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혈장내 염의 Poly(2-Hydroxyethyl Methacrylate) 격막 투과현상

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Transport of Some Solutes in Blood Plasma Through Poly(2-Hydroxyethyl Methacrylate) Hydrogel Membrane

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요 약. 혈장내의 중요한 성분인 몇가지 염들이 poly(2-hydroxyethyl methacrylate) 격막을 통과하는 상대투과계수(U_{re}), 분배계수(K_D), 확산계수(D_m)등을 측정하였다. 이 격막을 제조할 때 cross-linker로서 사용된 tetraethylene glycol dimethacrylate(TEGDMA)의 함량은 중량비로 2.8%였다. 이 염들의확산계수는 그 분자량이 증가함에 따라서 지수함수적으로 감소하였으며, 그 분자의 원통반지름(a)에 대해서는 요소를 제외하고는 직선적으로 감소하였다. 이와 같은 사실을 sieve pore flow 모델로서 설명하였다.

여러 온도에서 요소의 U_{re}와 D_m은 글리신, β-알라닌, D-글루코오스, 사카로스 및 말레산과 같은 다른 염들의 값보다 더 컸다. 이와 같은 결과는 이 poly(HEMA) 격막이 혈투석(血透析) 응용에 적합하다는 사실을 보여 주었다.

ABSTRACT. The relative permeabilities, distribution coefficients and diffusion coefficient of some salts which are important components in blood plasma through a poly(HEMA) membrane were measured. The crosslinker which was used for preparing the membrane was tetraethylenglycol dimethacrylate(TEGDA), the weight percentage of the latter was about 2.8. We found that the diffusion coefficients (D_m) of the solutes decreasee exponentially with increasing molecular weight, and also that D_m's decrease linearly (except urea) with cylindrical radius (a). These facts were explained by a sieve pore flow model.

The relative permeability and diffusion coefficient of urea at various temperature were larger than those of other solutes such as glycine, β-alanine, D-glucose, saccharose and maleic acid. The result indicates that the poly(HEMA) membrane might be suitable for hemodialysis application.

1. INTRODUCTION

The transport phenomena of several amide solutes through poly(2-hydroxyethyl methacrylate) membranes with varying crosslinker contents have been studied in our previous paper.[1]

In the region where the crosslinker weight percentage is about 2.8, the relative permeability and diffusion of urea were larger than those of other amides.

Although the transport properties of some poly(HEMA) membranes have been examined,[2~5] a systematic study of the transport of some solutes in blood plasma through the membrane in a given crosslinker region has not been undertaken. This paper has objectives to examine the transport rates of some components of interest in blood plasma and to analyze the data with respect to a potential usage as an artificial kidney membrane. From the transport experiments, the relative permeabilities, diffusion coefficients, activation enthalpies and the cylindrical radii of diffusing molecules through the membrane were obtained.

2. EXPERIMENTS

HEMA monomer (with low acid and low inhibitor content) and tetraethylene glycol dimethacrylate (TEGDMA) were obtained from Poly-Science Inc. All other chemicals were of reagent grade purity and were used as received.

A modified Leonard-Bluemle Cell containing two equal compartments of 228 cm^3 was employed to obtain the data of permeability through the poly(HEMA) membrane (crosslinker wt% is 2.8).[2] The containers in each chamber were stirred at a constant rate (220 rpm) to reduce a boundary layer effect. The solution of interest was filled in one of the two compartments and the other compartment was filled with tridistilled water. The solute in the solution diffuses through the HEMA membrane from the sample compartment to the solvent(water) compartment. The concentration of the solute was measured at intervals of 60 minutes by a differential refractometer for the sample taken from the solute compartment with a hypodermic syringe.

