tabolism of glucose is achieved, further addition of insulin is without effect on the action of phloretin. This would seem to indicate that insulin and phloretin are not acting competitively. Yet the action of phloretin and phlorizin are obviously different in certain respects. Further evidence for this is furnished by the fact that the inhibitory effect of phloretin can be only partially reversed by washing of the tissue.

The fact that neither phlorizin nor phloretin impairs the ability of insulin to initiate pinocytosis in adipose tissue further suggests that these inhibitors do not act by preventing access of insulin to a cell-membrane site, since the first step in the process of pinocytosis would appear to be the adsorption or attachment of the insulin molecule to the surface of the cell membrane (cf. Barrnett and Ball, 1960; Ball and Jungas, 1964). Unfortunately, the action of these inhibitors does not throw any light upon the question of the relationship that exists between the ability of insulin to induce pinocytosis and its ability to augment glucose uptake. In addition no further insight is provided into the possible role of vesicle formation as a means of transport of glucose into the cell, since if phlorizin or phloretin act by blocking permeability to glucose they could block the permeability not only of the cell membrane but of the membrane surrounding the vesicles.

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New Synthetic Membranes for Dialysis. I. A Copolyether-Ester Membrane System*

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Block copolymers based on polyoxyethylene glycol and polyethylene terephthalate were synthesized, and the effects of varying the molecular weight and the molar composition of the macroglycol on the membrane properties of these copolymers were determined. Membranes from the copolymer containing 0.3 mole % of polyoxyethylene glycol, molecular weight of 1540, dialyzed compounds such as urea, creatinine, and uric acid at a faster rate than did a Cuprophane membrane. However, sugar molecules such as glucose and sucrose showed relatively slower escape rates through the copolyester membrane than through the Cuprophane membrane. A dialysis cell suitable for laboratory studies on new polymeric membranes is described.

The fractionation of solutes by means of their differential rates of diffusion through a membrane is potentially an ideal technique for separating complex mixtures such as blood. However, owing to various shortcomings of existing commercial membrane materials the dialysis technique has been limited in its scientific and clinical applications. For example, gel cellophane is still considered to be the best available material for extracorporeal hemodialysis; yet the slow rate of dialysis of molecules having molecular weights greater than several hundred has limited this technique in treating blood chemistry disorders. Several recent studies (Biget, 1947; Immergut *et al.*, 1954; Craig and Konigsberg, 1961; Michaels *et al.*, 1962) have shown that membranes having improved porosity could be obtained by suitable aftertreatment, such as linear stretching of wet membranes, swelling and annealing of films at elevated temperatures, forming networks in the films by extracting compounds which had been dispersed in the original film, or by chemical reactions on the membrane material. Some of these membranes were reported to be permeable to polymers

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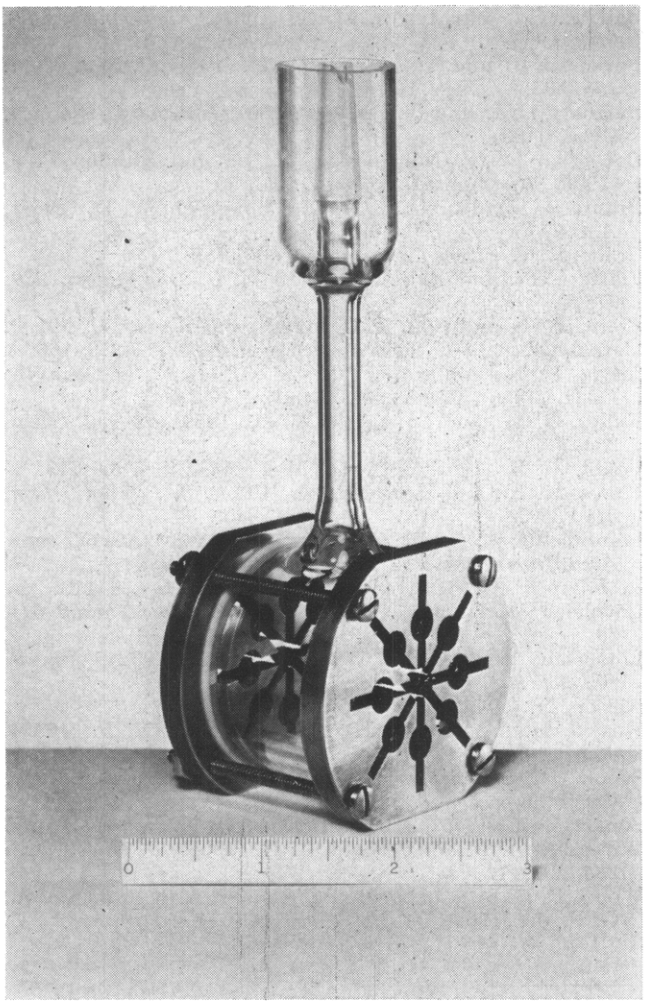


