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Model Barrier Affecting Drug Transport[1,2]

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With a view to establishing a method to investigate the effect of various barrier on the transport of drugs, a transport cell was devised which consisted of three compartments A, B and C partitioned with two semipermeable cellulose membranes, the central compartment B being thin and keeping a solution of non-permeable 3rd compornent as the model barrier to drug transport, and discussions were made on the relationship among the whole permeability constant, P, the permeability constant through the partitioning membrane, P_m, and the transport constant through compartment B, P^*. Then, the experimental examination was performed on the transports of barbital and benzoic acid through the central compartment solution of polyvinylpyrrolidone (PVP).

The transport cell devised was useful enough to obtain satisfactorily reproducible results. NaCl which was added in compartment C to make isotonic in the whole system gave no notable effect on the flow of drug. The reasonable results were obtained regarding P, P_m and P^*. Analyzing the obtained values of P^* on the assumption that the interaction between drug and PVP might be expressed by a Langmuir type isotherm, a quantitative indicator was given to the extent of the above interaction in kinetical process. As a result, the interaction of PVP-benzoic acid was greater than that of PVP-barbital in the present system.

In the biopharmaceutical system, regarding not only the whole system but such a minor portion as cell, the drug administered is transported accompanying various interactions with both endogeneous and exogeneous components. Therefore, these interactions are considered to have influence on the absorption, distribution, metabolism and excretion of drugs, eventually having influence on the drug availability.

Extensive investigations of the interaction between drug and other components have been made on the statical viewpoint, for example, protein binding studies by equilibrium dialysis method. However, the interactions in drug transport mentioned above are originally of kinetical process, accordingly being more closely approached by kinetical investigations.

The typical kinetical investigation of drug transport is represented by membrane transport studies, for which various methods have been presented, for example, uses of extracted biological membranes such as frog skin[4] or human abdominal skin[5] and of model membranes formed of phospholipids,[6] artificial polymers[7–9] or liquid

1) This paper forms Part XIII of "Physico-chemical Approach to Biopharmaceutical Phenomena." Preceding paper, Part XII: H. Nogami, T. Nagai, and N. Nambu, *Chem. Pharm. Bull.* (Tokyo), **18**, 1643 (1970).
2) A part of this work was presented at the 89th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1969.
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4) H.H. Ussing, *Acta Physiol. Scand.*, **19**, 43 (1949).
5) M.F. Coldman, B.J. Poulsen, and T. Higuchi, *J. Pharm. Sci.*, **58**, 1098 (1969).
6) J.A. Castleden, *J. Pharm. Sci.*, **58**, 149 (1969).
7) L.M. Lueck, D.E. Wurster, T. Higuchi, A.P. Lemberger, and L.W. Busse, *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 694 (1957).
8) *a*) F.A. Kinel, G. Benagiano, and I. Angee, *Steroids*, **11**, 5 May, 673 (1968); *b*) K. Sundaram and F.A. Kinel, *ibid.*, **12**, 4 Oct., 517 (1968).
9) *a*) E.R. Garrett and P.B. Chemburkar, *J. Pharm. Sci.*, **57**, 944 (1968); *b*) *Idem, ibid.*, **57**, 949 (1968); *c*) *Idem, ibid.*, **57**, 1401 (1968).

layers.[10–13] These methods, however, seem little valuable in studies of an interaction between the drug and the other moving components such as the permeability barrier in cell in the biopharmaceutical system.

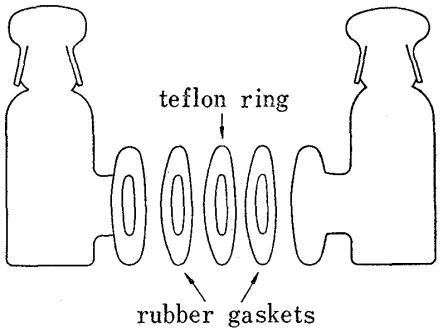

Fig. 1. Parts of Transport Cell

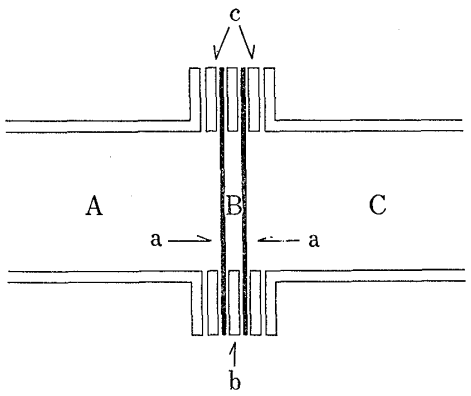

Fig. 2. Schematic Explanation of the Barrier Part of the Transport Cell Assembled

