Characterization of a Membrane Permeation System for Controlled Drug Delivery Studies

Hydrodynamic characteristics of an *in vitro* membrane permeation system for controlled drug delivery studies were investigated by measuring dissolution rates of benzoic acid in various aqueous solutions of polyethylene glycol 400. The mass transfer coefficient was well correlated in terms of three dimensionless numbers: Sherwood, Schmidt, and Reynolds numbers. By using the correlation equation, the intrinsic permeation rate of testosterone through silicone membranes was precisely extracted from the experimental data obtained under various nonideal flow conditions.

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SCOPE

Mass transfer through various polymeric membranes has received increasing attention in pharmaceutical and allied industries. Especially in the pharmaceutical industry, the novel approaches of drug delivery through a polymeric membrane have become one of the most challenging research areas (Chien, 1982). Although extensive researches on drug transport through a membrane have been done using various *in vitro* apparatus (Cardinal et al., 1981; Olanoff et al., 1981; Roseman and Yalkowsky, 1976; Flynn et al. 1976; Kent, 1976; Chien et al., 1974; Kalkowarf et al., 1972), no standardized setup for *in vitro* drug permeation studies has emerged. It is evident that the rate of drug permeation through a membrane should be accurately determined by using a wholly calibrated permeation cell. Otherwise, the rate of permeation may easily be distorted by the hydrodynamic characteristics of the permeation system used. Especially, a drug with a high lipophilicity or membrane/solution partition coefficient may give an experimental permeation rate which is markedly lower than the intrinsic rate under a nonideal flow condition. It is desirable that an *in vitro* system for controlled drug release studies assure the intrinsic permeation rate which is independent of its hydrodynamic condition. Once the intrinsic permeation rates of various drugs through various membranes have been well established, the deviation in the permeation rates among laboratories, which frequently appear, can be minimized and direct comparison of the data generated in different laboratories will become meaningful. In addition, *in vivo* data can be better explained using the *in vitro* intrinsic rate in terms of a diffusion boundary layer around the drug delivery device in an *in vivo* study. The most straightforward means of eliminating diffusion boundary layer resistance and obtaining the intrinsic permeation profile is simply to increase the stirring rate until the drug flux remains constant, and then to perform the measurement at that stirring rate or at higher stirring rates. However this approach is not always practical for controlled drug release studies because of a viscous fluid, a drug with a high interfacial partitioning property, and/or the mechanical strength of the membrane. Therefore it is rather logical to extract the intrinsic rate from the experimental permeation data.

In this investigation, an *in vitro* membrane permeation system is designed and calibrated with the intent to develop it into a standardized diffusion cell for routine membrane permeation studies. The hydrodynamic characteristics of this diffusion cell are evaluated by studying the dissolution process of a planar benzoic acid in various aqueous solutions of polyethylene glycol (PEG) 400. The correlation equation for the mass transfer coefficients, which characterize the diffusion boundary layer developed on the membrane surface, is established. A procedure for determining the intrinsic permeation rate which is independent of the flow field in the solution is discussed for permeation through polymeric unilayer membranes. As illustration, the permeation of testosterone, a lipophilic drug, through silicone membrane, a lipophilic polymer, is studied under various nonideal flow conditions. The permeation data are then used to determine the intrinsic rate of permeation of testosterone through silicone membranes. We intend to analyze the results in this report.

CONCLUSIONS AND SIGNIFICANCE

The hydrodynamic characteristics of an *in vitro* membrane permeation system for controlled drug delivery studies have been established by evaluating the dissolution rate profiles of a planar benzoic acid disc in various PEG400 solutions. The mass transfer coefficient, which characterizes the diffusion boundary layer thickness, was well correlated by a conventional dimensionless equation of Sherwood, Schmidt, and Reynolds numbers. The effect of the diffusion boundary layer on the rate of drug permeation was analyzed for unilayer membranes under

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various experimental conditions. A method for eliminating the effect of the diffusion boundary layer and for determining the intrinsic rate of permeation from the experimental data has been proposed in the present *in vitro* permeation system. The intrinsic rate of permeation of testosterone through silicone membrane was extracted under various experimental conditions. The intrinsic permeation rate obtained was independent of the flow conditions in the present experimental system.

