

PERMEABILITY OF METABOLITES THROUGH HYDROPHILIC MEMBRANES

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The permeability of urea, creatinine and water through hydrophilic membranes based on 2-hydroxyethyl methacrylate was investigated. The possibility to affect the permeability of these compounds by introducing ionogenic groups into the polymer matrix is experimentally demonstrated.

In earlier papers we investigated the effect of the content of ionogenic groups¹ and of the hydrophilicity of the polymer matrix² on the transport properties of membranes. We showed that by introducing ionogenic groups one might strongly affect the transport of inorganic salts (NaCl, MgSO₄) through hydrophilic membranes based on poly(2-hydroxyethyl methacrylate)¹. Ampholytic membranes, containing the same amounts of weakly acidic and weakly basic groups, possess a several times higher diffusion coefficient for NaCl and MgSO₄ than neutral membranes¹.

In this work we investigated the permeability of creatinine, urea and water through neutral and ampholytic membranes based on poly(2-hydroxyethyl methacrylate) crosslinked with ethylenedimethacrylate. This study was intended to check our hypothesis concerning the possibility of accelerating the transport of organic molecules by introducing ionogenic groups into the polymer matrix. The choice of creatinine and urea is justified by the fact that the polymers under investigation are biocompatible³, and the knowledge of permeation of metabolites is one of the necessary conditions of preparation of membranes for haemodialysis.

EXPERIMENTAL

Chemicals

The monomers were prepared and purified as described earlier¹: 2-hydroxyethyl methacrylate, b.p. 79°C/533.3 Pa, n_D^{20} 1.4525; ethylenedimethacrylate, b.p. 84°C/133.3 Pa, n_D^{20} 1.4549; methacrylic acid, b.p. 59°C/1333.22 Pa, n_D^{20} 1.4314; 2-(diethylamino)ethyl methacrylate, b.p. 80°C/1333.2 Pa, n_D^{20} 1.4435. 2,2'-Azobis(isobutyronitrile): commercial product was five times recrystallized from ethanol. Urea, NH₂-¹⁴C=O-NH₂, product of Radiochemical Center, Amersham, was recrystallized from an acetone solution with unlabelled urea (Lachema, Brno), so that the resulting radioactivity was 320 μCi/g. Creatinine (1-imino-3-methyl-2-imidazolidone),

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analytical purity grade (Lachema, Brno), was used without further purification. T_2O , a product of Radiochemical Center, Amersham, was diluted to an activity of $4 \mu\text{Ci/ml}$.

Analytical Procedures

Permeability was measured in a diffusometric cell described in ref.¹, consisting of two compartments of the same volume (50 ml). The transport properties were measured at 25°C . Concentration in the cell containing solution of the higher concentration (c_2): $\text{H}_2\text{O} - 4 \mu\text{Ci/ml}$; urea - $1.7 \cdot 10^{-2} \text{ mol/50 ml}$, activity $320 \mu\text{Ci/g}$; creatinine - $1 \cdot 10^{-2} \text{ mol/50 ml}$. Concentration changes were examined by analyzing $25 \mu\text{l}$ samples. Radioactivity of the samples was measured with a liquid scintillation Intertechnique spectrometer. The UV spectra of creatinine (at 280 nm) were recorded with a Cary 14 apparatus. The permeability coefficients were calculated using Fick's law.

Membranes

Neutral membranes were prepared by the copolymerization of 2-hydroxyethyl methacrylate with ethylenedimethacrylate^{1,2,4,5}; ampholytic membranes were prepared similarly, by the copolymerization of 2-hydroxyethyl methacrylate, ethylenedimethacrylate, methacrylic acid and 2-(diethylamino)ethyl methacrylate. Copolymerizations in butanol (20 wt.% calculated with respect to the starting reaction mixture), initiated with 2,2'-azobis(isobutyronitrile) ($6 \cdot 10^{-3} \text{ mol/l}$), were carried out up to a 100% conversion. Owing to the different copolymerization parameters and to their dependence on the reaction conditions^{1,6}, the composition of the starting monomeric mixture, though expressing the overall composition of the membranes (Table I), does not characterize distribution changes of the individual components along the polymer chain. Ampholytic membranes contained the same molar amounts of weakly acidic and weakly basic groups. Permeability was measured using membranes 0.1 mm thick.

