Membrane Permeability of Some Model Compounds Through Macroporous Membranes

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Synopsis

Membranes consisting of various amounts of poly(2-vinylpyridine) (PVN) and its oxide PVNO were prepared by casting from ethanol and pyridine solutions. Resultant membranes exhibited effective diffusion coefficients in the range of 10^{-9}–10^{-11} cm^2 s^{-1}. Effective diffusion coefficients were affected by the casting solvent, and by the hydrophilic polymer (PVNO) content.

INTRODUCTION

As the techniques of preparation and mathematical models for sustained release systems are refined, interest in the release of macromolecular compounds seems to increase. Release of macromolecules are governed by the same chemical principles as the low molecular weight compounds; but their large size puts some physical restrictions on their transport, and some routes such as simple diffusion through networks are not available to the macromolecules. It is therefore quite critical to study their permeation through membranes before attempting sustained and constant level release.

A monolithic device is normally the simplest solution to macromolecular release, but the first-order kinetics observed render them unsuitable for zero-order release. Membrane coated devices can yield zero-order release, but must have macropores or matrices which permit the transfer of these macromolecules. In order to create the macropores several techniques (e.g., incorporation of water-soluble salts in the membrane material followed by their extraction, coat formation while part of the device is masked, etc.) are used. In this work, incorporation of a hydrophilic polymer at various concentrations into the membrane material was employed to produce areas suitable for permeation of the macromolecules.

A hydrophobic polymer that is known to be nontoxic in the body of experimental animals, poly(2-vinylpyridine) (PVN), was chosen as the base material for the membrane. In order to create the macropores, this hydrophobic polymer was mixed with its hydrophilic analog, poly(2-vinylpyridine 1-oxide) (PVNO). Extraction of the hydrophilic component, after the membrane was cast, led to a series of membranes with varying properties. These properties were investigated.

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EXPERIMENTAL

Preparation of the Membrane

Poly(2-vinylpyridine) (MW 3.5×10^5, Polysciences Inc.) and its *N*-oxide (prepared from PVN according to Hasirci and Holt[1]) (PVNO) were weighed in molar PVNO : PVN ratios of 10 : 90, 20 : 80, and 30 : 70. This mixture was dissolved in the solvent of choice to yield a 10% (w/w) polymer solution. The solution was then poured in a glass mold (8×10 cm, wall height 0.15 cm), covered, and left to dry slowly at room temperature. The amount of polymer solution put into the mold directly controlled the membrane thickness. Once the membrane was dry to touch, the mold was submerged into distilled water for 10 min. Then 3-cm-wide membrane strips were marked with a blade and removed from the mold. These strips were stored in fresh distilled water for at least 3 days before use. Membrane thickness was measured in dry state both with a travelling microscope that had a calibrated mobile stage (accuracy ~ 0.1 μm), and also from the photographs obtained through scanning electron microscopy (SEM) (accuracy ~ 0.5 μm).

Measurement of Drug Permeation

In this process, two different cells were used: (a) for permeation in the direction opposite to that of gravitational force; (b) for horizontal permeation (Fig. 1). Both cells were made of plexiglass, and each had a membrane holder with an inner diameter of 1.90 cm. In cell (a), the lower compartment was filled with the drug solution of about 0.1% (w/v) and the upper compartment contained distilled water. Each compartment was 160 cm^3 in volume. At various intervals, aliquots of 1 cm^3 were removed from the upper compartment, absorbances were measured spectrophotometrically, and the amount of permeant was calculated from a calibration curve. Distilled water (1 cm^3) was added to make up for the loss in the volume. In cell (b), two upright cylinders of 435 cm^3 volume each were connected from the midsection via the membrane holder. One compartment contained the permeant and the other, distilled water. At intervals, 3 cm^3 aliquots were removed and replaced by distilled water. Measurement of the absorption was carried out on the aliquot.