FIG. 1.—View of the assembled dialysis cell.

having molecular weights as high as 134,000 (dimer of serum albumin). However, these techniques do not appear suitable for large-scale preparation of membranes needed for general clinical and medical research use.

New commercial polymer membranes prepared from polyvinyl alcohol, polyvinyl formal, polyamide, etc. have improved the practical aspect of commercial dialysis by providing stronger membranes. However, these still have about the same molecular-size limitations for dialysis as those of gel cellophane.

A program was recently initiated in this laboratory on the development of new synthetic polymer membranes which are designed molecularly for improved dialysis of blood. This paper reports the synthesis and the dialysis properties of copolymers from polyoxyethylene glycol and polyethylene terephthalate.

EXPERIMENTAL

Polymer Intermediates.—Ethylene glycol, suitable for polyesterification, was prepared by dissolving 1% of metallic sodium in the glycol under nitrogen and distilling through a spinning-band column under reduced pressure. Boiling point was 81–82°/4.0 mm.

Polyoxyethylene glycols (Carbowax 600, 1000, 1540, 4000, Union Carbide Corp.) were degassed at 60°/0.2 mm for 3 hours. Molecular weights, determined by acetylation with an acetic anhydride–pyridine mixture, were 638, 978, 1401, and 4000, respectively.

Dimethyl terephthalate was recrystallized from methanol. Melting point was 145.5–146°.

Antimony trioxide (reagent powder, Matheson, Coleman, and Bell) and calcium acetate monohydrate (reagent, Merck and Co.) were used as received.

Polymerization.—The block copolyesters were prepared using a modification of the polyesterification technique described by Coleman (1954). The condensations were carried out in a glass polymerization tube about 35 × 250 mm, sealed to a 10 × 150–mm neck carrying a side arm for distillation. A typical polyesterification reaction was carried out as follows: In the tube were placed 13.6 g (0.07 mole) of dimethyl terephthalate, 29.41 g (0.021 mole) of polyoxyethylene glycol, (mw 1401), 7.45 g (0.12 mole) of ethylene glycol, 0.022 g (0.15% based on dimethyl terephthalate) of calcium acetate monohydrate, and 0.005 g (0.035% based on dimethyl terephthalate) of antimony trioxide. The mixture was melted by placing the tube in the vapors of a boiling ethylene glycol–vapor bath (197°), and nitrogen was bubbled through the melt by means of a fine capillary. Methanol distilled rapidly for a few minutes. The reaction mixture was heated for 3 hours at 197°; then the tube was transferred to a 222° (methyl salicylate) vapor bath for 0.5 hour, during which time excess glycol distilled and polymerization began. The tube was then transferred to a 270° (diphenyl methane–orthophenyl phenol, 60:40) vapor bath and the side arm of the polymer tube was connected for vacuum distillation. After approximately 20 minutes vacuum was slowly applied, and the pressure was lowered to 0.2 mm in about 15 minutes. The reaction mixture was heated at 270°/0.2 mm for an additional 3 hours. The polymerization tube was then removed from the bath, the capillary was withdrawn from the melt, and the polymer was allowed to cool. The glass was cracked away from the plug of polymer, and the plug was filed with a coarse file to remove last traces of glass. Inherent viscosity was 1.05 in 1,1,2,2-tetrachloroethane-phenol (40:60) at 30° and 0.5% concentration.