INTRODUCTION

In the past decade, drug delivery systems using polymeric membranes to moderate the release of drugs have advanced remarkably in the pharmaceutical industry. The new drug formulations derived from the application of a controlled release drug delivery technology may lead to a renaissance for various old drugs which can not be used in conventional dosage forms due to their highly possible side effects. In the near future, perhaps, the therapeutic efficacy of new drugs will be specified not by the quantity of drug dose contained, but rather by the rate of drug delivery from the formulation.

Reflecting these future prospects, the novel approaches of drug delivery through a rate-controlling polymeric membrane have become one of the most challenging research areas in the pharmaceutical industry. A great many studies on drug permeation through membranes have been conducted by using various experimental setups for *in vitro* investigations (Chien, 1982; Kydonieus, 1980).

It is logical that permeation studies should be conducted in a well-calibrated diffusion cell; otherwise, the permeation rate obtained may be significantly distorted by the presence of hydrodynamic diffusion layers on the membrane surface. In spite of the possibility of the appreciable effect of diffusion boundary layers, the rate of permeation has been frequently analyzed on the assumption that no diffusion boundary layer exists on the surface of the membrane, or without any precise measurement of the diffusion layer thickness. In the usual membrane permeation studies, however, the effect of hydrodynamic diffusion layer on the rate of permeation can hardly be neglected. It is rather important to realize that only an *in vitro* membrane permeation system which has been calibrated rigorously by a careful study of its hydrodynamic characteristics can provide a reliable determination of the permeation rate. Once an *in vitro* system has been well calibrated, the apparent rate of permeation obtained in an *in vitro* permeation study can be used to accurately determine the intrinsic release rate in the absence of any hydrodynamic diffusion layer effect.

The main objective of this study is to establish the hydrodynamic characteristics of an *in vitro* membrane permeation system. The diffusion boundary layer in the present system was determined by measuring the dissolution rate profiles of a planar benzoic acid disc in an aqueous elution medium containing various concentrations of polyethylene glycol (PEG) 400. The effect of Sherwood number, which characterizes the thickness of the diffusion boundary layer, on the rate of membrane permeation was numerically analyzed. Finally, the intrinsic permeation rate of testosterone through silicone membrane was calculated from the experimental permeation data obtained under various operating conditions. The silicone elastomer has been frequently used as a device (membrane and matrix) for a drug delivery system, particularly for an implantable controlled drug delivery system, because of its excellent biocompatibility. The results obtained in the present work will be of practical significance for designing and formulating membrane-moderated controlled release drugs.

EXPERIMENTAL

An *in vitro* Membrane Permeation System

An *in vitro* membrane permeation system designed by two of the authors was constructed (by Bellco Glass, Inc., Vineland NJ) for the investigation of long-term membrane permeation kinetics under both finite and infinite dose conditions. As shown in Figure 1, each cell of the system consists of two cylindrical half-cells in mirror image. Each unit of the system is composed of triplicate sets of donor and receptor half-cells, in which the solution is agitated by a matched pair of bar magnet stirrers at a synchronous speed, in a specially designed rotating platform, by a 6-station driving unit. Each of the donor and receptor compartments, which were enclosed inside a water jacket, hold a volume of up to 250 mL of elution medium. The effective membrane area for drug permeation is 13.9 cm^2. The solution in the donor and receptor compartments are both maintained in a totally enclosed environment to minimize any loss in solution volume due to evaporation during a long-term permeation experiment. The rotation speed of the 3 pairs of magnetic stirring bars (2.54 cm in length) can be controlled at a constant rotation speed ranging from 60 to 1,000 rpm by an external synchronous driving unit. After assembly with a membrane sandwiched between the donor and receptor compartments, the whole permeation system becomes a totally enclosed system.