A: compartment A a: visking membrane
B: compartment B b: silicone ring
C: compartment C c: rubber gasket

The present study was attempted to establish an experimental method to investigate the effect of various barriers on drug transport, devising a transport cell consisting of three compartments partitioned with two semipermeable cellulose membarnes, as shown in Fig. 1 and 2, the central compartment being thin and keeping a solution of non-permeable 3rd component as the model barrier to drug transport. Then, the examination was made on the transports of barbital and benzoic acid through the central compartment solution of polyvinylpyrrolidone (PVP).

Theoretical Considerations

The transport of drug through the barrier system as shown in Fig. 2 is considered to be formed of the two stages upto and after reaching a uniform concentration gradient across the barrier, *i.e.*, upto and in a steady or quasi-steady state. The present study is concerned with the latter one.

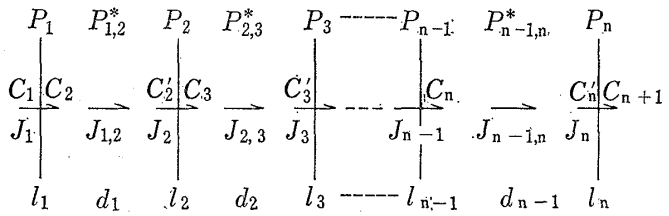

Fig. 3. General Multilayer Barrier System

Assuming that the drug-solvent and the solvent-solvent interactions have no notable influence on the flux of drug, the steady state diffusion of drug may be described by Fick's first law. This is considered to be applicable to the quasi-steady state diffusion if the change of concentration gradient with lapse of time is small enough to be negligible.[7,9b]

10) H.L. Rosano, *J. Phys. Chem.*, **65**, 1704 (1961).
11) H.L. Rosano and K. Breindel, *J. Colloid Interface Sci.*, **22**, 58 (1966).
12) H.L. Rosano, *J. Colloid Interface Sci.*, **23**, 73 (1967).
13) J. Perrin, *J. Pharm. Pharmacol.*, **19**, 25 (1967).

Then, for general consideration, the fluxes of drug, J_1, J_2,$\cdots J_n$; $J_{1,2}$, $J_{2,3}$,$\cdots J_{n-1,n}$ through the successive barrier membranes of the thicknesses of l_1, l_2,$\cdots l_n$ and liquid barriers of the thicknesses of d_1, d_2,$\cdots d_n$, as shown in Fig. 3, may be represented as follows:

$$J_1=\frac{P_1}{l_1}(C_1-C_2) \qquad J_{1,2}=\frac{P^*_{1,2}}{d_1}(C_2-C_2')$$

$$J_2=\frac{P_1}{l_1}(C_2'-C_3) \qquad J_{2,3}=\frac{P^*_{2,3}}{d_2}(C_3-C_3')$$

$$\vdots \qquad \vdots$$

$$J_n=\frac{P_n}{l_n}(C_n'-C_{n+1}) \qquad J_{n-1,n}=\frac{P^*_{n-1,n}}{d_{n-1}}(C_n-C_n')$$

where C_1, C_2,$\cdots C_n$,C_{n+1}; C_2', C_3',$\cdots C_n'$ are the concentrations of the solute in contact with the respective barrier membranes, P_1, P_2,$\cdots P_n$ the respective permeability constants, and $P^*_{1,2}$, $P^*_{2,3}$,$\cdots P^*_{n-1,n}$ the respective transport constants.