Preparation of Membranes.—Thin, clear, tough membranes of several copolyether esters were prepared by casting dichloromethane solutions of the polymer (containing approximately 15–20% polymer) on a glass plate, using a Doctor knife. The solutions had been pressure-filtered through a sintered-glass filter prior to being cast. The films were air-dried, and then removed from the glass plates by immersion in water.

Cuprophane membranes (a cuprammonium cellulose film) were obtained from the Kidney Disease Division, University Hospital, University of Washington.

Dialysis Apparatus.—The dialysis cell used in these studies is shown in Figure 1. The cell has a capacity of 38.0 ml and utilizes two membranes, 5 cm in diameter. Each membrane is held between two grooved stainless steel plates which gives maximum support with maximum membrane area. Total available membrane area for dialysis is 16.50 cm^2. Teflon gaskets are used between the stainless steel plate assembly and the glass cell, and the entire assembly is held together by four screws. An exploded view of the cell is shown in Figure 2. The dialysis cell is placed in a modified 1-liter resin kettle which is used as the dialysis bath, and the whole assembly is placed in a constant-temperature bath. A circulating tube pump having a capacity of 3.6 liters/min is used to circulate the bath fluid. The dialysis cell is stirred internally by the slow bubbling of nitrogen through a capillary which extends to the bottom of the dialysis cell. During long runs, a glass cover is placed over the bath to minimize loss of fluid by evaporation. A schematic diagram of the dialysis system is shown in Figure 3. The solution being dialyzed can be easily removed

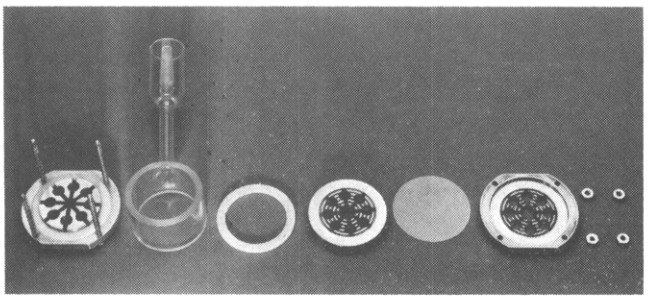


FIG. 2.—Exploded view of the dialysis cell.

from the cell by means of a syringe equipped with a 15-cm hypodermic needle. The cell is cleaned after each dialysis by placing it in a beaker of distilled water, removing the solution from the cell, and rinsing the cell six times with distilled water.

Rate studies were made at 30° (±0.1) using both distilled water and an aqueous salt solution as the medium. The aqueous salt solution contained the following ions (milliequivalents per liter): sodium, 139; calcium, 2.6; magnesium, 1.0; chloride, 120; and bicarbonate, 27. One g/100 ml of glucose was added to this solution and the *p*H was adjusted to 7.4 by the addition of 85% lactic acid.

The following represents a typical run. The dialysis cell, filled with 38 ml of water, was placed in a modified cylindrical glass flask which contained 500 ml of distilled water and the dialyzing system was maintained at 30° in a constant-temperature bath. The water in the cell was then removed using a syringe with a 15-cm needle, and 38 ml of a creatinine solution containing 750 mg of creatinine was immediately syringed into the dialysis cell. Aliquots (1.0 ml) of solution were removed from the dialysis bath at specific intervals and analyzed.

Analytical Techniques.—Samples removed from the bath were analyzed as follows: Urea was determined by the urease method of Van Slyke and Cullen (Hawke *et al.*, 1954); creatinine was determined by the photometric micro modification of Folin (Hawke *et al.*, 1954); uric acid was determined by the photometric method of Benedict and Franke (Hawke *et al.*, 1954); all other compounds were analyzed by the gravimetric procedure described by Craig (1951).

