
**Journal of Macromolecular Science, Part A**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

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**To cite this Article** Kesting, Robert E.(1970) 'Control of Polymer Morphology for Biomedical Applications. I. Hydrophilic Polycarbonate Membranes for Dialysis', Journal of Macromolecular Science, Part A, 4: 3, 655 — 664
**To link to this Article: DOI:** 10.1080/00222337008074368
**URL:** http://dx.doi.org/10.1080/00222337008074368

J. MACROMOL. SCI:–CHEM., A4(3), pp. 655-664, May, 1970

# Control of Polymer Morphology for Biomedical Applications. I. Hydrophilic Polycarbonate Membranes for Dialysis

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## SUMMARY

The control of polymer morphology for biomedical applications is discussed by a detailed reference to the tailormaking of polycarbonates for hemodialysis membranes, a case in which control was necessary on molecular, microcrystalline, and colloidal levels.

On the molecular level, the hydrophilicity of the parent polymer, bisphenol-A polycarbonate, was increased with the introduction of aliphatic ether groups by the copolymerization of bisphenol-A and the polyethylene glycols. On the microcrystalline level it was found that the bisphenol-A polycarbonate blocks formed crystallites within the amorphous matrix composed of the polyethylene oxide blocks. Because of this the modified polymer retained most of the strength of the parent bisphenol-A polycarbonate. Another striking property exhibited by the copolymer is that the tensile strength of the wet material was in excess of that of the dry. This has been attributed to plasticization and realignment of the polyethylene oxide blocks by water molecules. Finally, morphology on the colloidal level was controlled by the preparation of asymmetric membranes possessing a skin layer and a substructure whose void volume, and hence resistance to material transport, could be varied at will.

## INTRODUCTION

Because of the limitations of commerically available cellulose films (the only membranes in current clinical use for hemodialysis applications) with respect to dialysis rates, wet strength, thrombogenicity, and protein sorption, there has been considerable interest in the development of improved membrane types. The various efforts towards this end may be viewed as de facto attempts to control polymer morphology on the molecular, microcrystalline, and colloidal levels. Thus Lyman's [1] studies with the co(polyethylene glycol-polyethylene terephthalates) represented an attempt to maintain the excellent physical properties (primarily attributable to their microcrystalline structure) of the unmodified poly(ethylene terephthalates) while at the same time midifying their molecular structure so as to increase hydrophilicity and hence permeability. The work of Martin et al. [2] to produce asymmetric cellulose acetate dialysis membranes can be considered as an attempt to vary structure on the colloidal level so as to decrease the resistance to material transport. The present study, on the other hand, is based upon the assumption that geometric improvements may result through simultaneous control of membrane morphology on all three levels.



Bisphenol-A polycarbonate was chosen as the parent polymer because of its outstanding physical properties as well as its ease of processing (solubility in water-miscible organic solvents, heat sealability, etc.). The introduction of ether groups was intended to increase hydrophilicity as in Lyman's case. Control of the colloidal structure was accomplished through the utilization of multicomponent solutions and lends support to a published hypothesis [3, 5] concerning the effect of swelling agents upon the nature of the cellular structure of asymmetric membranes. Some of the advantages of the hydrophilic polycarbonates are outstanding wet strength (ultimate wet tensile strength actually exceeds ultimate dry tensile strength!), dry storage capability, and low protein sorption. Although no dialyses have yet been conducted with asymmetric hydrophilic polycarbonate membranes, their high water contents indicate the rates will be high.

## EXPERIMENTAL

### A. Polycarbonate Synthesis

Copolyether-polycarbonates were synthesized according to the solution polymerization procedure of Goldberg [4]. Varying amounts of bisphenol-A

(recrystallized 2x from aqueous ethanol) and polyethylene glycol (Carbowax 4000, Union Carbide) were dissolved in pyridine and added to a water-jacketed 3-necked flask fitted with a gas inlet tube, a stirrer, and an acetone-Dry Ice condenser. The reactions were carried out at 30 ± 5°C and the flow of phosgene was maintained until the solution became too viscous to stir. Pyridine was removed by extraction with isopropanol in a Waring Blendor. The raw polymer was dried in vacuo at 50°C before storage.