Dissolution Studies

A thin disc of benzoic acid of a suitable size (65 mm dia., 5–10 mm thick) was fabricated by pouring fused benzoic acid into a metal mold positioned on a pill tile. The disc was then mounted to the membrane permeation system. In order to avoid leakage of the elution medium from the receptor compartment, a parafilm was used as a gasket. With the benzoic acid disc in place, 170 mL of the aqueous solution containing 0–40% of PEG400, previously maintained at 37°C, were charged into the receptor compartment, while the donor compartment remained empty. The rotation speed of the magnetic stirrers was constant at from 125 to 900 rpm.

At predetermined time intervals, 1 mL samples were withdrawn from the receptor solution and diluted 10 to 1,000 times with the same solution medium (containing no benzoic acid) and then analyzed by using a UV/VIS spectrophotometer.

The physical parameters of benzoic acid-aqueous PEG400 solution system are summarized in Table 1 (Masi, 1984).

Drug Permeation Studies

The membrane permeation experiment with testosterone was carried out using medical grade silicone membranes with a thickness varying from 0.0127 to 0.1016 cm.

A saturated solution of testosterone prepared by suspending an excess amount of testosterone crystals in various PEG400 solutions, was placed in the donor compartment. Excess solid drug assured that the solution remained at a constant saturation concentration during the course of an experiment. The same elution medium with no drug was then added to the receptor compartment. Leakage of the donor and receptor fluids was avoided due to the elasticity of the membrane. The temperature in both donor and receptor compartments was maintained at 37°C.

At predetermined time intervals, 10 mL of receptor solution were withdrawn and an equivalent volume of fresh solution was quickly added to the receptor solution to maintain the same volume in the receptor compartment. The concentration of testosterone in the samples was then analyzed by the UV/VIS spectrophotometer. The cumulative amount of drug permeated was then calculated from the drug concentration in the receptor fluid and the cumulative amount of drug lost due to sampling.

Hydrodynamic Characteristics

The mass balance equation for the benzoic acid in the receptor solution is given by

$$V\frac{dC_0}{dt}=\frac{D_R}{\delta_R}A(C_s-C_0)=k_mA(C_s-C_0) \tag{1}$$

where V is the volume of the receptor compartment, C_0 is the concentration of the benzoic acid in the receptor solution at time t, A is the effective surface area for mass transfer, D_R is the diffusivity of the drug in the receptor fluid, δ_R is the thickness of diffusion boundary layer, C_s is the sat-

