DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(6&7), 1363-1371 (1985)

SIMPLE EVALUATION METHOD OF INTRINSIC DIFFUSIVITY FOR MEMBRANE-MODERATED CONTROLLED RELEASE

Kakuji Tojo, Ying Sun, Musa Ghannam and Yie W. Chien

Controlled Drug-Delivery Research Center
Rutgers University, College of Pharmacy
Piscataway, New Jersey 08854

ABSTRACT

The effect of diffusion boundary layers in an in vitro membrane permeation system on the membrane diffusivity of drugs was investigated based on the three-layer model. A simple method for evaluating the intrinsic diffusivity through the membrane was developed and the intrinsic diffusivity of progesterone and testosterone through a silicone membrane were determined using this approach.

INTRODUCTION

The membrane diffusivity of drug molecules has been frequently determined from the time-lag method of Daynes[1]:

$$D = \frac{\ell^2}{6t_o} \qquad (1)$$

where ℓ is the thickness of membrane, t_o is the time-lag obtained from the

0363-9045/85/1106-1363$3.50/0

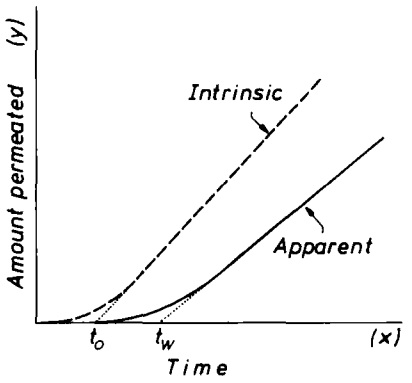

FIGURE 1
Hypothetical drug permeation profiles. Keys: (———) Apparent profile with diffusion boundary layer effect, (-----) Intrinsic profile without diffusion boundary layer effect.

X-axis intercept of the release profile(Fig.1). Equation(1) is applicable only when an ideal flow condition, i.e., no diffusion boundary layer resistance and under a sink condition is maintained, in a membrane permeation system. If the boundary layer resistance to drug transport is appreciable in the membrane permeation system, the effect of diffusion boundary layer on the time-lag must also be taken into account if one intends to determine the true(intrinsic) value of membrane diffusivity.

In this investigation, we intend to present a simple method for the evaluation of intrinsic time-lag and intrinsic diffusivity through a polymeric membrane. As the example, the intrinsic diffusivity of progesterone and testosterone is obtained by correcting the apparent diffusivity using the present approach.

CORRECTION METHOD

The apparent time lag t_w for drug permeation through a membrane with two diffusion boundary layer on each surface of the membrane, as shown in

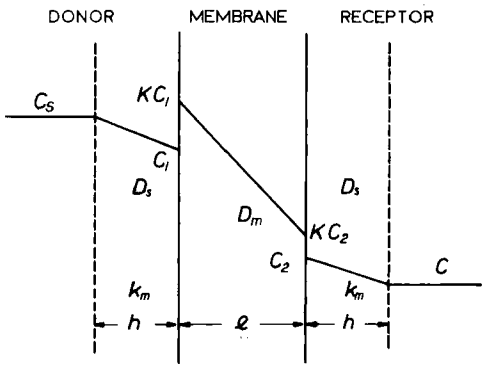

FIGURE 2
Concentration profile of drug in a membrane permeation system. Same elution medium and same intensity of fluid mixing are maintained in the donor and receptor compartments.

Fig.2, can be represented by Eq.(2) based on the three-layer model[2]:

$$t_w = \frac{\frac{D_s}{k_m}\left(\frac{4}{3} + \frac{\ell}{2D_m}\frac{k_m}{K}\right) + \frac{\ell^2}{D_m}\left(1 + \frac{\ell}{6D_m}\frac{k_m}{K}\right) + \frac{\ell K}{k_m}}{2 + \frac{k_m \ell}{D_m K}} \qquad (2)$$

where D_s = the drug diffusivity in the donor and receptor solutions,

D_m = the drug diffusivity in the polymer membrane,

k_m = the mass transfer coefficient which is defined as D_s/h,

ℓ = the thickness of membrane,

K = the partition coefficient(= $C_{solution}/C_{membrane}$).

If the resistance to the drug transport across the diffusion boundary layers is negligible, Eq.(2) can be simplified to:

$$t_o = \lim_{k_m \to \infty} (t_w) = \frac{\ell^2}{6D_m} \qquad (3)$$

where t_o is defined as the intrinsic time-lag.

From Eqs.(2) and (3), the ratio of the time-lags (t_o/t_w) is represented by

$$\frac{t_o}{t_w} = \frac{1}{6(1 + \frac{\alpha}{6} + \frac{1}{\alpha})}\left[(2 + \alpha) - \beta(\frac{4}{3} + \frac{\alpha}{4})\right] \quad (4)$$

where

$$\alpha = k_m C_s/(dQ/dt)_i \quad (5)$$

$$\beta = D_s/(t_w k_m^2) \quad (6)$$

and $(dQ/dt)_i$, the intrinsic rate of permeation, can be evaluated if an apparent steady-state rate of permeation is obtained in an in vitro membrane permeation system, in which the hydrodynamics is fully calibrated and the mass transfer coefficient k_m is available[3].

