Insulin Permeability of Hydrophilic Polyacrylate Membranes

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Received May 11, 1979, from the *Department of Chemical Engineering and Applied Chemistry, University of Toronto, Toronto, Ontario, M5S 1A4, Canada.* Accepted for publication August 22, 1979.

Abstract □ The diffusive permeability of insulin in polyhydroxyethyl methacrylate (37.1% water), polyhydroxyethyl acrylate (51.8% water), polymethacrylic acid (67.5% water), and cuprophane PT-150 membranes was determined and correlated with the weight fraction of water in the membrane. Insulin diffusivity in the membranes was determined to be 1.0×10^{-6} cm²/sec, which is in reasonable agreement with literature values for insulin diffusivity in water.

Keyphrases □ Polyacrylate membrane—effect on insulin diffusivity, extent of cross-linkage, hydration effect □ Insulin diffusivity—permeability through hydrophilic polyacrylate membranes □ Membrane permeability—hydrophilic polyacrylate membranes, effect on insulin diffusivity, extent of cross-linkage, hydration effect

Controlled-release insulin is desirable because of the recognized relationship between poor glycemia control associated with conventional insulin therapy and the degenerative sequelae of juvenile diabetes (1). Specifically, the development of a micropump for controlled-release delivery of insulin at variable rates (2) necessitated the investigation of the insulin permeability of a series of highly swollen polyacrylate membranes. In this device, basal delivery of insulin occurs through a polymeric membrane under a concentration and/or small pressure gradient while augmented delivery results when the membrane is repeatedly squeezed between the moving core of a solenoid and the membrane support. Augmentations as high as 50 times basal can be achieved to match insulin delivery to the postprandial insulin needs of a diabetic patient.

BACKGROUND

The diffusive permeability of solutes in hydrophilic membranes has been thoroughly studied (3–10). The effects of membrane hydration (3, 4), solute size (5–8), and cross-linker content (9, 10) were investigated. Various models were considered in analyzing the data. According to Yasuda *et al.* (3–5), the diffusive permeability, P, is related to the membrane diffusivity, D, by:

$$P = KD = \alpha HD \qquad \text{(Eq. 1)}$$

where H is the hydration or volume fraction of solvent in the membrane and K is the solute partition coefficient in the membrane. The parameter α reflects the proportionality between the partition coefficient and hydration and is unity for high hydration values (4). The solute diffusivity in the membrane generally is less than that in free solution because of the lower free volume (3) and the sieve effect (5) of the membrane. Yasuda *et al.* (5) found that the sieve effect was not evident for cellulose-based membranes with solutes up to the size of albumin (mol. wt. 66,000).

This study concerned the insulin permeability of highly swollen acrylate-based membranes and the membrane hydration effect on insulin permeability.

EXPERIMENTAL

Materials and Methods—Hydroxyethyl acrylate (I), hydroxyethyl methacrylate (II), and methacrylic acid (III) were polymerized *in situ* between two shim-separated glass plates over 24 hr. Triethylene glycol dimethacrylate was the cross-linking agent. Formulations are presented in Table I. The membranes were equilibrated in 0.9% saline prior to testing. A sample of cuprophane PT-150 was obtained from a Kolff twin-coil dialyzer[1].

The hydration, H, was assumed to be proportional to the weight fraction of water since the membrane densities were all 1.25 ± 0.05 g/cm³. The water fraction was determined by weighing the swollen membrane samples before and after drying *in vacuo*. The swollen membrane thickness was determined with a micrometer.

The membrane was supported by rubber gaskets between two Lucite chambers for permeability testing. It was tested in the horizontal position. The lower chamber, containing 65 ml of a radiolabeled insulin solution, was stirred by a magnetic stirrer. Initially, the upper chamber contained insulin-free saline and was agitated by an overhead stirrer, which was closely controlled because of frothing. The lower chamber was sealed to prevent bulk flow so that samples could be taken from this chamber only at the beginning and end of each run. The concentrations in this chamber were calculated by mass balance. The effective membrane area was 5.07 cm². The initial insulin solution was pH 7.4 phosphate-buffered saline containing 0.4 unit of insulin/ml[2] and 0.5 nCi of I-125 insulin/ml[3]. All experiments were conducted at $22 \pm 1°$.

Samples (1.3 ml) were removed at regular intervals from the upper chamber and were replaced by an equal volume of 0.9% saline. These samples, the two samples from the lower reservoir, and a background sample were each mixed with 10 ml of liquid scintillation cocktail[4] in

Table I—Formulations and Properties of Highly Swollen Polyacrylate Membranes

	Primary Monomer		
	Methacrylic Acid (III)	Hydroxyethyl Acrylate (I)	Hydroxyethyl Methacrylate (II)
Formulation (by volume)			
Monomer	10.0	10.0	10.0
Water	2.0	2.0	2.0
Triethylene glycol dimethacrylate	0.8	0.2	0.04
Ethylene glycol	3.0	3.0	3.0
Ammonium persulfate (40 g/100 ml of H_2O)	0.3	1.0	1.0
Sodium metabisulfite (15 g/100 ml of H_2O)	0.3	1.0	1.0
Reaction temperatures	20–25°	40–50°	20–25°
Properties			
Weight percent water[a,b]	67.5	51.8	37.1
Insulin permeability[c], $cm^2/sec \times 10^{-7}$	4.8	3.9	1.0
Compression modulus, $N/m^2 \times 10^5$	—	2.26	5.28
M_c, molecular weight between cross-links, g/mole	—	41,400	17,600

[a] Swollen in 0.9% saline. [b] Weight percent water for cuprophane PT-150 membrane was 44.7. [c] Insulin permeability through cuprophane PT-150 membrane was 1.4×10^{-7} cm²/sec.

