine, and uric acid were exhibited by the membranes of high ultrafiltration rate. The solute permeation values for inulin increased as a function of the ultrafiltration rate and ranged from one to six times that of Cuprophan. All of the cellulose acetate membranes reflected albumin quantitatively.

A cellulose acetate membrane having an ultrafiltration rate of 39×10^{-4} ml/cm^2-hr-mm Hg allowed up to 86% of the inulin in the feed solution to permeate by ultrafiltration. This is a significant improvement over the ultrafiltration rate and solute permeation value for Cuprophan of 1.1×10^{-4} ml/cm^2-hr-mm Hg and 14%, respectively.

The high permeability of the cellulose acetate membrane toward inulin and complete rejection of albumin represents a sharp separation in terms of molecular size. If one considers the molecules of inulin (MW $\approx$ 5000) [15] and albumin (MW $\approx$ 67,000) to be spherical and of the same density, the ratio of the molecular diameters is 2.4. Measurements of the dimensions of these two materials [16] indicate that the ratio may be as high as 3.4. In either case, the essentially quantitative separation of these molecules is indicative of a very uniform distribution of pore sizes in the cellulose acetate membrane. The small dimension of albumin indicates that any pores in the active layer must have a diameter of less than 45 Å.

Following the ultrafiltration test, fresh samples of the membrane were examined for solute transport in the dialysis test cell. The dialysis properties of cellulose acetate membranes are summarized in Table 4. The range of thickness of the cellulose acetate membranes was from 1.3 to 4.2 mils in comparison with Cuprophan of 0.9-mil thickness. As a result, the permeability values for the thicker membranes are low. Since permeability is

Table 3. Ultrafiltration Properties of Experimental Membranes

Membrane No.	Membrane polymer	Ultrafiltration rate [ml/cm^2-hr-mm Hg ($\times 10^4$)]		Solute permeation (%[b])						
		On water	On solution	NaCl	Phosphorus	Urea	Creatinine	uric Acid	Inulin	Albumin
-	Cuprophan	1.1	1.3	86	86	98	90	79	14	0
7905-46B	CA	4.3	3.6	-	62	96	96	79	18	0
7905-46C	CA	7.1	6.9	-	-	-	-	-	36	0
7179-64C	CA	-	19.6	-	-	-	-	97	49	0
7905-41A	CA	17.7	18.1	97	91	98	99	96	28	0
7905-41D	CA	39	-	-	-	-	-	-	86	0
7233-10	DEAECA-CA	60	60	-	-	-	-	-	89	0

[a]Symbols: CA, cellulose acetate; DEAECA, N,N-diethylaminoethylcellulose acetate.

[b]The solutions consisted of 5000 ppm NaCl, 500 ppm urea, 50 ppm creatinine, 50 ppm of uric acid, 150 ppm inulin, and 1000 ppm albumin in 0.01 M phosphate buffer (310 ppm phosphorus) at pH 7.2 to 7.4.

Table 4. Dialysis Properties of Experimental Membranes

Membrane				Permeability [cm/min (× 10^4)]					Permeability coefficient [cm^2/min (× 10^5)]				
Polymer[a]	Number	Thickness (mils)	U[a] [ml/cm^2-hr-mm Hg (× 10^4)]	NaCl	Phosphorus	Urea	Creatinine	Uric acid	NaCl	Phosphorus	Urea	Creatinine	Uric acid
Cuprophan	-	0.9	1.4	489	94	416	235	156	11.2	2.1	9.5	5.4	3.6
CA	7905-75A	1.3	6.0	-	-	415	-	-	-	-	13.7	-	-
CA	7905-46C	1.7	7.1	195	11	313	126	52	8.4	0.5	13.5	5.4	2.2
CA	7905-46D	2.0	16.0	-	-	299	-	-	-	-	15.2	-	-
CA	7179-64C	3.4	16.7	207	70	191	117	82	17.8	6.0	16.5	10.1	7.1
CA	7905-41A	4.1	17.7	150	55	169	95	61	15.6	5.7	17.6	9.9	6.4
CA	7905-41D	4.2	39.0	169	57	137	94	68	18.0	6.1	14.6	10.0	7.3
DEAECA-CA	7233-10	2.5	60.0	609	265	572	319	308	38.7	16.8	36.3	20.2	19.6

[a]Symbols: CA, cellulose acetate; DEAECA, N,N-diethylaminoethylcellulose acetate; U, ultrafiltration rate.