Summing the above equations, the following equation is given.

$$\sum_{i=1}^{n}\frac{l_i}{P_i}J_i+\sum_{i=1}^{n-1}\frac{d_i}{P^*_{i,i+1}}J_{i,i+1}=C_1-C_{n+1} \tag{1}$$

In the steady state, it is described that

$$J_1=J_2=\cdots=J_n=J_{1,2}=J_{2,3}=\cdots=J_{n-1,n}\equiv J \tag{2}$$

Representing the whole permeability constant by P and the whole thickness of the barrier system as $\sum_{i=1}^{n} l_i+\sum_{i=1}^{n-1} d_i=L$, the flux J is described as follows:

$$J=\frac{P}{L}(C_1-C_{n+1}) \tag{3}$$

Equation (1) is modified by equation (2) as

$$J\left\{\sum_{i=1}^{n}\frac{1}{(P_i/l_i)}+\sum_{i=1}^{n-1}\frac{1}{(P^*_{i,i+1}/d_i)}\right\}=C_1-C_{n+1} \tag{4}$$

Equations (3) and (4) give the following one.

$$\frac{1}{(P/L)}=\sum_{i=1}^{n}\frac{1}{(P_i/l_i)}+\sum_{i=1}^{n-1}\frac{1}{(P^*_{i,i+1}/d_i)} \tag{5}$$

Thus, equation (5) expresses the general relationship among the whole permeability constant and the permeability and the transport constants of the unit barriers in the steady state. Actually, the present system is formed of three compartments as described already, that is, n=2 in equation (5). Therefore, representing as $P_1=P_2=P_m$, $P^*_{1,2}=P^*$, $d_1=d$, and $l_1=l_2=l$, the following equation is given.

$$\frac{1}{(P^*/d)}+\frac{1}{(P_m/2\cdot l)}=\frac{1}{(P/(d+2\cdot l))} \tag{6}$$

Comparing the barrier system to a membrane, the whole permeability constant, P, in equation (6) essentially should correspond to that in the permeation of drug though a membrane expressed by Lueck, *et al.* as follows:

$$\log\{(A_0-2C)/A_0\}=(-2P/2.303\cdot L)\cdot t \quad (7)$$

$$P=f\cdot D\cdot K\cdot S/V \quad (8)$$

where C is the concentration in compartment C at time t, A_0 the initial concentration in compartment A, P the permeability constant, f the membrane constant, D the diffusion constant in the membrane, K the distribution constant to the membrane, V the volume of solution in compartment A and C, S the apparent surface area of the membrane, and L the thickness of the membrane.

Experimental

Materials——Visking tubing (36/32″) obtained commercially was boiled in distilled water, washed, stored in fresh distilled water, and then used to make the membranes of the transport cell as described later. Benzoic acid, G.R., and barbital, J.P. VII, were recrystallized twice from distilled water to use. Polyvinylpyrrolidone (PVP) marketed as "PVP-K30" by Gokyo Sangyo Co. Ltd. was dialyzed with the Visking tubing mentioned above against distilled water for a week, lyophilized, and stored in a sealed container to use.

Apparatus and Procedure——The transport cell devised for this study is shown in Fig. 1 and 2, assembled of two glass vessels, two rubber gaskets, a silicone ring of a given thickness and a set of binding accessories. Two 8.5×15 cm square sheet membranes were prepared using the Visking tubing mentioned above and set between the silicone ring and the rubber gaskets, to which the respective glass vessels were attached tightly with the binding accessories. The area of the membrane available to transport was 28.3 cm^2. PVP solution of a given concentration was injected into compartment B with a injection needle. Compartments A and C contained 200 ml of the solutions. This assembly was shaken mechanically in a constant temperature incubator (Taiyo M-1N). From the fact that PVP was not detectable in compartments A and C after 4×10^{-2} g/ml of PVP in compartment B was shaken for 300 hr, it was considered that PVP did not permeate through the Visking membranes into both compartments A and C.

Prior to the transport experiment, the solution of NaCl having the same osmotic pressure as the solution of drug to be tested was put in compartments A and C and then shaken overnight to attain to equilibrium osmotic pressure in the whole system, being exchanged for the solutions of drug and of NaCl, respectively, upon the transport experiment. At appropriate intervals, samples were pipetted out from compartments A and C to determine the concentration of drug.