[1] Ultra-Flow 145, Travenol Laboratories, Toronto, Ontario, Canada.
[2] Toronto Insulin.
[3] Amersham-Searle, Toronto, Ontario, Canada.
[4] ReadySolv GP, Beckman Instruments, Fullerton, Calif.

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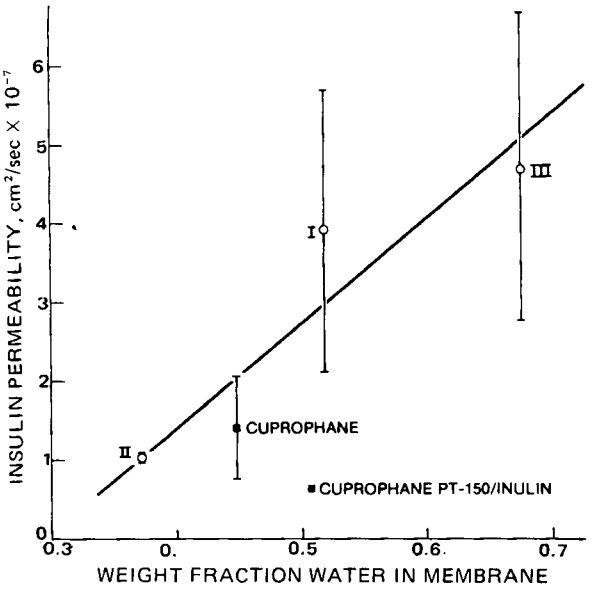

Figure 1—*Effect of weight fraction of water on insulin permeability of highly swollen polyacrylate membranes. Permeability of inulin in cuprophane PT-150(6) (■) is shown for comparison.*

polyethylene vials and counted using a liquid scintillation spectrometer.

Calculation of Membrane Permeability—Permeability was calculated using the following equations (6):

$$\ln \prod_{i=0}^{i=n} \left[\frac{(C_2 - C_1)_{i+1}}{(C_2' - C_1)_i}\right] = \frac{PA}{t_m}\left(\frac{1}{V_1} + \frac{1}{V_2}\right)\theta_n \quad \text{(Eq. 2)}$$

$$C_{2,i}' = (1 - V_r/V_2)C_{2,i} \quad \text{(Eq. 3)}$$

where:

$C_{1,i}$ = concentration of ith sample in lower (concentrated) reservoir, calculated by mass balance
$C_{2,i}$ = concentration of ith sample in upper (dilute) reservoir
$C_{2,i}'$ = concentration in upper reservoir corrected for dilution
V_1 = volume of lower reservoir
V_2 = volume of upper reservoir
V_r = sample volume (1.3 ml)
A = effective membrane area
t_m = membrane thickness
θ_n = time for sample n

The left side of Eq. 2 was plotted against time to determine the slope for calculating the membrane permeability, P. To compensate for mass balance errors, the lower reservoir concentration, C_1, was calculated forward from the initial concentration and backward from the final concentration. These two permeability values rarely differed by more than 10%; this variation was less than the intrasample variation. The averaged results are presented in Table I and were plotted against the weight fraction of water (Fig. 1). At least two experiments were performed for each membrane.

The compression moduli of 2-mm thick samples of I and II water-swollen hydrogels were determined at 10% strain on a tensile testing machine[5] having a crosshead speed of 0.1 cm/min. The hydrogels were prepared as given in Table I in 7-mm o.d. glass tubes at 10°. The molecular weight between cross-links, M_c, was determined (Table I) from these moduli and the hydrogel densities (11).

DISCUSSION

Despite the differences in membrane chemical structure, insulin permeability correlated well with the weight fraction of water in the membrane. Specific interactions between membrane chemical structure and solute were apparently negligible (within experimental error). With the assumption that α (Eq. 1) was unity, the membrane diffusivity of insulin was proportional to the slope of the line (Fig. 1) and was 1.0×10^{-6} cm²/sec. This value agrees with the literature values of 0.73×10^{-6} and 1.6×10^{-6} cm²/sec for insulin diffusivity in water at infinite dilution at 20° measured by ultracentrifugation techniques (12). The differences in the free volume and the molecular state within the membrane relative to that in free solution should account for this deviation.

The effect of cross-linking is as expected. At a higher M_c value (lower extent of cross-linking), the permeability is higher since the membrane swells more. Although the hydrogels absorbed more water than saline, the M_c values should not be different in saline. However, the differences in reaction conditions (temperature and geometry) may be significant despite the longer reaction times; for example, the number of free chain ends was ignored in this calculation. The dramatic increase in permeability at a low extent of cross-linking noted by others (9, 10) was not detected since the extent of cross-linking was greater in this work.

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ACKNOWLEDGMENTS

Supported by the National Research Council of Canada.

The authors thank Ms. E. Bobet for the establishment of the formulations and the measurements of compression modulus.

[5] Instron Corp, Canton, Mass.