### B. Membrane Fabrication

Both modified and unmodified polycarbonate membranes were prepared by the evaporation of solutions of the polymer in a solvent system consisting of dioxane and tetrahydrofuran (50/50) to the point of incipient gelation prior to their immersion in water at 0°C.

### C. Bacteriophage Retention

One milliliter aliquots of a stock solution of $^{32}P$ labeled bacteriophage were diluted to 20 ml with particle-free water and passed through 0.45 $\mu$ pore size Millipore HA and bisphenol-A polycarbonate membranes ~2 cm in diameter. After filtration the membranes were washed twice with 20 ml of distilled water. The samples were then dried and counted.



## EXPERIMENTAL RESULTS AND DISCUSSION

### A. Asymmetric Membranes of the Bisphenol-A Polycarbonates

Prior to the synthesis of the hydrophylic polycarbonates described in the following section, a program to produce membranes of the unmodified bisphenol-A polycarbonates was undertaken. The primary objective of this program was to test the feasibility of producing asymmetric membranes of this material. A second objective was to test, with a readily available non-cellulosic polymer, the generality of a published hypothesis [3, 5] relative to the role of swelling agents in the preparation of phase inversion membranes. The results proved to be consistent with previously established relationships between the concentration of swelling agent in the casting solution and the degree of swelling and permeability of the resultant membranes (Table 1) [3, 5].

As was shown to be the case for cellulose acetate ultrafiltration membranes, polymer-volatile solvent systems containing no swelling agent did not

**Table 1.** Effect of Swelling Agent Concentration on Degree of Swelling and Permeability of Bisphenol-A Polycarbonate Membranes

| Concentration of swelling agent (wt%) | Degree of swelling (wet wt/dry wt) | Efflux time [to collect 10 ml effluent at 30 mm Hg (min)] |
|---|---|---|
| 0 | 1.01 | ∞ |
| 4 | 4.16 | 132.5 |
| 8 | 6.00 | 2.9 |
| 12 | 10.10 | 0.6 |

separate into two interdispersed liquid phases prior to gelation so that dense (nonporous) films resulted (Fig. 1). Such structures were highly impermeable. With low concentrations of swelling agent, phase separation occurred rather late in the desolvation process so that the droplets of the second phase were few in number and relatively widely spaced. For this reason closed cell structures, exhibiting a substantial resistance to material transport, were produced (Fig. 2). At a high concentration of swelling agent, on the other hand, droplets of the second liquid phase appeared very early in desolvation (owing to the decreasing solvent power of the solvent-swelling agent system as the volatile solvent evaporated). The droplets of the second phase (in effect the sol precursors of the membrane gel structure) were, owing to the necessity of the surface-active polymer molecules to spread themselves over a large total surface area, so thin walled as to rupture upon gelation and solvent depletion (Fig. 3). Thus membranes possessing open-celled pores in their substructure may be produced from multicomponent polymer solutions containing swelling agents that are less volatile than the solvents. This fact is relevant to hemodialysis because if the substructures of asymmetric membranes can be made so porous that dialysis solutions can flow virtually unimpeded through them, the resistance to material transport can be limited to that offered by the thin skin layer.

Asymmetry in depth results from the more rapid desolvation of both volatile solvents and swelling agents which occurs at the air/solution interface than in the interior solution. Because of this a gelled skin which is comparatively denser in polymer than the still fluid substructure results. Although the density of both surface and substructure layers will increase with evaporation time, the higher initial density of the former will favor the formation of a nonporous skin before the latter has lost its porosity (Fig. 4). If the evaporation is allowed to proceed to completion in such a manner that no