RESULTS

A series of copolymers based on polyoxyethylene glycol (Carbowax) and polyethylene terephthalate were prepared in which both the molecular weight and the mole per cent of the polyoxyethylene glycol in the copolymer were varied. The polymers synthesized in this study and their bulk properties are tabulated in Table I.

A group of these copolymers which appeared to have a proper balance of polymer melt temperature, wet and dry strength, and solubility were then prepared in film form for further investigation. Thin crystal-clear films of these copolymers were readily prepared by solution-casting of filtered polymer solutions. By controlling the quantity of polymer in the solutions as well as the drying temperatures, and by using Doctor knives to control film thickness, very reproducible films were obtained. The films could be stripped from the glass casting plate if care was taken not to stretch them. However, a better technique was to cut the film with a circular cutter, and then dip the glass plate into water to float the film free of the plate. It was of interest to note that the copolymer membranes on being immersed in water swelled in both

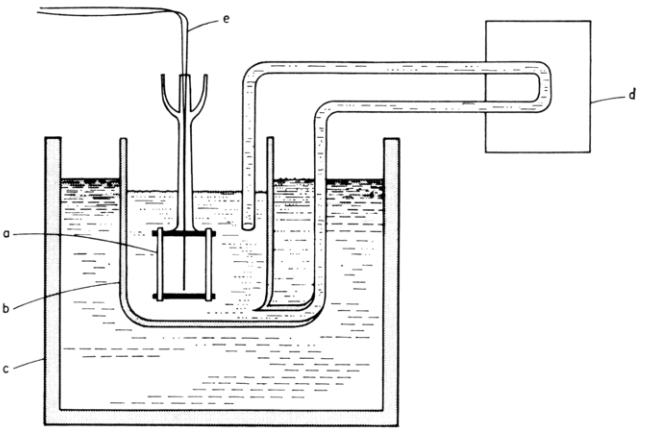


FIG. 3.—Schematic drawing of the dialysis assembly. (a) Dialysis cell; (b) modified cylindrical flask; (c) constant temperature bath; (d) circulating pump; (e) nitrogen bubbler.

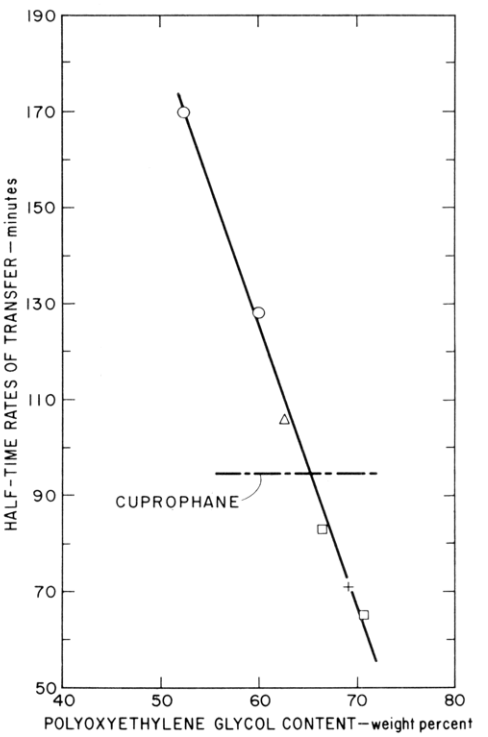


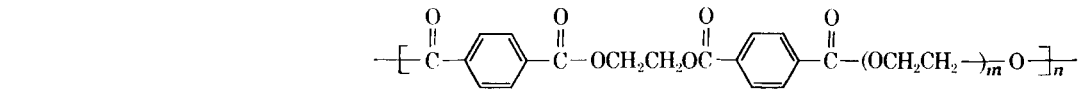
FIG. 4.—The effect of the weight per cent of polyoxyethylene glycol in the copolymer on the half-time rates of transfer of urea. Molecular weights of polyoxyethylene glycols: O, 600; △, 1000; □, 1540; +, 4000. The dashed line represents the half-time rate through Cuprophane.

dimensions, while those of Cuprophane swelled primarily in the thickness dimension. As a result, in order to prepare copolyester films having a wet thickness similar to the Cuprophane, thicker films had to be prepared initially.