The diffusion coefficients of the solutes have been determined and have been utilized to interpret the mechanism of the solute permeation through the poly(HEMA) membrane. The diffusion coefficients were obtained from the following equation:[1]

$$\ln\left(\frac{2C_t}{C_0}-1\right)=-\left(\frac{1}{V_1}+\frac{1}{V_2}\right)\frac{AU_{te}t}{L} \quad (1)$$

Here C_t is the solute concentration in the higher concentration cell compartment at time t, C_0 is the initial solute concentration, V_1 and V_2 are the cell compartment volumes, A is the membrane area, L is the membrane thickness, and U_{te} is the permeability and is defined as

$$U_{te}=D_mK_D \quad (2)$$

where D_m is the diffusion coefficient of the solute in the membrane, and K_D is the distribution coefficient. The permeability, U_{te}, can be obtained from the straight line portion of a plot of $\ln\left(\frac{2C_t}{C_0}-1\right)$ *vs.* t (see *Fig.* 1).

The distribution coefficient(K_D) is defined as the ratio C_i^m/C_i^s where C_i^m is the concentration (mole/cc) of solute in the membrane phase, and C_i^s is the solute concentration in solution phase. K_D is calculated from the following equation:

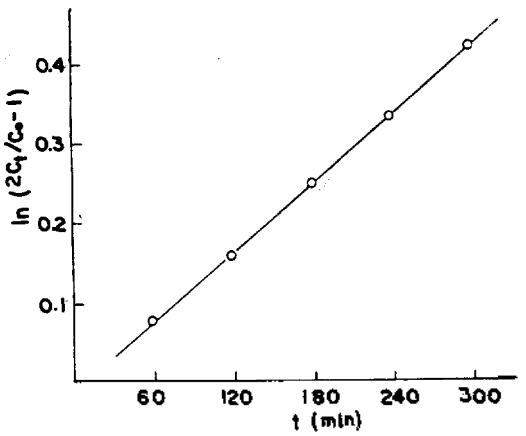


Fig. 1. Diffusion of urea through a poly(HEMA) membrane with crosslinker content of 2.8 wt percent at 37°C. Urea concentration: 1 g in 100 *ml* water.

$$K_D = \frac{C_i^m}{C_i} = \frac{(C_i^0 - C_i)V_i^0}{C_i V_m} \quad (3)$$

Where C_i^0 and V_i^0 are the initial concentration and the initial volume of the solution before the membrane was immersed, V_m is the volume of the swollen membrane after the latter was soaked into the solution in a small glass vessel (about 20 cm^3) for at least 24 hrs. These concentrations were measured by using a differential refractometer (Visual Laboratory Type Model BP-2000-V).

The initiator for polymerizing HEMA monomer was a redox system, ammonium persulfate and sodium metabisulfite from Fisher Scientific Company. The casting solution for the 2.8% crosslinked membrane was obtained by mixing 10 m*l* of HEMA monomer, 0.7 m*l* of crosslinker TEGDA, 5.0 m*l* of mixed solvent (2.0 m*l* of tridistilled water and 3.0 m*l* of ethyleneglycol) and 2 m*l* of initiator [1.0 m*l* of $(NH_4)_2S_2O_8$ solution (40 g in 100 m*l* of water) and 1.0 m*l* of $Na_2S_2O_5$ solution (15 g in 100 m*l* of water)]. This casting solution was stirred vigrously to mix sufficiently, and the dissolved air in the solutionwas removed with an aspirator. The membrane was formed by polymerizing the monomer in the solution which was placed between two separated glass plates. The polymerization allowed to proceed for 24 hours at 24~25 °C, the membrane thus formed was removed from the glass plates by soaking in distilled water. The membrane was placed in a large volume of distilled water which was frequently replaced to remove the organic solvent and the initiator remained in the membrane for at least 2 weeks before use, and the membrane was never allowed to dry out. In order to measure the thickness of the water equilibrated membrane, the wet film was inserted between two thin plastic acetate planes. The thickness of the sandwiched plates was measured at various points with a Model 549 Micrometer (Tasting Machines, Inc., Amityville, N.Y.). From the adveraged value and the predetermined thickness of the thin acetate planes, the membrane thickness was obtained.

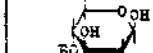
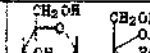
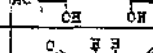
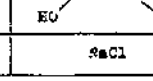
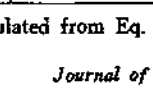
3. RESULTS AND DISCUSSION

The solutes in blood plasma studied are shown in *Table* 1. The values of cylindrical radii of the solutes were calculated from Eq. (5) using a pore radius of 5.3Å.[6] One notes that the radius increases with increasing molecular weight. The fact that sodium chloride has a large cylindrical radius in spite of its small molecular weight is caused by its large hydration.