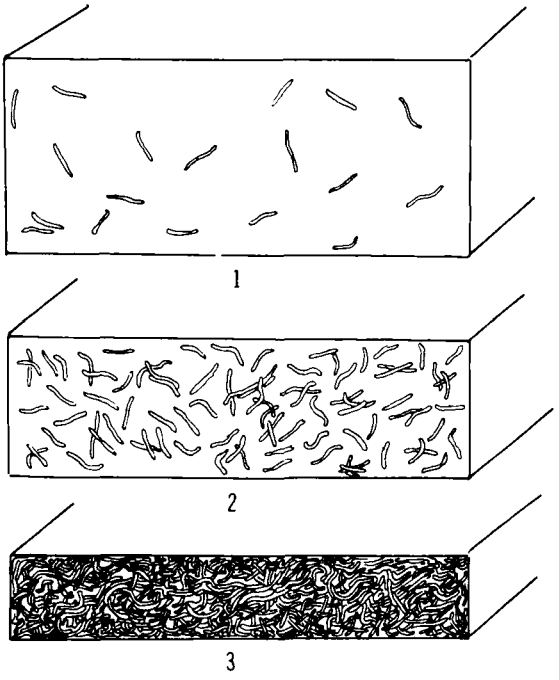



**Fig. 1.** Polymers in solvent with no swelling agent. 1: Dilute solution. 2: Concentrated solution. 3: Gel.



abrupt sol-gel transition occurs prior to dryness, the skin layer will in fact be equal to the total thickness of the membrane.

In utilizing membranes for dialysis and ultrafiltration of biological solutions or suspensions, the extent to which blockage (owing to the sorption of proteinaceous matter smaller than the pore size) occurs is of considerable interest. Such blockage may account for part of the decrease in dialysis rates that are observed during hemodialysis. In addition the removal of proteins from the blood, even if only temporarily, might result in denaturation and unknown but perhaps deleterious effects upon the well-being of the patient. The retention of radioactively-labeled ($^{32}P$) bacteriophage through cellulosic and polycarbonate membranes of identical pore size was utilized as a model system for studying nonspecific protein sorption (Table 2).

The results indicate that the polycarbonate membrane exhibits only 1/30 the capacity of its cellulosic counterpart to sorb proteinaceous materials. This result is at least partially attributable to the lesser polarity of the polycarbonates, although differences in rugosity may also be partially responsible.

Table 2. Retention of $^{32}P$-Labeled Bacteriophage by Cellulosic[a] and Polycarbonate Membranes with 0.45 $\mu$ Pores

| Membrane | Approximate counts/min | Ratio of counts given membrane counts on other membrane |
|---|---|---|
| Cellulosic | 6000 | 30/1 |
| Polycarbonate | 200 | 1/30 |

[a]Millipore (cellulose acetate-nitrocellulose blend).



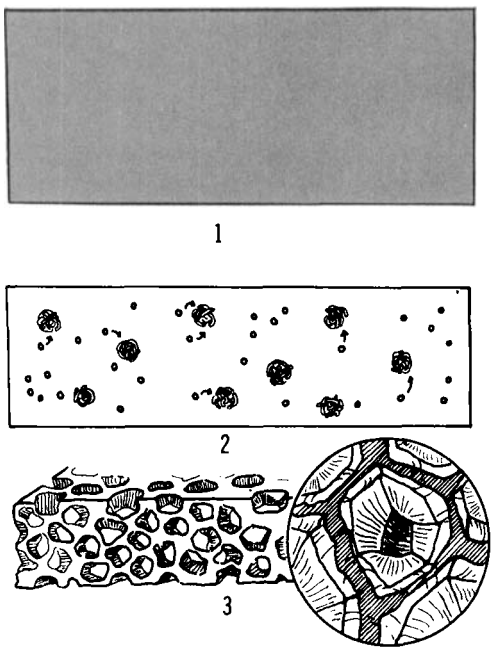



Fig. 2. Polymer in solvent with low concentration of swelling agent. 1: Dilute solution. 2: Concentrated solution. 3: Gel with closed cells.

Once the feasibility of producing asymmetric polycarbonate membranes which were superior in many respects to the corresponding cellulosic types had been demonstrated, their subsequent modification for hemodialysis applications was deemed appropriate. Of the many possible approached to this end, the preparation of the poly(oxyethylene) glycol-bisphenol-A copolycarbonates has thus far proven to be the most suitable.