In order to study the dialysis properties of new synthetic polymer membranes prepared in this program, a dialysis cell of improved design suitable for laboratory studies was developed. This cell allows accurate control over both the membrane area and the volume of the dialyzing solution. The grooved plates give maximum support to the membranes and minimize stretching or rupturing of them during repeated dialyzing studies. Also, since flat membranes rather than a sac or tube are utilized, membrane thickness, both wet and dry, as well as surface uniformity can be

TABLE I

PROPERTIES OF LINEAR COPOLYESTERS BASED ON POLYOXYETHYLENE GLYCOL



	Reactants			Bulk Properties			Solubility[a]				
No.	Macroglycol	Mole Ratio of Glycols[b]	Weight % of Polyoxyethylene Glycol in Copolymer	η_{inh}[c]	PMT[d] (°C)	Description	CH_2Cl_2	Trichlene[e]	Chlorobenzene	Cyclohexanone	DMF[e]	H_2O
I	Carbowax 600[f]	0.8 :0.2	41.4	0.49	160	Tough, white	2	0	4	3	3	0
II	Carbowax 600	0.7 :0.3	52.3	0.97	138	Tough, flexible	5	4−	4	0	1	0
III	Carbowax 600	0.6 :0.4	60.1	0.98	91	Soft, tough, rubbery	5	5	5	5	5−	0
IV	Carbowax 600	0.55:0.45	63.4	0.92	61	Tough, elastic	5	4	5	4	5	0
V	Carbowax 600	0.50:0.50	66.3	0.79	45	Moderately tough	5	5	5	4	5	1
VI	Carbowax 600	0.4 :0.6	70.0	0.48		Soft, tacky	5	5	5	5	5	1
VII	Carbowax 1000[f]	0.8 :0.2	52.0	0.96	155	Tough, flexible	2	0	0	0	0	0
VIII	Carbowax 1000	0.7 :0.3	62.7	0.92	130	Tough, elastic	5	4−	4	4	4	0
IX	Carbowax 1000	0.65:0.35	66.7	1.04	106	Tough, elastic	5	5	5	4	4	0
X	Carbowax 1000	0.6 :0.4	70.0	0.88	98	Soft, white	5	5	5	4	5	0
XI	Carbowax 1000	0.5 :0.5	75.1	0.78	67	Soft, crumbly	5	5	5	5	5	1
XII	Carbowax 1540[f]	0.8 :0.2	60.8	0.37	170	Moderately tough, flexible	2	1	2	0	2	1−
XIII	Carbowax 1540	0.75:0.25	66.4	0.99	145	Tough, flexible	5	4	4	4−	4	0
XIV	Carbowax 1540	0.7 :0.3	70.7	1.05	124	Tough, flexible	5	4	4−	4−	4	0
XV	Carbowax 1540	0.65:0.35	74.1	1.12	114	Waxy solid	5	5	4	4	5	1
XVI	Carbowax 1540	0.6 :0.4	77.0	0.68	70	Waxy, crumbly	5	5	5	5	5	1
XVII	Carbowax 4000[f]	0.9 :0.1	69.4	1.15	163	Tough, hard	5	3	3	3	4	0
XVIII	Carbowax 4000	0.85:0.15	77.5	0.43	50	Waxy, crumbly	5	5	5	5	5	1
XIX	Carbowax 4000	0.8 :0.2	81.5	0.73	50	Waxy, crumbly	5	5	5	5	5	1