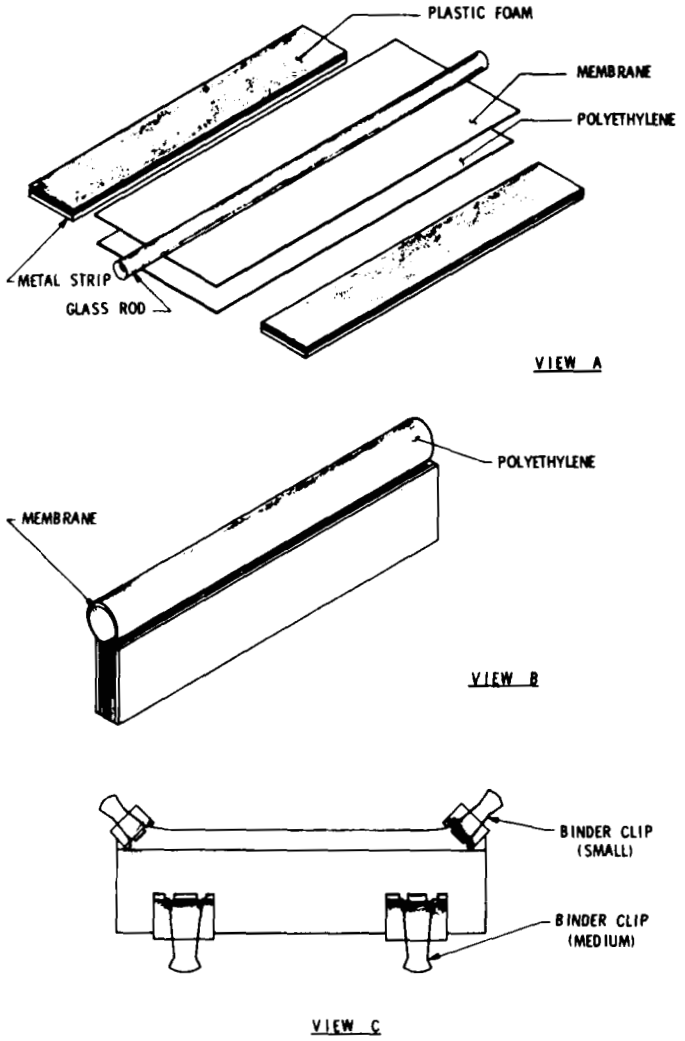

Fig. 2. Blood clotting test apparatus.

inversely proportional to membrane thickness, the permeability of the various solutes is also reported as the product of the permeability and membrane thickness. This "permeability coefficient" compares the permeability through membranes of unit thickness.

Modified Cellulose Acetate Membranes

Membranes containing basic groups capable of binding heparin were prepared from a 50:50 blend of N,N-diethylaminoethylcellulose acetate (DEAECA) and cellulose acetate. These membranes had ultrafiltration rates up to 60×10^{-4} ml/cm^2-hr-mm Hg (i.e., 30 times Cuprophan) and reflected albumin quantitatively while allowing up to 89% of the inulin in the feed solution to permeate (Table 3). This is the highest solute permeation value for inulin attained thus far for cellulosic membranes.

The DEAECA-cellulose acetate blend membrane, as compared to Cuprophan, exhibited permeability values 25 to 35% higher for sodium chloride, urea, and creatinine, 100% higher for uric acid, and 180% higher for phosphate ion (Table 4). The high transport of solutes through the membrane is more apparent when expressed in terms of permeability coefficients. A comparison of the permeability coefficients of the blend membrane with that of Cuprophan shows that for membranes of the same thickness the blend membrane should exhibit permeabilities for sodium chloride, urea, creatinine, uric acid, and phosphate ion which are 3.5, 3.8, 3.7, 5.5, and 8.0 times that of Cuprophan, respectively.