Measurement of the Thickness of Visking Membranes——Immediately after all the samplings were finished, the thickness of the membranes was measured with a Mitsutoyo 109—101 micrometer at 12 different places on each of 6 membranes, and the mean was obtained as 0.0053 cm with a very small deviation.

Determination of the Thickness of Compartment B——It was unable to measure the thickness of compartment B directly. Therefore, the thickness was estimated by the following preliminary experiment: the volume of the liquid in compartment B was measured twice for each of 6 runs, *i.e.*, after the assembly was shaken overnight to attain to equilibrium osmotic pressure prior to the transport experiment as described already and after the samplings were finished, being devided by the area of the membrane available to transport (28.3 cm^2 as described). The mean of thickness thus obtained was 0.707 cm and accordingly the thickness of the whole barrier system seemed to be 0.718 cm. The volume of liquid of compartment B seemed to be the same to the measurements twice for each run with a statistical significance.

Quantitative Determination of Barbital, Benzoic Acid and PVP——The concentrations were determined according to ultraviolet (UV) absorption method, using a Hitachi 124 spectrophotometer: Barbital at 239 mμ after dilution with borate buffer of pH 10.0; benzoic acid at 227 mμ or 272 mμ after dilution with distilled water; PVP at 205 mμ, 210 mμ and 220 mμ after dilution with distilled water.[14]

Measurement of the Viscosity of PVP Solution——This was done by a Ubellode viscometer.

Result and Discussion

Reproducibility of Quasi-Steady State Transport Studies

Plotting the concentration of drug in compartment C against time, as shown in Fig. 4 and 5, the curve gained a straight line after a certain time, corresponding to the quasi-steady state. Making correction for the induction period, t_0, which was given by extraporating the

14) The optical density was recongnized preliminarily to follow Lambert–Beer rule.

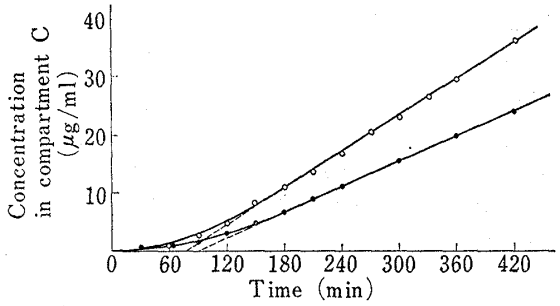

Fig. 4. Concentration–Time Curves of Transport of Barbital through the Barrier Systems

○: control barrier
●: PVP (2×10^{-2} g/ml) barrier

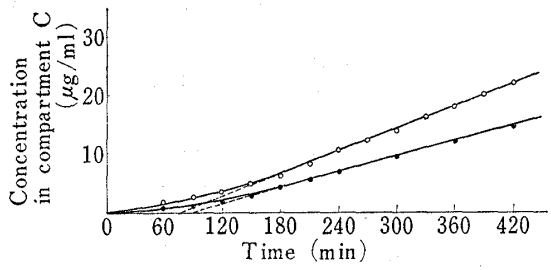

Fig. 5. Concentration–Time Curves of Transport of Benzoic Acid through the Barrier Systems

○: control barrier
●: PVP (2×10^{-2} g/ml) barrier

above straight line to the abscissa, $-\log\{(A_o-2C)/A_o\}$ was plotted against $(t-t_o)$ according to equation (7), as shown in Fig. 6 and 7, the slope giving $(2P/2.303\cdot L)$.