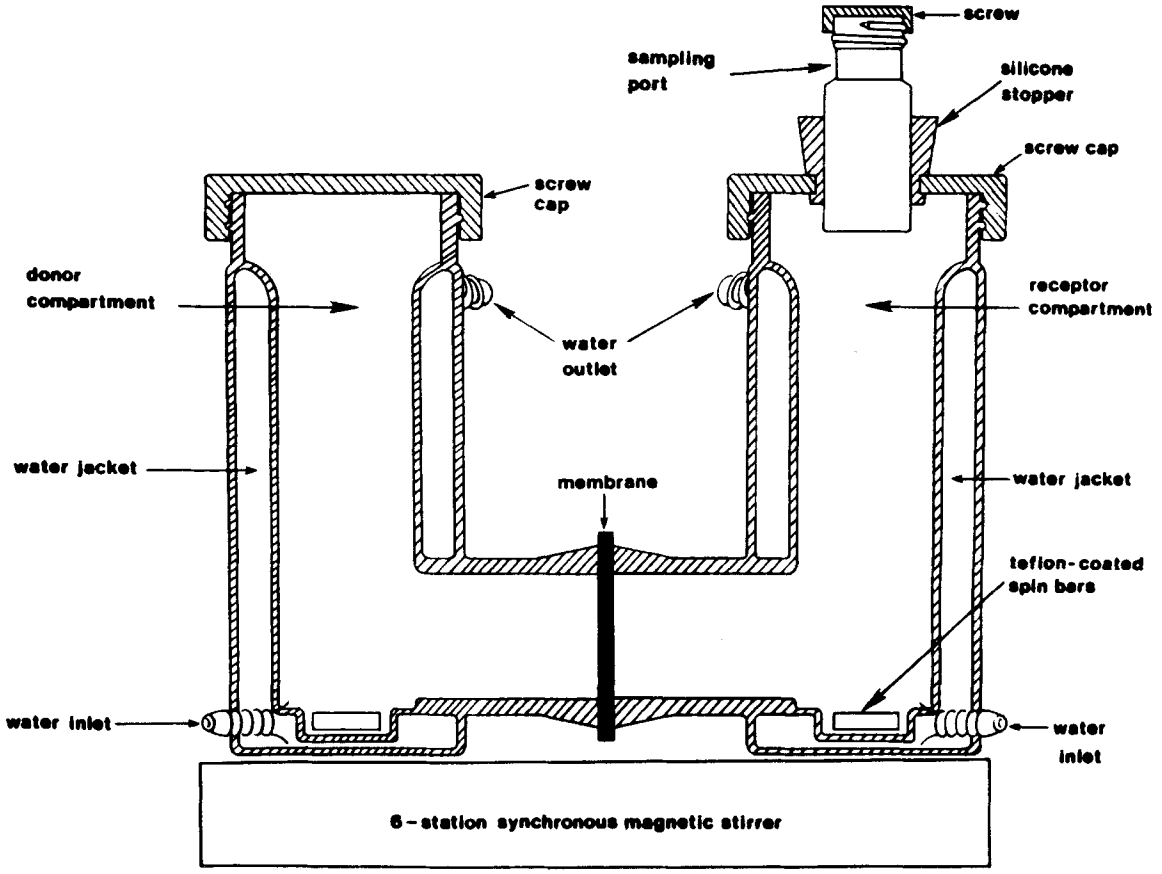

Figure 1. *In vitro* membrane permeation system.

urated drug concentration, and k_m is the mass transfer coefficient. By solving Eq. 1, subject to the appropriate initial concentration C_i, the diffusion boundary layer thickness δ_R and the mass transfer coefficient k_m can be determined from the following relationship:

$$\delta_R = \frac{D_R A t}{V \ln\{(C_s - C_i)/(C_s - C_0)\}} \tag{2}$$

$$k_m = \frac{V}{At} \ln\left[\frac{C_s - C_i}{C_s - C_0}\right] \tag{3}$$

The mass transfer coefficient k_m can be correlated with the conventional Sherwood-Reynolds-Schmidt (*Sh-Re-Sc*) number relationship (Frank-Kamenetskii, 1969):

$$Sh = \text{const.}\ Re^m\, Sc^n \tag{4}$$

where

$$Sh = k_m d/D_R \tag{5}$$

$$Re = Nd^2\rho/\mu \tag{6}$$

$$Sc = \mu/\rho D_R \tag{7}$$

and d is the characteristic length of the *in vitro* system and is defined as the length (2.54 cm) of the agitator in the present study. The constant and the exponents m and n in Eq. 4 can be determined empirically.

Effect of Diffusion Boundary Layer on Rate of Permeation

If the pseudosteady state can be assumed and the drug permeates through a unilayer membrane under a perfect sink condition ($C_0 = 0$) as shown in Figure 2, the steady state rate of permeation per unit membrane area can be represented by the following equation:

$$\frac{dQ}{dt} = k_D(C_s - C_1) = \frac{D_p}{\ell}(K_1C_1 - K_2C_2) = k_R(C_2 - C_0) = k_R C_2 \tag{8}$$

where

D_p = diffusivity of drug through the membrane
K_1 = partition coefficient between the donor phase and membrane
K_2 = partition coefficient between the receptor phase and membrane
k_D = mass transfer coefficient in the donor-side boundry layer
k_R = mass transfer coefficient in the receptor-side boundary layer
ℓ = thickness of the membrane

Rearranging Eq. 8 yields:

$$\frac{dQ}{dt} = \frac{C_s}{\frac{1}{k_D} + \frac{\ell}{K_1 D_p} + \frac{K_2}{K_1}\frac{1}{k_R}} \tag{9}$$

where the denominator consists of the sum of resistances due to the donor-side boundary layer, membrane, and receptor-side boundary layer.