EXPERIMENTAL

The permeation of progesterone and testosterone through silicone (PDMS) membrane with and without filler was investigated by using a recently developed in vitro membrane permeation system(Fig.3). The thickness and the filler content in the membrane were varied and both the time-lag and the steady-state rate of permeation were measured. The membrane was mounted between the two half-cells of the membrane permeation system. A 170ml of 40% v/v aqueous PEG 400 solution without drug was filled into the receptor compartment, and a drug suspension in the same valume of aqueous PEG 400 solution was added into the donor compartment. At each of the predetermined time intervals, a sample was withdrawn and analyzed by a UV/VIS spectrophotometer. The time-lag and the steady-state rate of permeation were then determined from the Q vs. t profiles. The details of experimental setup and its procedure were described in our previous paper[3].

RESULTS AND DISCUSSION

The steady-state rate of permeation and the time-lag obtained experimentally are listed in Table 1.

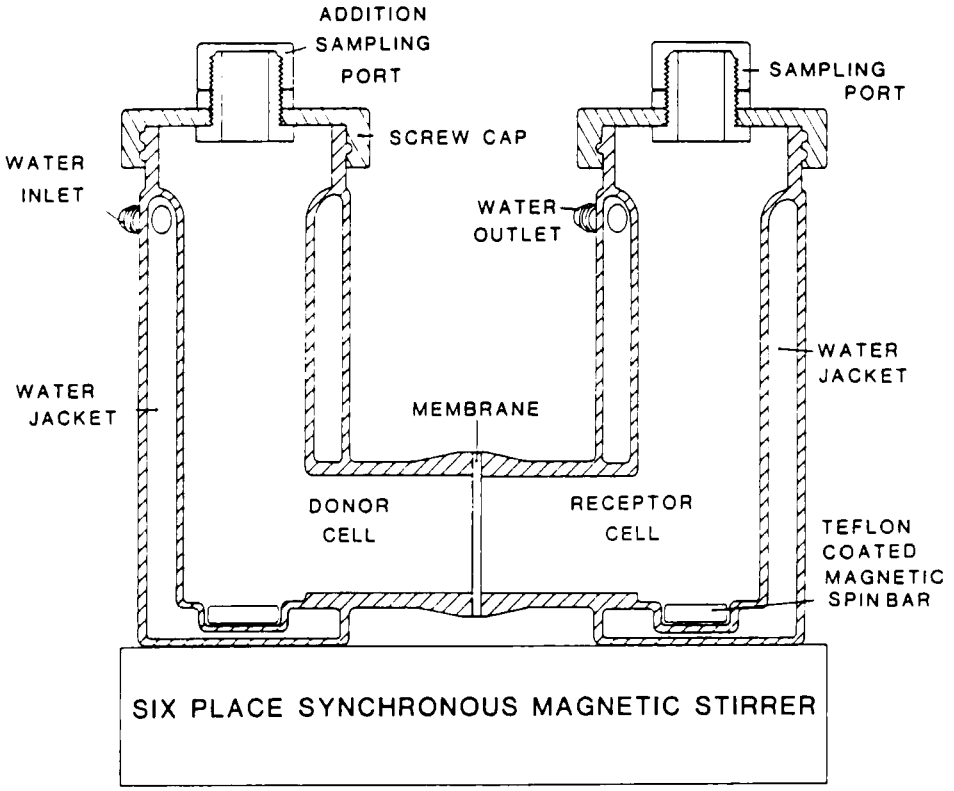

FIGURE 3
Membrane permeation system used in this investigation. The solution in donor and receptor cell is maintained in a totally enclosed environment - for temperature stability and for minimization of volume loss to solvent evaporation. Water-jacketed cells allow isothermal control with external circulating water baths.

The intrinsic and apparent diffusivities calculated from Eqs.(2) and (3) using the intrinsic time-lag and the apparent time-lag, respectively, are compared in Fig.4 for progesterone and in Fig.5 for testosterone, as a function of membrane thickness. As can be seen from Fig.4, for the fillerless membrane, the intrinsic diffusivity of progesterone is almost independent of the membrane thickness. The apparent diffusivity of progesterone for both filled and fillerless membranes was observed to increase as the membrane thickness increased. This is mainly due to the decreased contribution of diffusion boundary layer resistance as increasing

TABLE 1

Rate of drug permeation and time-lag through silicone membrane.