[a] 0 = insoluble; 1 = swells; 2 = slightly soluble hot; 3 = soluble hot, ppt cold; 4 = soluble hot; 5 = soluble cold. [b] Mole ratio of ethylene glycol to polyoxyethylene glycol. [c] Inherent viscosity measured in 1,1,2,2-tetrachloroethane–phenol at 30° (concn 0.5%). [d] Polymer melt temperature is that temperature at which the polymer leaves a molten trail when stroked along a temperature-gradient bar. [e] Trichlene is 1,1,2-trichloroethylene; DMF is *N*,*N*-dimethylformamide. [f] Trademark of Union Carbide polyoxyethylene glycols.

accurately measured. The use of a circulating pump to stir the dialysis bath and of a nitrogen bleed to stir the dialysis solution gave very reproducible results.

A series of copolyether-ester membranes were then examined to determine the effect of both molecular weight and weight per cent of polyoxyethylene glycol in the copolymers on the rate of dialysis of selected compounds. Figure 4 shows the effect of copolymer type and composition on the transfer rate of urea through the membrane.

When the dialyses were conducted using a salt solution similar in composition to that currently being used in clinical hemodialyses, instead of water, no appreciable change was noted in the escape rates of urea or creatinine for either the copolyester membrane or the Cuprophane membrane. This would indicate that these ions had no effect on either the membrane or the urea or creatinine molecule.

The copolyester containing 0.3 mole % polyoxyethylene glycol, mw 1540, [2G-T/PO4(1540)G-T (0.7:0.3)] was then investigated in more detail as a dialysis membrane.[1] The relative dialysis rates for various compounds through this membrane are contrasted with similar rates for a Cuprophane membrane in Table II.

The effect of temperature on the dialysis was studied for both the copolyester membrane and the Cuprophane membrane. From the rate of escape at 30°, 40°, and 50° (Fig. 5), temperature coefficients were determined.

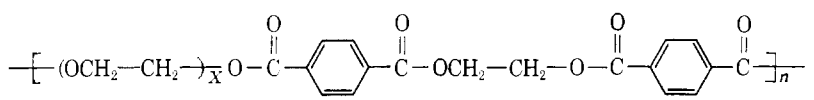
Table II
Relative Dialysis Rates of Various Compounds

Compound	Molecular Weight	Half-Time Escape Rates (min)	
		Copolyester Membrane[a]	Cuprophane Membrane
Urea	60.8	58	68
Creatinine	113.1	117	123
Uric acid	168.1	217	320
Ascorbic acid	176.1	135	178
Glucose	180	268	223
Thiamine chloride	337.3	150	160
Sucrose	342	397	270
Raffinose	504.5	930	450
Bacitracin	1411	568	720
Insulin[b]	6000	26% in 30 hrs.	None
Polysarcosine	6700	36% in 30 hrs.	15% in 30 hrs.

[a] 2G-T/PO2(1540)G-T (0.7:0.3). [b] Dialysis bath and solution contains 1.6 ml of 85% aqueous lactic acid per liter of H_2O. At this *p*H and concentration (1 mg/ml) the insulin may be present as the dimer (mw 12,000).

Discussion

Membranes suitable for the dialysis of blood must possess a high degree of swelling in aqueous media and good mechanical strength. Such a combination of properties is difficult to achieve in homopolymers, and it was therefore of interest to investigate copolymers as new membrane materials. In particular we investigated block copolymers, since preliminary studies indicated that a balance of these properties might be possible. Initial studies on new synthetic-membrane polymers have been concerned primarily with block copolymers based on polyoxyethylene glycol (Carbowax) and polyethylene terephthalate



This system was chosen because of the high water solubility of the polyoxyethylene glycols and the relative ease of synthesizing these polyesters. In addition, the size of the macroglycol segment as well as the amount of it in the copolymer could be varied. In general, it was found that the size of the polyoxyethylene glycol macrosegment had little effect on the polymer melt temperature (Fig. 6), this property being primarily determined by the mole per cent of polyoxyethylene glycol in the copolymer. However, the degree of swelling of the polymers in water, their solubility in organic solvents, and their bulk properties were greatly affected by both the size of the macroglycol and its weight per cent in the copolymer.