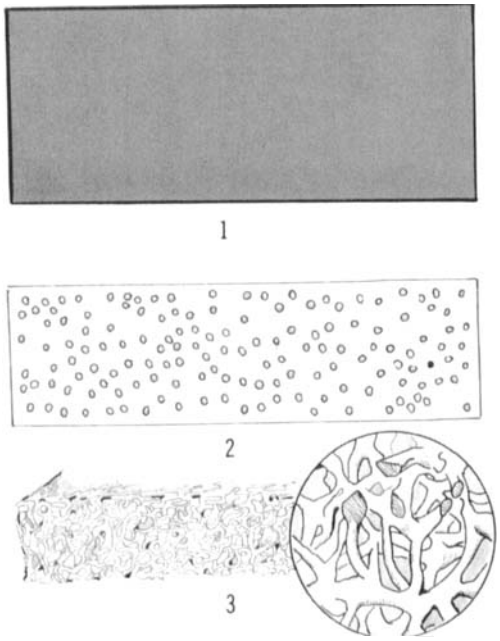
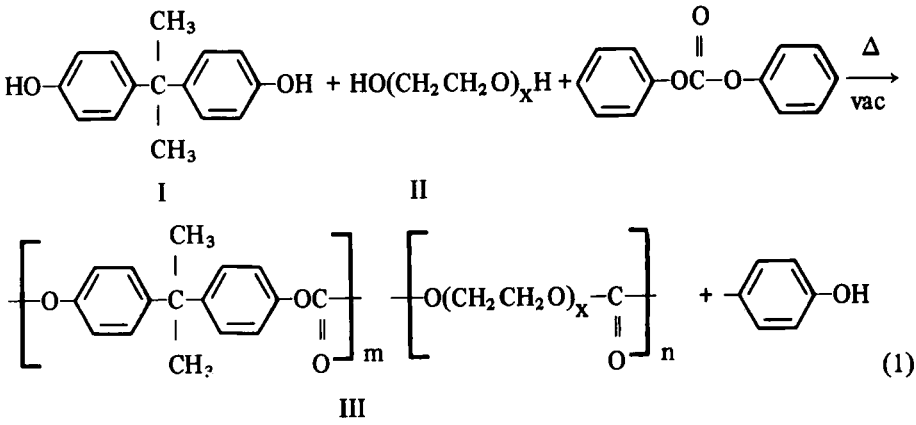



**Fig. 3.** Polymer in solvent with high concentration of swelling agent. 1: Dilute solution. 2: Concentrated solution. 3: Gel with open cells.



### B. The Poly(oxyethylene) Glycol–Bisphenol-A Copolycarbonates

After a few abortive attempts to carry out the bulk polymerization ester interchange reaction:




(1)

the solution polymerization reaction:

$$\text{I} + \text{II} + \text{COCl}_2 \xrightarrow{\text{pyridine}} \text{III} + \text{pyridine HCl} \qquad (2)$$

was employed for all subsequent syntheses.