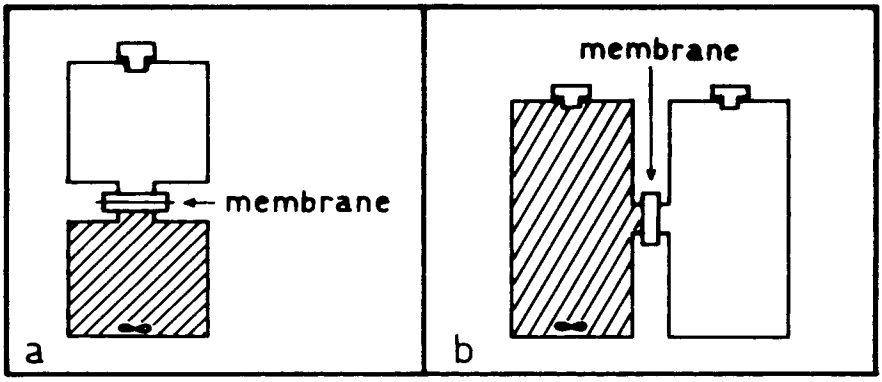

Fig. 1. Permeation cells: (a) vertical; (b) horizontal.

In both cell systems the permeant containing compartments were stirred unless otherwise stated. The permeation tests were continued for at least 11 days unless equilibration was achieved before this time.

Two types of permeants were used. One, a low molecular weight chemical, Alizarin Red S (MW ~ 400) (ARS) with an absorption maxima at 506 nm, and a macromolecular Dextran, Spectrum Orange (MW 15–20,000) (SO) with an absorption maxima at 435 nm. The thicknesses of the membranes used in these tests were between 42.3 and 141.1 μm.

Calculation of Membrane Permeability

Rate of release, R, was calculated from the initial straight line region of M_t vs. t plots, where M_t is the total weight of the drug transferred to the receiving compartment. Flux (J) and effective diffusion coefficient (D_{eff}) were calculated from Fick's second equation,

$$J = R/A = D_{\text{eff}} \cdot (\Delta C/l) \tag{1}$$

where l is thickness (cm) and A is the area of the membrane (cm^2), ΔC is the concentration difference between the two compartments ($g\ cm^{-3}$), R is the rate of release ($g\ s^{-1}$), J is the flux ($g\ s^{-1}\ cm^{-2}$), and D_{eff} is the effective diffusion coefficient ($cm^2\ s^{-1}$).

RESULTS AND DISCUSSION

Membranes cast from ethanol when tested for their permeability (horizontal direction) led to the results presented in Figure 2. It is observed when the membrane contained no hydrophilic component initially, even the low molecular weight compound ARS cannot permeate (line 4). Introduction of PVNO at a level of 10% substantially increases the permeation of both permeants (lines 1 and 3), indicating that the hydrophilic component is essential for the membrane to become permeable. The permeation of the macromolecule takes place in accordance with this conclusion (lines 1 and 2). As the amount of PVNO is increased, permeability of the membranes for the macromolecule increase. More important, however, is that the membrane is permeable to a macromolecule with a molecular weight around 15,000. Quantitation of these results are presented in Table I.

It is observed that a 10% inclusion of PVNO leads to a D_{eff} of 2.47×10^{-9} $cm^2\ s^{-1}$ for ARS instead of zero in pure PVN membrane. For the macromolecule, D_{eff} is low by an order of magnitude, but there still is significant permeation of the macromolecule. HEMA membranes were found to have permeabilities of about $10^{-7}\ cm^2\ s^{-1}$ for the much smaller urea and sodium chloride,[2] indicating that the PVNO–PVN membrane permeability is quite reasonable. Besides Sada et al.[3] found that when myoglobin (MW 17,800) replaces urea (MW 60) as permeant, the diffusion coefficient fell by a factor of 10. Thus, our results are quite in accordance with those reported in the literature. When PVNO content is increased to 30%, a ninefold increase in D_{eff} is observed. These values indicate that permeation of macromolecules is possible with this technique and the extent of permeation can be controlled by the hydrophilic polymer content.