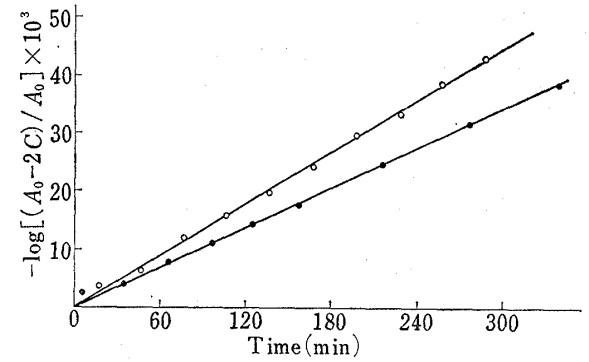

Fig. 6. Transport of Barbital through the Barrier Systems

○: control barrier
●: PVP(2×10^{-2} g/ml)barrier

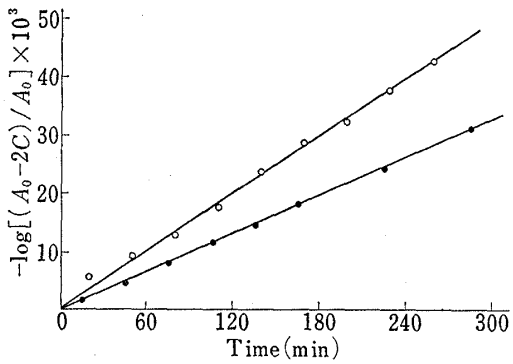

Fig. 7. Transport of Benzoic Acid through the Barrier Systems

○: control barrier
●: PVP (2×10^{-2} g/ml) barrier

Under the conditions that the initial concentration of barbital in compartment A was 0.6 g/liter and that PVP in compartment B was 2×10^{-2} g/ml at 40°, the transport experiments were carried out four times for each of three different assembled transport cells and values of $(2P/2.303\cdot L)$ obtained by the method of least squares according to equation (7) are listed in Table I. The analysis of varience of $(2P/2.303\cdot L)$ is given in Table II and then the effects

Table I. Values of $(2P/2.303\cdot L)$ in Quasi-Steady State Transport of Barbital through the Barrier of the Thickness of 0.718 cm Containing 2×10^{-2} g/ml of PVP in Compartment B

Apparatus	Experimental runs			
	1	2	3	4
I	1.83	1.80	1.67	1.72
II	2.00	1.92	2.12	1.80
III	1.92	2.05	1.98	1.36

Table II. Analysis of Varience of Values of $(2P/2.303 \cdot L)$

Source of variation	S.S.	D.F.	M.S.	F_0	F value at 5% level
Apparatus	0.08645	2	0.04323	1.2788[a)]	5.14
Run	0.09516	3	0.03172	0.9385[a)]	4.76
Error	0.20042	6	0.03380		
Total	0.38203	11			

a) not significant

of transport cell and of experimental run were not significant at 5% level, showing the permeability constant was obtainable with a satisfactory reproducibility.

Effect of NaCl on Transport of Drug

As described already, the different initial concentrations of drug accompanied the respective different concentrations of NaCl which was added in compartment C to make isotonic in the whole system so that the volume flow of water was suppressed. Therefore, if the flux of NaCl gave effect on that of drug causing "coupling phenomena," the permeability constant should change with the initial concentration of drug, *i.e.*, of NaCl. However, Table III shows that the permeability constant, P of barbital had no relation to the initial concentration of drug in compartment A, giving almost the same value.

Table III. Transport of Barbital through Control Barriers of the Thickness of 0.718 cm

A_0(g/liter)	$P \times 10^6$(cm/sec)	A_0(g/liter)	$P \times 10^6$(cm/sec)
2.97	2.21	0.623	2.30
2.98	2.16	0.608	2.30
3.00	2.21	0.587	2.07
3.04	2.21	0.587	2.07
3.04	2.34		

Thus, it was concluded that the coupling phenomenon by NaCl seemed negligible and accordingly the flux of drug was independent from that of NaCl under the experimental conditions.

Applicability of the Theory

Table IV shows the effect of the thickness of control barrier system (containing no PVP) on the permeability constants of barbital and benzoic acid. If the transport of drug through the barrier system followed equation (7), the slope of the plot of $-\log\{A_0-2C/A_0\}$ against $(t-t_0)$, *i.e.*, $(2P/2.303 \cdot L)$, should change with the thickness of the barrier system. However, as shown in Table IV, the values obtained seemed almost constant regarding the respective drugs. Therefore, it was considered that the permeation through the Visking membranes was rate-determinant in the transport of drug through the control barrier system, and this result followed the concept that the permeability constants through the unit and the multilayer membranes coincides with each other in the steady state if controlled by the diffusion in membrane.[15)]

15) M. Nakagaki, "Yakubutsu no Seitainai-Iko (Drug Transfer in Biological Systems)," Nankodo Co. Ltd., Tokyo, 1968, p. 28.