RESULTS AND DISCUSSION

In this work the permeability of creatinine, urea and water through neutral and ampholytic membranes based on 2-hydroxyethyl methacrylate was investigated. It has been shown earlier¹ that the salt transport (NaCl , MgSO_4) through ampholytic membranes is accelerated by a change in their diffusivity and not by a change in their distribution coefficient. We have also demonstrated^{1,2} that the approximation of the free volume using the solvent volume in the membrane⁷ does not hold for gels swollen in a thermodynamically poor solvent. In the latter case (and thus in our case too) the free volume in the membrane will depend predominantly on the length of the polymer segments, *i.e.* on the density of the three-dimensional network.

The main problem which we intended to elucidate in this work was the possibility of influencing the permeation of organic compounds by changing the structure of the membrane. The composition of membranes under investigation and their transport properties are given in Table I and in Figs 1–3. The dependence of the permeability of creatinine, urea and water through neutral membranes (membranes 1–6 in Table I) on the network density (expressed as the concentration of ethylene-

dimethacrylate) is shown in Fig. 1. Obviously, the permeability of all compounds under investigation decreases monotonically with increasing network density. The increasing network density relatively reduces the transport of organic compounds with respect to water (an increase in $P_{\text{H}_2\text{O}}/P_x$, subscript x denotes the respective permeant). The decrease is more pronounced for creatinine than for urea, which can be explained by a difference in the size of the two molecules.

The dependence of permeability of the same compounds through ampholytic membranes (in Table I membranes 10–14 made of copolymers with constant contents (10 mol.%) of methacrylic acid and 2-(diethylamino)ethyl methacrylate units) on the network density is shown in Fig. 2. The shape of the curves resembles dependences obtained with neutral membranes. On the other hand, however, the permeabilities are higher in all cases; in other words, the transport of organic molecules through ampholytic membranes is accelerated. Although this effect must in part be assigned to a change in the equilibrium degree of swelling (Table I), it is certainly connected also with the fact that both for creatinine and for urea one may assume

TABLE I

Composition and Properties of Membranes Based on Copolymers of 2-Hydroxyethyl Methacrylate

Starting concentrations of 2-hydroxyethyl methacrylate (*I*), ethylenedimethacrylate (*II*), methacrylic acid (*III*) and 2-(diethylamino)ethyl methacrylate (*IV*) in the reaction mixture are identical with the contents of the respective constitution units in the copolymer. v_2 is the volume fraction of the copolymer in the state swollen to equilibrium (H_2O , pH 7, 25°C), P is permeability (subscripts c and u stand for creatinine and urea, respectively).

Membrane No	[I] ₀	[II] ₀	[III] ₀	[IV] ₀	v_2	P_c	P_u	$P_{\text{H}_2\text{O}}$	$P_{\text{H}_2\text{O}}$	$P_{\text{H}_2\text{O}}$
	mol %					$10^{-7} \text{ cm}^2 \text{ s}^{-1}$			P_c	P_u
1	99.9	0.1	—	—	0.549	2.22	2.33	—	—	—
2	99.5	0.5	—	—	0.560	1.84	2.03	8.29	4.51	4.08
3	98.0	2.0	—	—	0.586	1.34	1.28	6.71	5.01	5.24
4	96.0	4.0	—	—	0.616	0.60	0.91	5.66	9.43	6.22
5	94.0	6.0	—	—	—	0.20	0.62	2.61	13.05	4.21
6	92.0	8.0	—	—	—	—	0.30	2.25	—	7.50
7	93.0	2.0	2.5	2.5	0.568	1.31	2.05	5.97	4.56	2.91
8	88.0	2.0	5.0	5.0	0.509	2.44	2.95	9.42	3.86	3.19
9	83.0	2.0	7.5	7.5	0.476	3.68	4.00	12.24	3.33	3.06
10	78.0	2.0	10.0	10.0	0.443	4.02	4.31	12.31	3.06	2.86
11	79.9	0.1	10.0	10.0	0.360	9.27	8.43	20.42	2.20	2.42
12	76.0	4.0	10.0	10.0	0.503	2.61	3.72	11.20	4.29	3.01
13	74.0	6.0	10.0	10.0	0.555	1.70	2.81	7.36	4.33	2.61
14	72.0	8.0	10.0	10.0	0.587	1.34	1.60	5.75	4.29	3.59