A typical plot of data from a transport experiment is shown in *Fig.* 1.

The relative permeabilites (U_{re}) for the transport of various solutes in blood plasma through a hydrophillic poly(HEMA) membrane are listed in *Table* 2. The relative permeabilities increase with increasing concentration and temperature while they decrease with increasing molecular weight of the solutes. The elevation of the

Table 1. The solutes in blood plasma studied.

Solutes	Structural formula	Molecular weight	Cylindrical[a] radius (Å)
Urea		60.06	2.18
Glycine		75.07	2.41
β-Alanine		89.09	2.47
β-D-Glucose		198.17	2.58
Saccharose		342.30	2.77
Maleic acid		116.07	2.52
Sodium chloride	NaCl	58.44	2.44

[a] Calculated from Eq. (5).

Table 2. Relative permabeility coefficients ($U_{re} \times 10^7$ cm^2/sec) for various solutes through poly(HEMA) membranes at several temperatures.

Concentration (g in 100 m*l*)	25°C				30°C	37°C				42°C
	0.5 g	1 g	2 g	4 g	1 g	0.5 g	1 g	2 g	4 g	1 g
Solutes Urea	4.27	5.06	6.11	7.70	6.06	5.42	7.14	7.96	8.22	7.77
Glycine	0.95	1.01				0.90	1.06			
β-Alanine	0.80	0.85				0.83	0.91			
D-Glucose	0.48	0.50				0.57	0.59			
Saccharose	0.15	0.19				0.18	0.22			
Maleic Acid	1.23	1.58				1.78	1.82			
NaCl	1.97	2.26	3.24			2.06	2.35	3.68		
NaCl 0.5 g Urea 2 g in 250m*l*	5.63					7.73				
NaCl 1 g Urea 1 g in 250m*l*	4.11					4.44				
NaCl 2 g Urea 0.5 g in 250m*l*	4.74					5.41				

Table 3. Distrbiution coefficients (K_D).

Solutes	25°C	30°C	37°C	42°C
Urea	0.54	0.52	0.50	0.49
Glycine	0.23		0.20	
β-Alanine	0.22		0.19	
β-*D*-Glucose	0.36		0.32	
Saccharose	0.24		0.21	
Maleic Acid	0.77		0.72	
NaCl	0.44		0.39	
NaCl 1 g in Urea 1 g 200m*l*	0.70		0.64	

relative permeability with temperature is caused by the flexibility of membrane matrix and the kinetic motion of permeating solutes both increasing with temperature. It is natural that the relative permeability decreases with increasing molecular weight since the cylindrical radius of a diffusing molecule increases with molecular weight. For the reason of the deviation from this rule by maleic acid and NaCl reference is made to the discussion for K_D in the following paragraph. Urea has the largest U_{re} value among the solutes studied about 5~10 times of others although it has roughly a similar molecular weight with sodium chloride and glycine. This may be due to the fact that, because of the action of two NH_2 groups, urea has the strongest power of breaking a secondary noncovalent network structure formed between the α-methyl groups of two neighboring HEMA monomers in the membranes.[1,5] From *Table* 2. one also notes that the permeability of a solution of sodium chloride and urea mixed one to one proportion in weight percentages is smaller than other solutions mixed in unequal proportion.[5]

The distribution coefficients K_D are shown *Table* 3. The solutes such as urea, maleic acid and sodium chloride (hydrated) have large hydrogen bonding ability, consequently have shown large distribution coefficients because of the strong complex formation between the

Table 4. Diffusion coefficients ($D_m \times 10^7$ cm^2/sec) for various solutes through poly(HEMA) membranes at several temperatures.