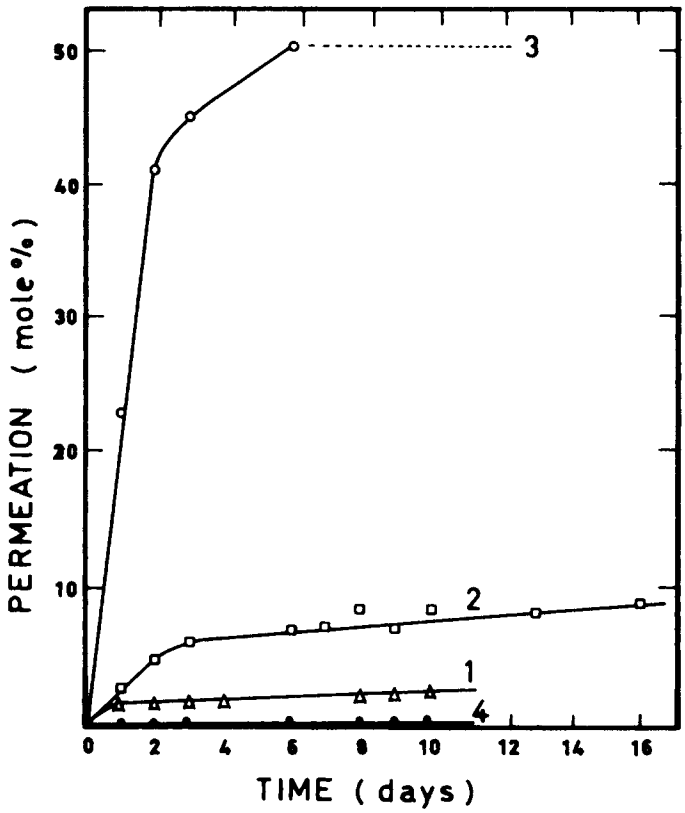

Fig. 2. Transport of permeants through membranes of various compositions; spectrum orange through 10% PVNO (1) and 30% PVNO (2). Alizarin Red S through 10% PVNO (3) and 100% PVN (4).

TABLE I
Permeation of ARS and Spectrum Orange through Membranes of Different Compositions

PVNO : PVN input (mol)	Permeant	$R \times 10^9$ (g s^{-1})	$J \times 10^{14}$ (g cm^{-2} s^{-1})	$D_{eff} \times 10^{10}$ (cm^2 s^{-1})
1 : 9	ARS	24.8	25.0	24.7
1 : 9	SO	1.06	1.10	1.05
3 : 7	SO	9.62	9.95	9.06