Table IV. Effect of Thickness of Control Barriers on Permeability Constants at 40°

	Thickness of Barier (cm)	$P/L(\times 10^6)$ (sec^{-1})	$P(\times 10^6)$ (cm/sec)
Barbital[a]	0.107	3.70	0.396
	0.188	3.32	0.624
	0.188	3.38	0.635
	0.718	3.32	2.38
	0.718	3.20	2.30
Benzoic Acid[b]	0.188	3.78	0.711
	0.364	3.61	1.32
	0.718	3.90	2.80

a) Initial concentration of compartment A was 3 g/liter.
b) Initial concentration of compartment A was 2 g/liter.
Every value mentioned in this table is the mean of three determinations.

Table V. Transports of Barbital and Benzoic Acid through Barriers of 0.718 cm at Various Temperature

			$P/L(\times 10^6)$ (sec^{-1})	$P(\times 10^6)$ (cm/sec)	$P^*(\times 10^6)$ (cm/sec)	$D(\times 10^6)$ (cm^2/sec)
Barbital	a sheet of Visking membrane	20°	4.16	0.0220	—	—
		30°	5.80	0.0307	—	—
		35°	6.49	0.0344	—	—
		40°	7.71	0.0409	—	—
	control barrier[a]	20°	1.64	0.0106	5.53	3.91
		30°	2.40	0.0254	9.67	6.84
		40°	3.24	0.0343	14.6	10.3
	barrier containing 2×10^{-2} g/ml of PVP	20°	0.958	0.688	1.25	0.884
		30°	1.44	1.03	2.02	1.43
		40°	2.10	1.51	3.29	2.33
		50°	3.20	2.30	5.08	3.59
Benzoic acid	a sheet of Visking membrane	30°	6.08	0.0313	—	—
		35°	7.35	0.0390	—	—
		40°	9.56	0.0506	—	—
	control barrier[a]	30°	2.17	0.0230	5.32	3.76
		35°	2.80	0.0297	8.21	5.80
		40°	3.90	0.0413	14.8	10.5
	barrier containing 2×10^{-2} g/ml of PVP	30°	1.23	0.883	1.46	1.03
		35°	1.52	1.09	1.83	1.29
		40°	2.05	1.47	2.53	1.79

a) Values of control barriers were calculated by putting twice the thickness of Visking membrane (2×0.0053 cm) for L in equation (7).

Table V shows the permeability and the transport constants obtained at various temperatures. Regarding the control barrier system, the permeability constant, P, was obtained by putting twice the thickness of Visking membrane (2×0.0053 cm) for the value of L in equation (7), based on the consideration that the permeation through the Visking membranes was rate-determinant as described above.

Comparing the values of P thus obtained for barbital and benzoic acid with the respective cases of a sheet of Visking membrane only, the former were lower than the latter, respectively. Considering that the permeation of drug through Visking membrane was controlled not by the intake to membrane but by the simple diffusion through pore,[16] the result in

16) H. Nogami, T. Nagai, and H. Uchida, *Chem. Pharm. Bull.* (Tokyo), **17**, 176 (1969).

Table V. Might be due to a non-homogeneity in concentration of drug in compartment B. In other words, the transport might not be in the exact steady state.

However, if the concentration gradient of drug in compartment B might with sufficient accuracy be assumed to be constant, the transport was considered to be in a quasi-steady state and the diffution constant should be obtainable. Then, first the transport constant, P^* in compartment B was obtained according to equation (6). Next, comparing compartment B to a membrane, the diffusion constant, D, was obtained according to equation (8) on the assumption that $f=K=1$. The value of D at 40° thus obtained for barbital was 10.3 $\times 10^{-6}$ cm^2/sec, as shown in Table V, being in agreement with that obtained by the rotating disk method (11.7×10^{-6} cm^2/sec) reported in a previous paper.[16]

Conclusively, the value of $(2P/2.303 \cdot L)$ did not change with the thickness of the barrier system, L, but the permeability constant, P, depended on L, and also P could be described by equation (6).

Discussion Regarding the Effect of Barrier on the Transport of Drugs

Table VI shows the values of (P/L), D and P^*, which were obtained according to equations (7), (8) and (6), respectively.