A group of these copolyether-esters which appeared to have a proper balance of polymer melt temperature, wet and dry strength, and solubility were solution cast into films for preliminary dialysis studies. Since the results of this study are being coordinated with clinical studies under way in the Division of Kidney Diseases, University of Washington School of Medicine, the transfer of urea, creatinine, and uric acid through these new synthetic polymer membranes was of particular interest.

Initial experiments indicated that the rate of transfer of urea is dependent on the weight per cent of the water-soluble polyoxyethylene glycol in the copolymer, and that copolymers containing 65% by weight or more of the macroglycol have transfer rates as good as or better than Cuprophane membranes (Fig. 5). The dialysis rate determined using our apparatus relates the over-all dialysis resistance of the membranes (i.e., the membrane resistance plus the combined liquid film resistance). No attempt was made to eliminate or minimize the liquid-film resistance, such as by high speed stirring, since these techniques do not appear to be compatible with actual hemodialysis techniques.

Since copolymers containing more than 65% by weight of polyoxyethylene glycol were of particular interest, the copolymer containing 0.3 mole % (70.7 weight %) of polyoxyethylene glycol, mw 1540, was investigated in more detail. Transfer of urea, creatinine, and uric acid through this membrane was faster than through the Cuprophane membrane; the half-escape times were 58, 117, and 217 minutes, respectively. The half-escape times of these compounds through the copolyester membrane varied linearly with thickness over the measured range of 0.001–0.005 cm.

Since this copolyester membrane was found to be more permeable to urea, creatinine, and uric acid, the dialysis of additional compounds of varying molecular weights and structure was then examined to see if the upper molecular-weight limit for transfer was also increased. The half-escape times for the compounds dialyzed are shown in Table II. In general, increasing the molecular weight of the compound being dialyzed decreases the rate at which it is transferred through the membrane. However it is of particular interest to note that, while most compounds showed

[1] 2G refers to ethylene glycol; PO4(1540)G refers to polyethylene glycol, mw 1540; T refers to terephthalic acid; 0.7:0.3 refers to water ratio of the glycols.