Conc. (g/100 m*l*)	25°C				30°C	37°C				42°C
Solutes	0.5 g	1 g	2 g	4 g	1 g	0.5 g	1 g	2 g	4 g	1 g
Urea	7.91	9.37	11.32	14.26	11.66	10.83	14.28	15.92	16.44	15.86
Glycine	4.18	4.41				4.51	5.32			
β-Alanine	3.66	3.87				4.38	4.82			
β-*D*-Glucose	1.32	1.40				1.77	1.85			
Saccharose	0.64	0.81				0.85	1.04			
Maleic Acid	1.59	2.05				2.48	2.53			
NaCl	4.48	5.13	7.36			5.29	6.01	9.43		
NaCl 0.5 g / Urea 2 g in 250m*l*	8.05					12.08				
NaCl 1 g / Urea 1 g in 200m*l*	5.87					6.93				
NaCl 2 g / Urea 0.5 g in 250m*l*	6.77					8.45				

solutes and membrane matrix. The K_D's decrease with increasing temperature. This may be due to the fact that the bond strength of the complex between solute and membrane matrix decreases with increasing temperature.

The diffusion coefficients D_m calculated from Eq. (2) for the transport of various solutes are listed in *Table* 4, and are plotted as a function of molecular weight of the diffusing solutes in *Fig.* 2. The facts that the diffusion coefficients increase with the temperature and decrease with increasing molecular weight of the solutes can be interpreted by a similar way as mentioned with regard to the relative permeability. Among the diffusion coefficients of various solutes through the menbrane at 25 °C and 37 °C, one sees that those of urea are markedly higher than other tested solutes in blood plasma as shown in *Fig.* 2. Accordingly, the poly(HEMA) membrane having 2.8 % weight of the TEGDA crosslinker may potentially be used as a hemodialysis membrane.

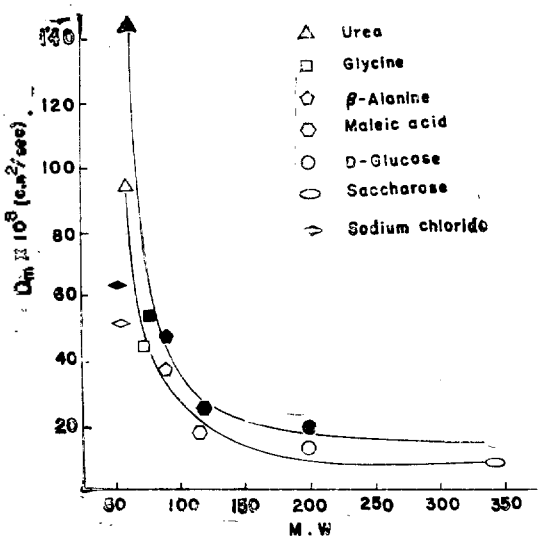


Fig. 2. Diffusion coefficients (D_m) *vs.* molecular weight of solutes in blood plasma. Open marks represent the data at 25° C, and filled marks are those for at 37 °C. The concentration of the solutes is 1 g in 100 m*l* water.

The diffusion coefficients of solutes in the blood plasma through poly(HEMA) membrane

Table 5. "True" apparent diffusion coefficients. ($D_0 \times 10^7$ cm/sec) for various solutes through poly(HEMA) membranes (crosslinker 2.8 %) at 25 and 37 °C.

Solutes	Urea	Glycine	β-Alanine	D-Glucose	Saccharose	Meleic acid	Sodium choride
25 °C	6.03	2.56	2.95	1.26	0.52	1.25	3.73
37 °C	8.91	3.80	3.47	1.69	0.71	2.40	4.37

have been found to increase with increasing solute concentration as shown in *Table* 4. This phenomenon occurs virtually in every case when there is significant interaction between an amorphous polymer and the penetrant.[6,7] The variation of the diffusion coefficient with increasing penetrant concentra tion usually follows a relationship of the type:

$$D_m = D_0 \exp(\beta C) \quad (4)$$

The "true" apparent diffusion coefficient D_0 in the poly(HEMA) membrane (crosslinker 2.8%) is obtained by extrapolation to zero concentration using Eq. (4). The D_0 values listed in *Table* 5 are those obtained by the extrapolation process. By using a sieve-pore flow model, Ferry[8] derived the following equation:

$$D_m = D_0[1-(a/r)]^2 \quad (5)$$

where a is the radius of the diffusing molecule, and r is the radius of the membrane pore. In deriving Eq. (5), it was assumed that the solute molecule can pass only a circular cylindrical space of radius $r-a$. The motion of the diffusing molecule, however, experiences friction because of the interation between the pore wall and the molecule. The correction for the friction was considered by Faxen[9], Lane[10] and Renkin[11], the result is expressed by the fallowing equation.