Table VI. Permeability Constants of Barbital and Benzoic Acid through PVP Barriers of the Thickness of 0.718 cm

	Concentration of PVP in barrier (g/ml)	P/L ($\times 10^6$) (sec^{-1})	P($\times 10^6$) (cm/sec)	P^*($\times 10^6$) (cm/sec)	D($\times 10^6$) (cm^2/sec)	α($\times 10^{-2}$)
Barbital	control	3.24	2.33	14.6	10.3	—
	1×10^{-2}	3.13	2.24	11.8	8.34	0.24
	2×10^{-2}	2.10	1.51	3.29	2.33	1.72
	4×10^{-2}	1.47	1.06	1.69	1.19	1.91
Benzoic acid	control	3.90	2.80	14.8	10.5	—
	1×10^{-2}	3.07	2.20	6.02	4.26	1.46
	2×10^{-2}	2.05	1.47	2.53	1.79	2.43
	4×10^{-2}	1.53	1.10	1.55	1.10	2.39

Every value mentioned in this table is the mean of three determinations.

In general, if there is involved no special interaction between the diffusing species and the medium such as chemical reaction, the viscosity of the medium is considered to be the most important factor affecting the diffusion at a given temperature. The relationship between the diffusion constant, D, and the viscosity of medium, η, at the absolute temperature, T, is expressed by Stokes-Einstein equation as follows:

$$D = \frac{kT}{6\pi\eta r} \tag{9}$$

where r is the radius of the spherical particle and k Boltzman constant.

Table VII shows the temperature dependence of the viscosity of PVP. Although the value of $D\eta/T$ should be constant according to equation (9), the results obtained did not follow it, as shown in Table VIII.

Moreover, the activation energy of the diffusion of drug decreased with the concentration of PVP, as shown in Table IX. Therefore, some interaction between the drug and PVP should be taken into consideration, that is, an exothermic interaction such as general adsorption phenomena. Then the decrease in the activation energy of diffusion with the addition of PVP mentioned above might correspond to the energy of the interaction between the drug and PVP. From the result obtained, this energy of the interaction seemed to be of the same

Table VI. Temperature Dependendence of the Viscosity of PVP Solution

Concentration of PVP in barrier(g/ml)	Relative viscosity (centi-poise)			
	20°	30°	35°	40°
1×10^{-2}	1.256	1.233	1.227	1.208
2×10^{-2}	1.552	1.502	1.480	1.454
4×10^{-2}	2.274	2.172	2.121	2.070

Table VII. The Value of $D\eta/T$ in the Barrier System Containing 2×10^{-2} g/ml of PVP at Various Temperatures

	Temperature	$D\eta/T(\times10^3)$		Temperature	$D\eta/T(\times10^3)$
Barbital	20°	4.68	Benzoic acid	30°	5.12
	30°	7.08		35°	6.20
	40°	9.23		40°	8.35

The values of D and η in Table V and VII, respectively, were used to the calculation of $D\eta/T$.

Table IX. Activation Energy, ΔE, of Diffusion in the Barrier

Concentration of PVP (g/ml)	ΔE	
	Barbital (kcal/mole)	Benzoic acid (kcal/mole)
0	6.86	10.9
2×10^{-2}	5.95	9.61

order of magnitude as the energy of hydrogen bonding, and thus the interaction assumed to be expressed by a Langmuir type isotherm, such as the sorption-diffusion in heterogeneous systems[17,18] or protein binding.[19]

Based on the Langmuir-type isotherm assumed above, the following equations were derived. In general, two species of different diffusion constants, D and D^*, can be described by Fick's second law where the rate of change of total concentration in a small volume element is given by

$$\frac{\partial(C+C^*)}{\partial t}=D\frac{\partial^2 C}{\partial x^2}+D^*\frac{\partial^2 C^*}{\partial x^2} \tag{10}$$

where C and C^* are the concentrations of species (per unit volume of diffusion matrix).[18]

In the steady state, $\partial(C+C^*)/\partial t=0$ and thus,

$$D\frac{\partial^2 C}{\partial x^2}=-D^*\frac{\partial^2 C^*}{\partial x^2} \tag{11}$$

Integration of equation (11) by two steps with respect to x gives

17) P.B. Weisz, *Trans. Farad. Soc.*, 63, 1801 (1967).
18) K. Liang and L.K.J. Tong, *J. Phys. Chem.*, 73, 3125 (1969).
19) I.M. Klotz, "The Proteins," Vol. 1, Part B, Academic Press, 1953, p. 727.

$$Mx+N=-(D\cdot C+D^*\cdot C^*) \tag{12}$$

where M and N are the integration constants.