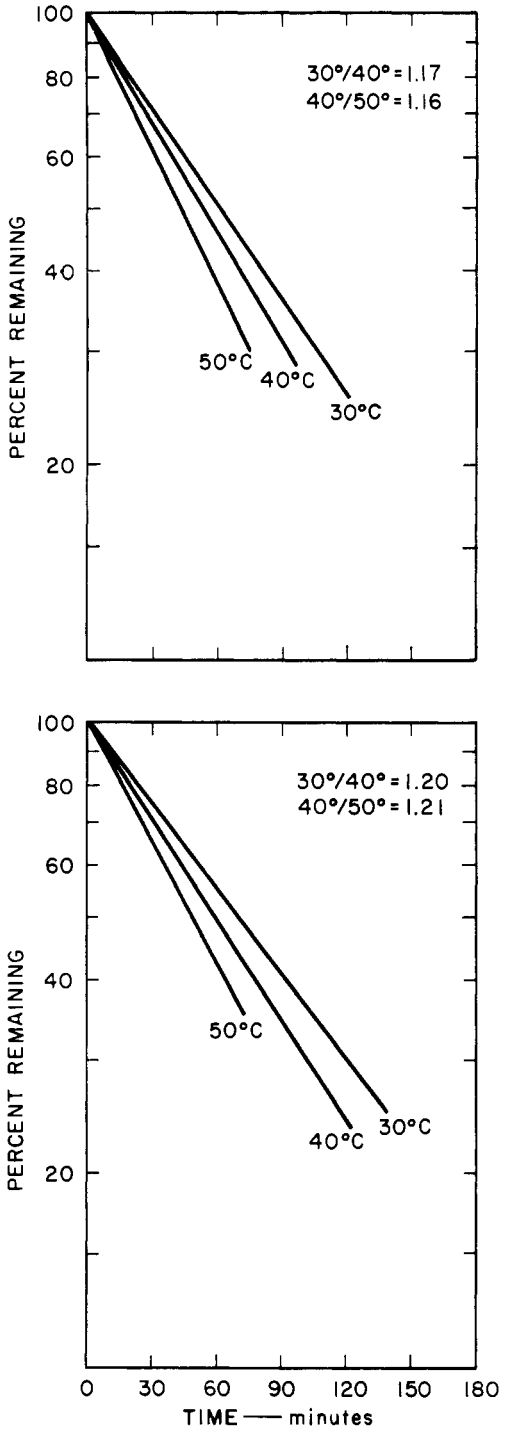


FIG. 5. Temperature coefficients for the copolyester membrane (upper curves) and the Cuprophane membrane (lower curve).

faster dialysis rates through the copolyester membrane than through the Cuprophane membrane, the sugars showed the opposite effect, i.e., their escape times were relatively slower through the copolyester membrane. These differences may be related to differences in the solubility of the compound in the macrosegment or to configurational effects which may be more pronounced for the copolymer membrane. This is being investigated in more detail.

The effect of temperature on the dialysis of urea through both the copolyester membrane and the Cuprophane membrane was determined.

For low-molecular-weight solutes, a modification of the Stokes-Einstein equation (Wilke and Chang, 1955), $D = 7.4 \times 10^{-8} [(XM)^{0.5}T/\eta V^{0.6}]$, should hold, and

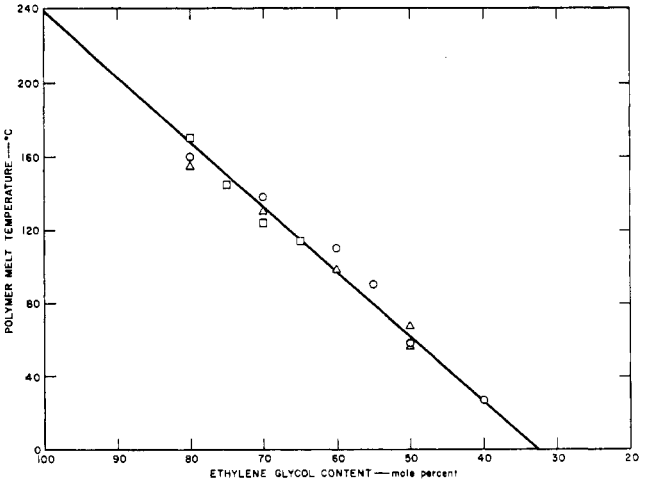


FIG. 6.—The effect of the molar composition of the polyoxyethylene glycol–ethylene terephthalate copolymers on their polymer melt temperature. Molecular weights of polyoxyethylene glycols: ○, 600; △, 1000; □, 1540.

the rate of dialysis should be directly proportional to the absolute temperature and inversely proportional to the viscosity.[2] From the data of Wilke and Chang it can be calculated that urea in water should dialyze 1.26 times as fast at 40° as at 30° and 1.25 times as fast at 50° as at 40°. The ratios noted in Figure 5 are somewhat lower than this, indicating either that the urea is hydrated or that the swollen membrane contributes to the viscosity factor. The slight increase in the ratios at higher temperatures could also result from a decrease in hydration of the urea or a decrease in the viscous resistance within the film.

This work on block copolymers indicates that synthetic polymer membranes having improved dialysis characteristics can be synthesized. Also, by proper design of the macrosegment, a high degree of selective semipermeability appears to be possible, which would allow the separation of molecules having similar molecular weight or configuration but differing in their molecular structure. This could be of particular importance in separation of abnormal structures in blood. The synthesis and characterization of new copolymer systems is continuing and will be reported in later papers.

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[2] X = association parameter defining the effective molecular weight of the solvent with respect to the diffusion process (for H_2O, 2.6), and V = molal volume of the solute.