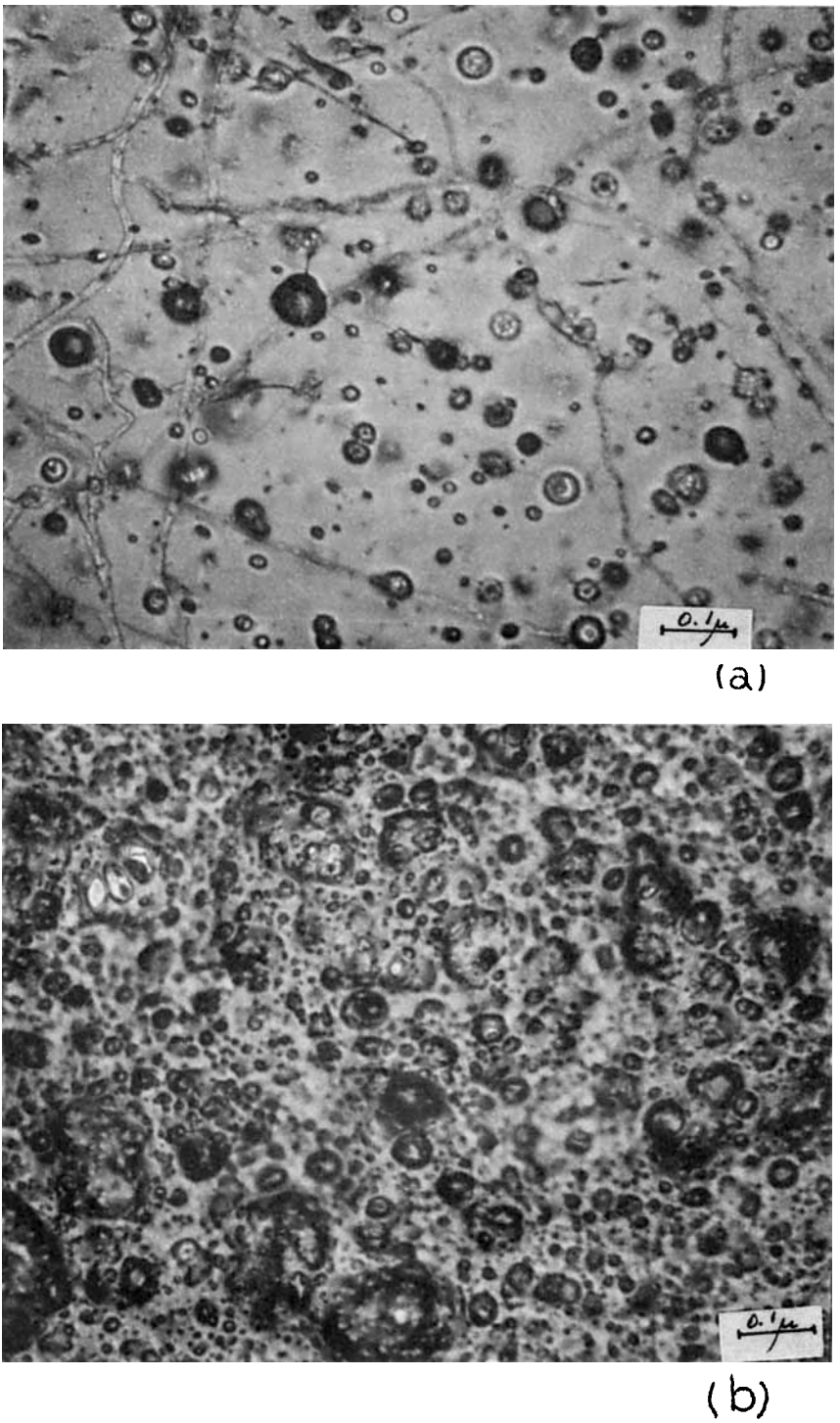

Fig. 3. Optical micrographs of PVNO–PVN membranes with different PVNO contents: (a) 10%; (b) 20%; (c) 30%.

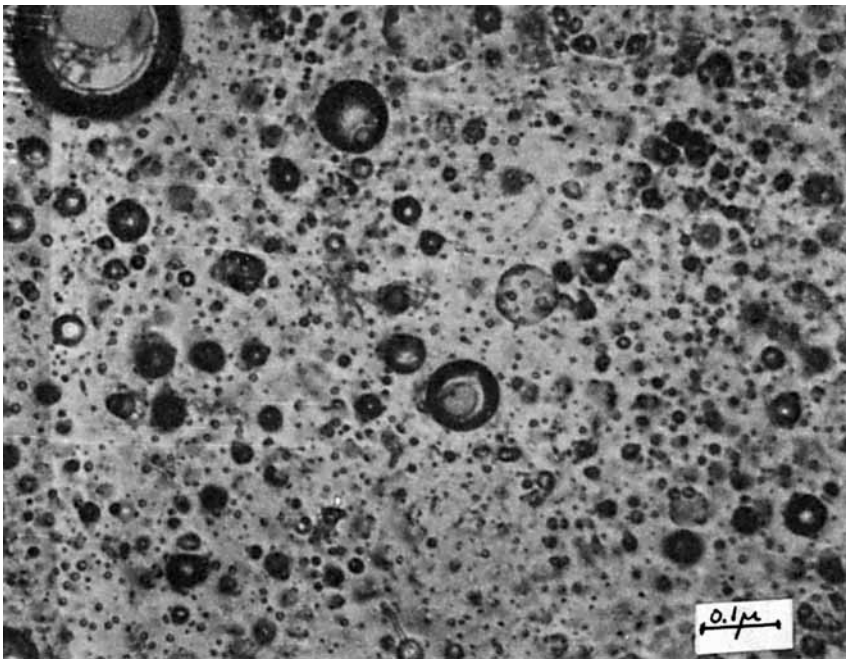

Fig. 3. (*Continued from the previous page.*)