TABLE 1. PHYSICAL PROPERTIES OF POLYETHYLENE GLYCOL 400 SOLUTIONS AT 37°C

Physical Property	Volume Fraction of PEG400			
	0%	10%	20%	40%
Density (g/mL)	0.9934	1.007	1.020	1.047
Viscosity (g/cm·s)	0.0069	0.0102	0.0180	0.0460
Saturated concentration of benzoic acid (mg/mL)	4.39	7.85	15.36	54.2
Diffusivity of benzoic acid (cm^2/s)	1.45×10^{-5}	0.986×10^{-5}	0.549×10^{-5}	0.216×10^{-5}

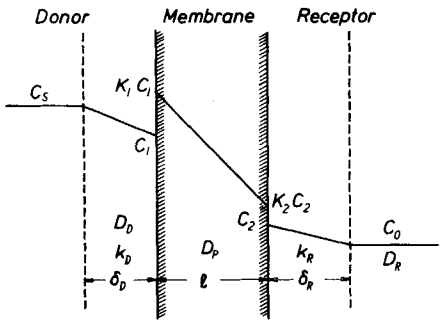

Figure 2. Steady state concentration profile in the membrane and in the solution.

If agitation of the fluid is so vigorous that the diffusional resistance in the diffusion boundary layer is negligible, Eq. 9 is reduced to

$$\frac{dQ}{dt_\infty} = \frac{C_s}{\ell/(K_1 D_p)} \tag{10}$$

The correction factor γ for the calculation of the intrinsic permeation rate from the experimental data under nonideal mixing conditions can be determined:

$$\gamma = \frac{dQ/dt}{dQ/dt_\infty} = \left[1 + (\alpha + \beta)\frac{K_1}{Sh_R}\frac{d}{\ell}\frac{D_p}{D_R}\right]^{-1} = 1 - \frac{(\alpha + \beta)}{Sh_R}\frac{(dQ/dt)}{D_R C_s/d} \tag{11}$$

where $\alpha = k_R/k_D$ and $\beta = K_2/K_1$.

For the special case that the same solution and same agitation speed are used in the donor and receptor compartments, Eq. 11 can be simplified as follows:

$$\gamma = \left[1 + \frac{2K_1}{Sh_R}\frac{d}{\ell}\frac{D_p}{D_R}\right]^{-1} = 1 - \frac{2}{Sh_R}\frac{(dQ/dt)}{D_R C_s/d} \tag{12}$$

The intrinsic rate of membrane permeation dQ/dt_∞ is given by

$$dQ/dt_\infty = (dQ/dt)/\gamma \tag{13}$$

where dQ/dt is the permeation rate obtained under a nonideal flow condition.

The correction factor, γ, calculated by Eq. 11 is plotted as a function of the ratio of Sherwood number to partition coefficient, Sh_R/K_1 in Figure 3. Because the range of the ratio of Sherwood number to partition coefficient is approximately less than 1,000 under normal operating conditions, the effect of the diffusion boundary layer on the rate of drug permeation is usually appreciable and therefore should be precisely evaluated so that the intrinsic permeation rate can be determined from the experimental permeation data. The detailed approach to evaluating the correction factor γ for both unilayer and bilayer membranes has been reported elsewhere (Masi, 1984).

RESULTS AND DISCUSSION

Hydrodynamic Characteristics

The mass transfer coefficients for the dissolution of a benzoic acid disc in various PEG400 solutions in the present permeation cell were calculated from the slopes of $\ln\{(C_s - C_i)/(C_s - C_0)\}$ vs. t plots (Eq. 3). The dissolution profile of the benzoic acid disc in the 40% PEG400 solution and in pure water were plotted according to the relationship of $\ln\{(C_s - C_i)/(C_s - C_0)\}$ vs. t in Figure 4. The observation of perfect straight lines suggests that the bulk of the receptor solution was well-stirred under the experimental conditions employed. The mass transfer coefficients obtained experimentally were then correlated by the conventional dimensionless *Sh-Re-Sc* equation (Eq. 4).