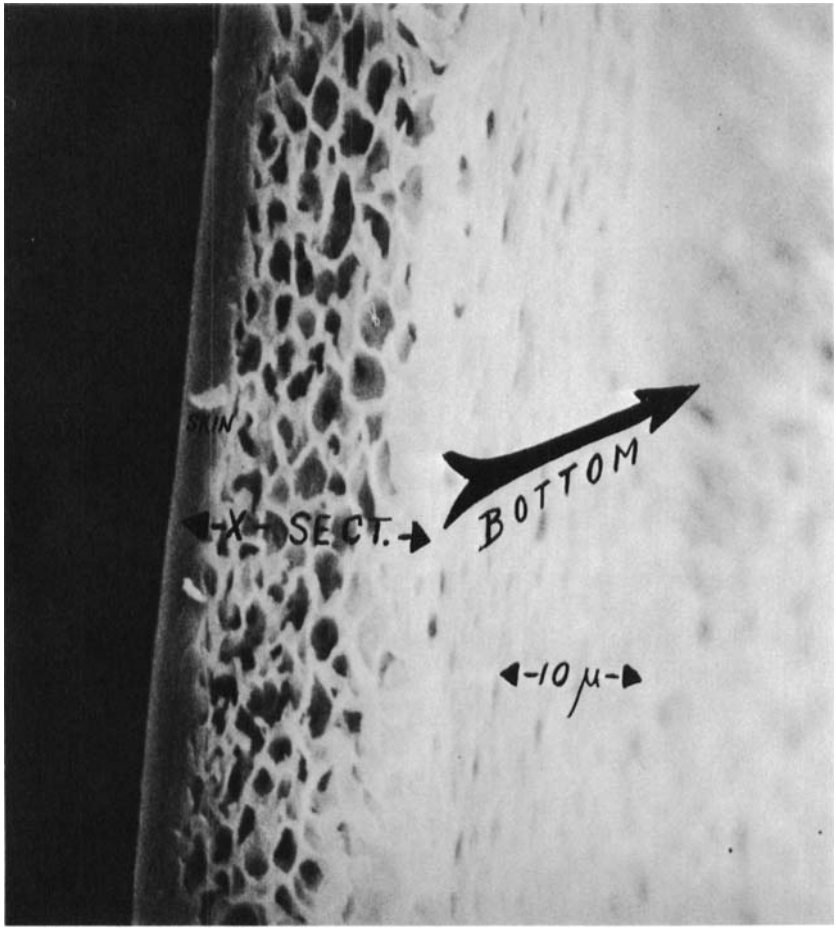



**Fig. 4.** Scanning electron photomicrograph of cross-section of an asymmetric polycarbonate membrane.

The products of route (1) were discolored and tended to decompose at the high temperatures necessary to achieve high molecular weights. In addition, phenol condensed in the vacuum system, necessitating the interuption of the polymerization procedure. By contrast, route (2) gave trouble-free synthesis whose only difficulty was the complete removal of pyridine from the product. The ultimate tensile strengths of this series of copolymers was reported by Goldberg [4] to vary between 8200 psi for the unmodified bisphenol-A polycarbonate to about 6500 psi for the poly(oxyethylene) glycol-bisphenol-A copolycarbonate containing 55 wt% Carbowax 4000. Tensile strength decreased rapidly at higher concentrations of polyethylene glycol, dropping to below 4000 psi at 65 wt%. X-ray diffraction studies [4, 6] showed that the bisphenol-A carbonate segments exhibited a moderate degree of molecular order, with no crystallinity attributable to the polyethylene oxide segments although the poly(oxyethylene) glycols are themselves highly crystalline polymers.

Inasmuch as membranes were to be utilized in the water-swollen condition, tensile strengths were measured for wet as well as dry specimens. The data are not presented here because they were not sufficiently quantitative. Nevertheless, the finding that ultimate tensile strengths were substantially higher for the wet than for the dry membranes (measured for copolymers containing 40, 50, and 60 wt% Carbowax) was qualitatively evident. Furthermore, these values appear to be 3-4 times those exhibited by dense water-swollen cellulose films.

This unexpected but highly desirable result may be due to increased order within the polyethylene oxide segments owing to the combined effects of plasticization by water and stress-induced orientation. Evidently the polyethylene oxide blocks are not sufficiently mobile as to permit substantial realignment during stretching in the absence of water. A particularly desirable processing variable exhibited by these copolymers is that the entire range of compositions is soluble in single solvents such as methylene chloride and p-dioxane. Of paramount importance to the fabrication of asymmetric phase inversion membranes is the fact that the polymer-solvent solutions can tolerate the presence of large amounts of the swelling agents which are essential to the formation of a porous substructure.

The hydrophilic polycarbonates do, however, possess certain disadvantages consistent with their elastomeric nature. For example, the dry polymers containing more than 40 wt% polyethylene glycol exhibit sufficient tack as to make handling difficult. A second disadvantage is the lack of sufficient dimensional stability to permit a significant amount of ultrafiltration during hemodialysis. However, if these problems can be overcome, both dense and

and asymmetric hydrophilic polycarbonate membranes may prove to be a valuable addition to the ranks of dialysis membranes.

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*Received for publication January 20, 1970*