$$D_m = D_0(1-a/r)^2[1-2.104(a/r) + 2.09(a/r)^3 - 0.95(a/r)^5 + \cdots\cdots] \quad (6)$$

This equation has been applied to membrane diffusion by Lane.[10] It was recently demonstrated that this equation very closely describes the

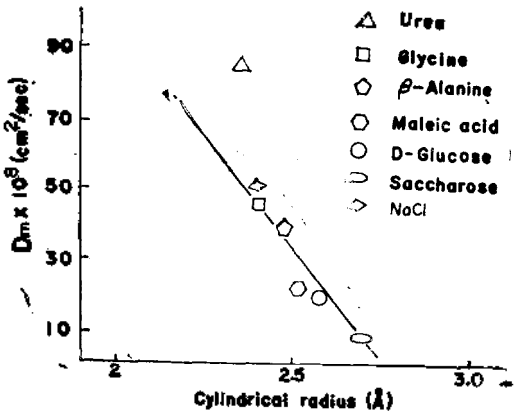


Fig. 3. The diffusion coefficients for various solutes at 25 °C versus cylindrical radius. The concentration of the solutes is 1g in 100 m*l* water.

hindrance to the diffusion of solutes as a function of molecular size at least to an a/r ratio of 0.4 in experiments with electron micrographically calibrated etched mica membranes.[12]

In *Fig.* 3, the D_m values for various solutes obtained in our experiment are plotted against the cylindrical radius calculated from Eq. (5) using the pore radius of 5.3 Å of the poly (HEMA) membrane. From *Fig.* 3, one notes that all solutes except urea are positioned in a straight line. This indicates the superiority of urea in diffusion rate through the membrane.

In calculating a cylindrical radius, we have not used Eq. (6) which includes more terms of interaction between the diffusing molecule and the pore wall. It may be due to the fact that the pore radius of our membrane is relatively large because of the relatively small of the crosslinker, consequently the interaction is very

Table 6. The activation enthalpy of diffusion (kcal/mole).

	Urea (1g in 100m*l*)	Glycine (1g in 100m*l*)	β-Alanine (1g in 100m*l*)	*D*-Glucose (1g in 100m*l*)	Saccharose (1g in 100m*l*)	Maleic acid (1g in 100m*l*)	NaCl (1g in 100m*l*)	NaCl 2g Urea 0.5g (250 m*l*)
Enthalpy (ΔH_D^*)	3.50	2.88	3.34	4.28	4.33	3.19	3.80	3.39

Urea diffusion in H_2O : 4.47[13], Na^+ diffusion in H_2O : 4.69[13], Cl^- diffusion in H_2O : 4.22[13].

small. The following consideration on the activation enthalpy provides another evidence for the week interaction.

The values of diffusion activation enthalpy (ΔH_D^*) calculated from the following equation are listed in *Table* 6:

$$D_m=\lambda^2\frac{kT}{h}\exp\left(\frac{\Delta S_D^*}{R}\right)\exp\left(-\frac{\Delta H_D^*}{RT}\right) \qquad (7)$$

where, λ is the average jumping distance of the solute permeating through the membrane. The activation enthalpies of diffusion for urea and sodium chloride through the poly(HEMA) membrane are about same magnitude as the free diffusion coefficients for these solutes in water.[13] This fact seems to be contrast with the work of Spack and Kubin,[14] which indicated a much higher activation enthalpy for potassium chloride diffusion in HEMA gels than in water in agreement with Ratner and Miller results.[6] The fact that activation enthalpy of diffusion is comparable with that for free diffusion is explained by assuming that the solute could be diffusing in the membrane in an environment similar to the free diffusion. Accordingly, one may conclude that these solutes may indeed be moving through the "water regions" in the poly(HEMA) membrane (crosslinker 2.8%), the "water regions" being considered to have an environment similar to the free diffusion in water.

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