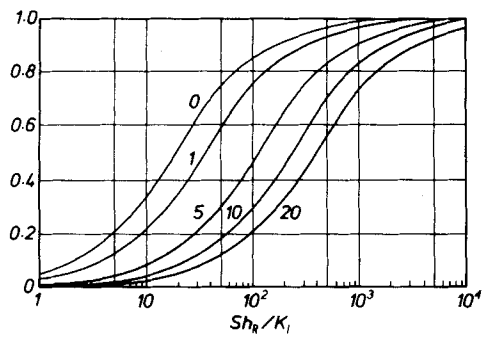

Figure 3. Effect of Sh_R/K_1 on the correction factor γ defined by Eq. 11; D_P/D_R = 0.1, d/ℓ = 200, α = 1. Numbers on the curves are values of β.

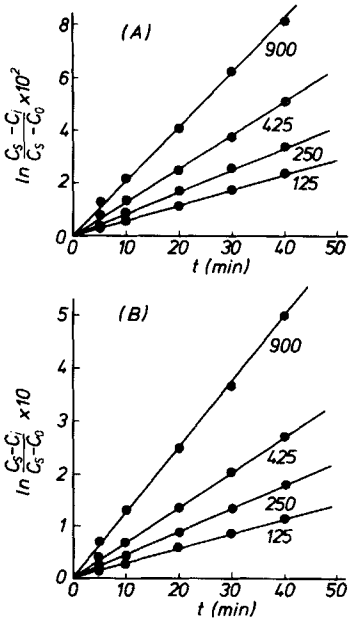

Figure 4. Dissolution profiles of benzoic acid disc in the G-C diffusion cell: A, 40% PEG400 solution; B, pure water, V = 170 mL. Numbers on the curves are values of rotation speed of magnetic stirring bar N (rpm).

Figure 5 shows the effect of Schmidt number *Sc* on the Sherwood number *Sh* at two Reynolds numbers. The exponent n of the Schmidt number was found to agree well with the theoretical value (n = 1/3; Levich, 1962).

All the experimental data were then plotted as $\log(Sh/Sc^{1/3})$ vs. $\log(Re)$ in Figure 6. It can be seen that the mass transfer coefficients in the present cell design were well correlated by the following dimensionless equation:

$$Sh = 0.154\, Re^{0.61}\, Sc^{1/3} \tag{14}$$

Equation 14 can be used only for the present *in vitro* membrane permeation system at 37°C. The effect of the diffusion boundary layer on the rate of membrane permeation is then evaluated by substituting Eq. 14 into the Sherwood number Sh_R in Eq. 11 or 12.

Effect of Physicochemical Properties on the Steady State Drug Permeation Rate

To investigate the effect of the physicochemical properties of the drug on the steady state rate of membrane permeation, three drug molecules with a similar molecular structure but with a substantial difference in membrane/water partition coefficient were selected for the present simulation study.

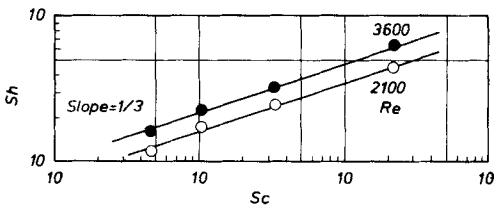

Figure 5. Effect of Schmidt number on Sherwood number at two Reynolds numbers.

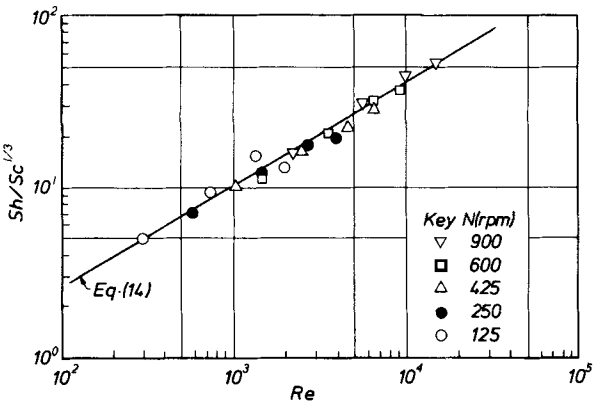

Figure 6. Correlation of the $Sh/Sc^{1/3}$ values in the G-C membrane permeation system with the *Re* numbers (Eq. 4).