FIG. 1

Dependence of the Permeability (P) of Creatinine 3, Urea 2 and Water 1 through Neutral Membranes (membranes 1–6 in Table I) on Network Density (expressed as mol.% of ethylenedimethacrylate units)

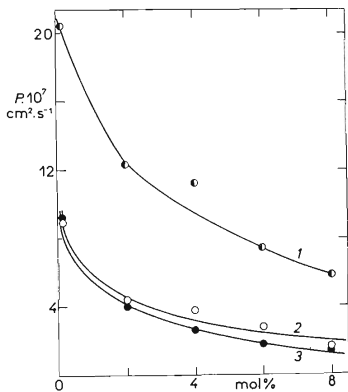


FIG. 3

Dependence of the Permeability (P) of Creatinine 3, Urea 2 and Water 1 through Ampholytic Membranes (membranes 7–10 in Table I) on the Content of Ionogenic Groups in the Copolymer

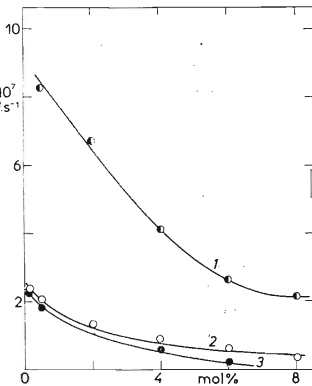
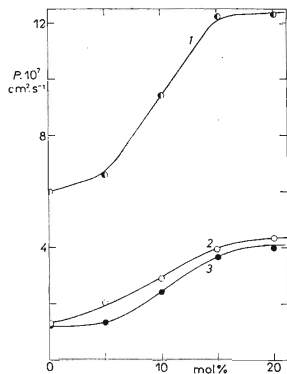


FIG. 2

Dependence of the Permeability (P) of Creatinine 3, Urea 2 and Water 1 through Ampholytic Membranes (membranes 10–14 in Table I) on Network Density (expressed as mol.% of ethylenedimethacrylate units)



a nonuniform charge distribution in the molecule, and thus interactions with ionogenic groups in the membrane. It also seems to be of interest that in ampholytic membranes there is no essential change in the ratio of the permeabilities of water and of the organic compound.

Fig. 3 shows the dependence of the permeability of creatinine, urea and water on the content of ionogenic components of ampholytic membranes (Table I: membranes 7–10 from the copolymer with a constant (2 mol.%) content of the ethylenedimethacrylate units). At constant $P_{\text{H}_2\text{O}}/P_x$ ratio the permeability of all three compounds increases with increasing content of ionogenic groups in the membrane.

It can be seen, therefore, that ampholytic membranes can accelerate the transport of organic compounds. Probably only molecules which are able to participate in interactions with ionogenic groups of the polymer can be thus accelerated. Ampholytic membranes could replace neutral membranes in a number of cases. Špaček and Kubín⁸ suggest to employ neutral poly(2-hydroxyethyl methacrylate) as a material in the preparation of membranes for haemodialyzers. The results summarized in this work indicate the possibility of using improved transport properties of the ampholytic membranes. In other cases, *e.g.* in the modelling of biological membranes, it is possible to use the opportunity of influencing the properties of these membranes by changing (pH, ionic strength) the ambient medium⁹.

It can be said, in conclusion, that introduction of ionogenic groups into hydrophilic membranes based on poly(2-hydroxyethyl methacrylate) allows to vary their properties within a wide range.

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