Blood Clotting Studies

Promising nonthrombogenic properties were demonstrated by heparinized DEAECA-cellulose acetate blend membranes. These evaluations were made in an apparatus (Fig. 2) designed to form a tube from a piece of flat, wet, and very thin membrane so that a single surface of the membrane may be evaluated for blood-clotting tendencies. Figure 2, View A, shows the placement of the membrane, a polyethylene film for support and protection against drying, and a glass rod to give the membrane tube the proper dimension. Two metal strips covered with polyurethane foam are used to hold the assembled pieces as shown in View B. View C shows the assembled tube. Binder clips are used to seal the ends of the membrane tube and to hold the two metal strips in position. The tube dimensions found most satisfactory were a diameter of 0.25 in. and a distance between binder clips of about 7 in. This assembly was filled about one-half full with blood and tilted every 100 sec until clotting was detected. Blood clotting times determined in this apparatus for fresh rabbit blood are shown in Table 5.

Blood in contact with the heparinized DEAECA-cellulose acetate blend membrane had an indefinite clotting time. It would not clot when removed from the membrane tube and placed in contact with glass. Although it had been previously established that heparin was not leached from the membrane

Table 5. Blood Clotting Times

Membrane	Clotting time (sec)
Cuprophan	700
DEAECA-CA blend	600
DEAECA-CA blend[a]	Indefinite
Glass	300

[a]Heparinized membrane.

by normal saline, the possibility was considered that the blood may have remained fluid because of heparin having been leached from the membrane by the fresh rabbit blood. It was determined, however, that when this nonclotting blood was mixed with normal rabbit plasma, the clotting time of the plasma was not prolonged. These data indicate that the heparin was not leached from the membrane, at least in sufficient quantity to be responsible for the indefinite clotting time obtained. The failure to clot in glass may have been caused by adsorption of a clotting factor during contact with the heparinized membrane. Since normal plasma still contains this factor, admixture of it with the nonclotting blood would allow clotting to proceed normally.

Clinical Evaluation

Cellulose acetate membranes exhibiting high rates of ultrafiltration are being made available to the Hemodialysis Unit at the Wadsworth Veterans Hospital at Los Angeles for clinical evaluation. A membrane (No. 7179-64C) having an ultrafiltration rate 8 times that of Cuprophan has been evaluated using a 1 m^2 MiniKlung [17]. During a 10-hr dialysis of a 78-kg patient, a total of 9.4 kg of body fluids was removed and 7.4 kg was replaced. The 2 kg of body weight was removed during the first 80 min of dialysis; thereafter, liquid was removed at 800-1250 g/hr with total body weight being maintained constant by infusion of normal saline solution into the arterial blood tubing. A maximum ultrafiltration rate of 35 g/min at a transmembrane pressure of 250 mm Hg and a blood flow of 200 ml/min was observed during this dialysis. An increase in the hematocrit of 15% occurred during transit of the blood through the dialyzer. This increase correlated reasonably well with measured water loss. Observations made during the dialysis are reported in Table 6. The decrease

Table 6. Clinical Dialysis Data Using a Cellulose Acetate Membrane

	Time (min)	
	40	140
Blood flow, ml/min	210	210
Dialysate flow, ml/min	990	990
Mean transmembrane pressure gradient, mm Hg	257	353
Ultrafiltration rate, ml/min	29	17
Dialysance, ml/min		
Urea	76	53
Creatinine	62	31
Uric acid	54	30
Phosphorous	62	31

in ultrafiltration rate and dialysance with time was apparently due to a coating, presumably fibrin, which was deposited on the membrane surface.

The dialysis was well tolerated by the patient and the results of this first clinical test are considered promising. Additional quantities of asymmetric membranes of cellulose acetate have been delivered to the Wadsworth Veterans Hospital to permit continuation of clinical testing.

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