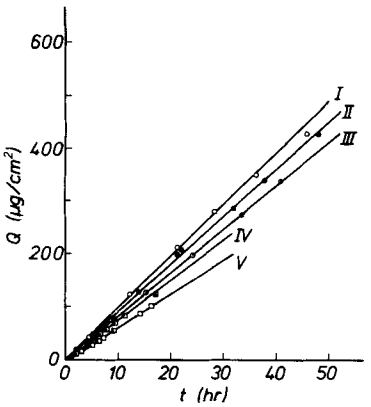

Figure 7. Permeation profile of testosterone through silicone membrane (0.0127 cm thick) under various operating conditions: I, 40% PEG400, 900 rpm; II, 40% PEG400, 425 rpm; III, 40% PEG400, 125 rpm; IV, 0% PEG400-pure water, 425 rpm; V, 0% PEG400-pure water, 125 rpm.

The permeation profiles of progesterone, testosterone, and hydrocortisone, through silicone membrane (0.0127 cm thick) were simulated on the basis of the permeation system designed. The drug molecular weight and the physicochemical properties are listed in Table 2, for which the drug solubility in the elution medium was measured using a UV/VIS spectrophotometer within an accuracy of 4% S.D. The diffusivity of the drugs in water and the solubility of drug in polymer were determined previously by Roseman and Higuchi (1970). The diffusivities in 40% PEG400 solution were estimated from the Stokes-Einstein equation, based on the values in water.

If the permeation cell is operated at 425 rpm in pure water, the value of the Sherwood number calculated from Eq. 14 is $Sh = 335$. Therefore, the correction factor γ for each drug can be calculated from Eq. 12 as follows:

$$\gamma = \begin{cases} 0.200 \text{ for progesterone} \\ 0.800 \text{ for testosterone} \\ 0.996 \text{ for hydrocortisone} \end{cases}$$

The permeation rates obtained at 425 rpm for progesterone, testosterone and hydrocortisone are, therefore, 20, 80, and 99.6% of their individual intrinsic permeation rate, respectively. The results indicate that a drug with high lipophilicity or with a high value of membrane/solution partition coefficient, e.g., progesterone, may achieve an experimental permeation rate which is markedly lower than its intrinsic rate ($\gamma = 0.20$), so the hydrodynamic diffusion layer on both sides of the membrane should be taken into consideration. On the other hand, the experimental permeation rate for a drug with low lipophilicity or with a low value of membrane/solution partition coefficient, e.g., hydrocortisone, is very close to the intrinsic rate of membrane permeation ($\gamma = 0.996$). In this case, the effect of the hydrodynamic diffusion layer on the rate of membrane permeation can be neglected.

Calculation of Intrinsic Rate of Membrane Permeation

The experimental data on the permeation of testosterone through silicone membrane (0.0127 cm thick) obtained under various operating conditions are plotted in Figure 7. It is interesting to see the difference in the steady state rate of membrane permeation, which implies that the diffusion boundary layer varies with the experimental conditions employed. The intrinsic rates of permeation calculated from the present approach are listed in Table 3. The results demonstrated that the intrinsic permeation rates calculated under various experimental conditions are almost identical (9.80 $\pm$ 0.47 $\mu g/cm^2 \cdot h$), indicating that the effect of the hydrodynamic

TABLE 2. PHYSICOCHEMICAL PROPERTIES OF DRUGS USED IN THE SIMULATION STUDIES

Parameters	Progesterone	Testosterone	Hydrocortisone
Molecular weight	314.5	288.4	362.5
Solubility in water C_{aq}, mg/mL	0.0114	0.025	0.28
Solubility in 40% PEG400 C_{aq}, mg/mL	0.200	0.508	2.27
Diffusivity in water D_f, cm^2/s	6.54×10^{-6}	6.54×10^{-6}	6.54×10^{-6}
Diffusivity in 40% PEG400 D_f, cm^2/s	9.81×10^{-7}	9.81×10^{-7}	9.81×10^{-7}
Membrane/water partition coefficient, K	50.2	5.38	0.05
Membrane/40% PEG400 partition coefficient, K	2.86	0.265	0.0062