Putting the condition that $C=C_A$ and $C^*=C^*_A$ at $x=0$, equation (12) becomes

$$N=-(D\cdot C_A+D^*\cdot C_A^*) \tag{13}$$

Combining equations (12) and (13), the following one is given.

$$M=\frac{1}{x}\left\{D\cdot(C_A-C)+D^*(C_A^*-C^*)\right\} \tag{14}$$

M in equation (14) corresponds to the flux of two different diffusing species at x. Therefore, the diffusion of two species through the barrier of the thickness, L, the available area, S, and the volume of solution, V, is expressed as

$$-\frac{d(C+C^*)}{dt}=\frac{S}{V}\cdot\frac{1}{L}\left\{D\cdot(C_A-C)+D^*(C_A^*-C^*)\right\} \tag{15}$$

Regarding the present barrier system, the second species, *i.e.*, the drug bound to (or associated with) PVP, was considered to be immobilized. Thus, $D^*\to 0$ and equation (15) becomes

$$-\frac{d(C+C^*)}{dt}=\frac{S}{V}\cdot\frac{1}{L}\cdot D(C_A-C) \tag{16}$$

where C^* is not necessary zero, although it can not diffuse.[18]

As discussed already, if the interaction between the drug and PVP is expressed by a Langmuir-type isotherm, the concentration of the drug bound to (or associated with) PVP, C, is given as follows.

$$C^*/C_p=\frac{\alpha C}{1+(\alpha/\beta)C} \tag{17}$$

where C_p is the concentration of PVP, and α and β are the parameters similar to those in Langmuir adsorption equation.

Considering that there exist a very large number of binding (or association) sites of PVP compared with the amount of drug, the value of β may be predominantly large compared with that of α, and equation (17) approximates to

$$C^*=\alpha\cdot C_p\cdot C \tag{18}$$

and then equation (16) becomes

$$-(1+\alpha\cdot C_p)\frac{dC}{dt}=\frac{S}{V}\cdot\frac{1}{L}\cdot D(C_A-C) \tag{19}$$

Considering that the concentration of drug in compartment B was negligible compared with those of compartments A and C, it can be expressed that $A_0=C_A+C$, where A_0 is the initial concentration of drug in compartment A. Then, integration of equation (19) with respect to t gives

$$\log\{(A_0-2C)/A_0\}=-\left\{\frac{S}{(1+\alpha\cdot C_p)V}\cdot\frac{2D}{2.303L}\right\}t \tag{20}$$

Comparing compartment B to a membrane, combination of equations (20) and (8) under the assumption that $f=K=1$, the following one is obtained as a result.

$$\log\{(A_0-2C)/A_0\}=-\left\{\frac{P_0^*}{1+\alpha\cdot C_p}\cdot\frac{2}{2.303L}\right\}t \qquad (21)$$

where P_0^* is the transport constant in compartment B containing no PVP, *i.e.*, $P^*=P_0^*/(1+\alpha\cdot C_p)$, and $P^*=P_0^*$ in the control barrier because $\alpha\cdot C_p=0$.

From the values of P^* for the control and the PVP barriers, the value of α was calculated as shown in Table VI. The reliability of the obtained value seemed to increase with the concentration of PVP because (α/β) approaches zero, as discussed upon the derivation of equation (18).

The value of α thus obtained was considered to indicate the extent of the interaction between drug and PVP in the kinetical process, which might be some different from that obtained by statical studies. In the present study, the interaction of PVP-benzoic acid was greater than that of PVP-barbital.

Although the present study was limited to the synthetic polymer containing system, the method is considered to be used in a protein containing one, and also it was concluded that the method might afford a useful means for an investigation of drug interaction on the kinetical viewpoint with a high possibility of making a physicochemical approach to an understanding of the permeability barrier to drug transport in biopharmaceutical system.