TABLE II
Permeation of ARS through Membranes with Different Compositions and Casting Solvents

PVNO : PVN input (mol)	Casting solvent	$R \times 10^{10}$ ($g\ s^{-1}$)	$J \times 10^{14}$ ($g\ s^{-1}\ cm^{-2}$)	$D_{eff} \times 10^{10}$ ($cm^2\ s^{-1}$)
1 : 9	Ethanol	4.63	1.43	1.24
2 : 8	Ethanol	8.33	5.85	5.08
3 : 7	Ethanol	141	43.5	37.8
1 : 9	Pyridine	0.463	0.29	0.25

The optical micrographs of the membranes are quite explanatory as to why this is so. It is observed that, at 10% PVNO content, the membrane has humps, some of which appear hollow. As the PVNO content is increased, the number of humps as well as the sizes of the holes increase (Fig. 3). These might be explained by the segregation of PVN and PVNO regions due to their incompatibility in the casting solvent, ethanol. Thus, the higher the PVNO content, the larger (and more numerous) are these segregated areas, which upon extraction lead to passageways for the permeants.

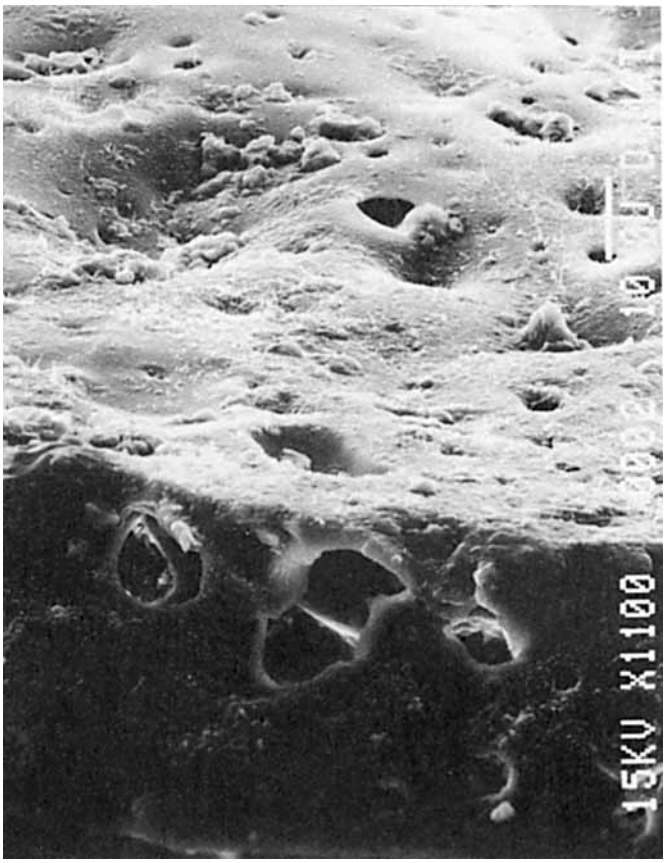

Fig. 4. Scanning electron micrograph of 10% PVNO membrane cast from pyridine (magnification × 1100).

In Table II, the results of permeation in the vertical direction (against gravity) of the low molecular weight permeant are presented. The increase in permeation with increasing PVNO content is also observed here. Another observation is that when the casting solvent is changed from ethanol to pyridine, a fivefold decrease in permeation is obtained. In Figure 4, a scanning electron micrograph of the membrane cast from pyridine is presented. It is observed that the surface does not show any sign of segregation (such as humps). Only the holes due to solvent evaporation are visible both on the surface and the cross section. This can be taken as an indication of the compatibility of the two polymers in pyridine being higher than that observed in ethanol. Although the solubility parameters of pyridine (10.7) and ethanol (12.7) leads one to expect that segregation should be more in the former case, structural similarities between the solvent and the two polymers seem to alter this.

Finally a 20-fold decrease in the effective diffusion coefficient is observed when the direction of flow is changed from horizontal to vertical (against

gravity) (see Tables I and II). At this point, no conclusive evidence is at hand to enable us to offer a satisfactory explanation.

References

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