TABLE 3. CALCULATION OF INTRINSIC PERMEATION RATE FROM EXPERIMENTAL PERMEATION RATE

Testosterone permeation through silicone membrane (0.0127cm thick)

Rotation Speed N rpm	Volume Fraction of PEG400 % vol.	Experimental Permeation Rate dQ/dt; $\mu g/cm^2 \cdot h$	*Re*	*Sc*	*Sh*	Correction Factor, γ Eq. 12	Intrinsic Permeation Rate dQ/dt_∞; $\mu g/cm^2 \cdot h$
900	40	9.80	2,202	44,786	598	0.954	10.27
425	40	9.10	1,040	44,786	379	0.931	9.77
425	0 (pure water)	7.75	6,579	1,062	335	0.800	9.69
425	20	8.25	2,590	7,031	356	0.885	9.32
125	40	8.30	306	44,786	180	0.869	9.54
125	0 (pure water)	6.51	1,935	1,062	159	0.673	9.67

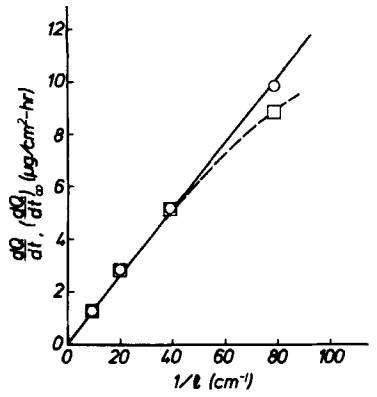

Figure 8. Effect of membrane thickness ℓ on the rate of steady state testosterone permeation; N = 425 rpm, elution media = 40% PEG400 solution. □: dQ/dt, ○: $(dQ/dt)_\infty$.

diffusion layer is completely eliminated in the intrinsic permeation.

The effect of membrane thickness on the intrinsic rate of testosterone permeation is shown in Figure 8. The experimental permeation rates are also plotted in this figure for comparison. It can be seen that the intrinsic rates agree excellently with the theoretical relationship expected from Eq. 10, while the experimental data, in which the boundary layer effect is still uncorrected, deviate appreciably from the theoretical relationship with the decrease in membrane thickness. It is obvious that the membrane permeation data can be explained more logically in terms of the intrinsic rate of permeation. This corrected permeation rate can be utilized for reliable determination of the *in vitro/in vivo* correlation of drug delivery through membrane.

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NOTATION

A = effective surface area of device
C = concentration of drug molecules
C_s = saturated concentration of drug in the donor phase
C_1 = concentration of drug molecules on the surface of the donor-side boundary layer, Figure 2
C_2 = concentration of drug molecules on the surface of the receptor-side boundary layer, Figure 2
C_0 = concentration of drug molecules in the receptor fluid
D_P = diffusivity of drug molecules through the membrane
D_R = diffusivity of drug molecules in the receptor phase
d = characteristic length of the system; length of the magnetic stirrer
k_m = mass transfer coefficient
k_R = mas transfer coefficient in receptor-side boundary layer
k_D = mass transfer coefficient in donor-side boundary layer
K_1 = partition coefficient for interfacial partitioning of drug molecules from the donor compartment toward the membrane
K_2 = partition coefficient for interfacial partitioning of drug molecules from the receptor compartment toward the membrane
ℓ = thickness of the membrane
m = exponent of Reynolds number in Eq. 4
n = exponent of Schmidt number in Eq. 4
N = rotation speed of magnetic stirrer
Q = cumulative amount of drug permeated
Re = Reynolds number, defined by Eq. 6
Sh = Sherwood number, defined by Eq. 5
Sc = Schmidt number, defined by Eq. 7
t = time
V = volume of receptor or donor compartment

Greek Letters

α = ratio of mass transfer coefficient defined by k_R/k_D
β = ratio of partition coefficient defined by K_2/K_1
γ = correction factor defined by Eq. 11
δ = thickness of diffusion boundary layer
ρ = density of the elution medium
μ = viscosity of the elution medium

Subscripts

R = receptor phase
D = donor phase

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