Filler content(% w/w)	Drug*	Membrane thickness(cm)		
		0.025	0.16	0.27
		Rate of permeation($\mu g/cm^2$-hr)		
0	P	32.2	10.2	6.02
	T	10.1	2.01	1.25
10	P	29.1	9.76	5.60
	T	6.34	1.46	0.88
23.4	P	16.9	7.70	4.26
	T	4.57	1.20	0.68
		Time-lag(sec $x10^{-3}$)		
0	P	0.36	11.5	14.6
	T	0.32	9.43	22.7
10	P	0.71	15.3	32.4
	T	0.58	20.2	41.0
23.4	P	3.42	26.2	51.7
	T	0.94	23.8	59.0

*) P: progesterone, T: testosterone.

the membrane thickness. The corrected diffusivity of progesterone through fillerless membrane, however, was almost independent of the membrane thickness and provided the intrinsic diffusivity. The corrected diffusivity of progesterone through the membrane with low filler content(10%) was also essentially unchanged by the membrane thickness, while the diffusivity of progesterone through the membrane with high filler content(23.4%) increased significantly as increasing the membrane thickness. This finding implies that the adsorption process of drug

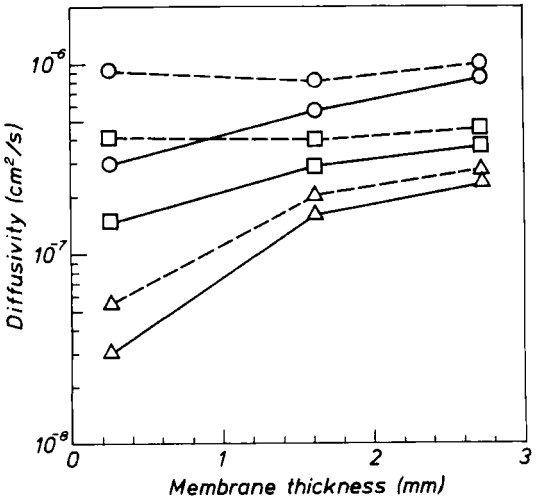

FIGURE 4
Effect of membrane thickness on the progesterone diffusivity through silicone(PDMS) membrane. Keys: (○) without filler, (□) with filler(10% w/w), (△) with filler(23.4% w/w). (———) Apparent diffusivity based on t_w, (-----) Corrected (intrinsic) diffusivity based on t_o.

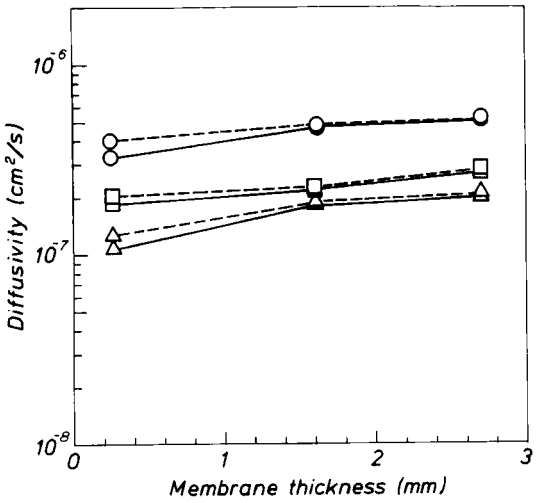

FIGURE 5
Effect of membrane thickness on the testosterone diffusivity through silicone(PDMS) membrane. Keys: (○) without filler, (□) with filler(10% w/w), (△) with filler(23.4% w/w). (———) Apparent diffusivity based on t_w, (-----) Corrected (intrinsic) diffusivity based on t_o.

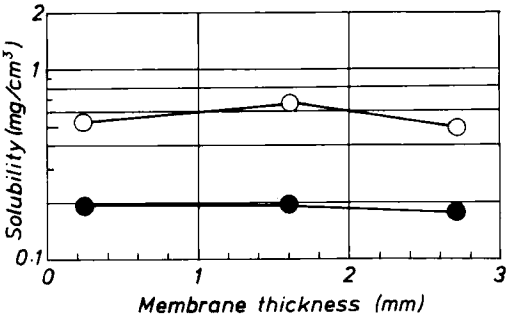

FIGURE 6
Effect of membrane thickness on the solubility of progesterone and testosterone, calculated from Eq.(7), in PDMS membrane without filler. Keys: (○) progesterone, (●) testosterone.

molecules onto the surface of filler particles might also need to be considered for the polymer membrane with high filler content.

On the other hand, the effect of hydrodynamics of the in vitro membrane permeation system on the testosterone diffusivity was relatively insignificant and an apparent diffusivity can be considered approximately equal to the intrinsic diffusivity(Fig.5). This observation is apparently due to the fact that the partition coefficient of testosterone is markedly smaller than that of progesterone[3].

The solubility of progesterone and testosterone in the fillerless silicone membrane can be calculated from the intrinsic steady-state rate of permeation and the intrinsic diffusivity:

$$C_p = \left(\frac{dQ}{dt}\right)_i \ell / D_m \qquad (7)$$

The results are plotted as a function of membrane thickness in Fig.6. The solubility calculated appears to be rather independent of the variation in membrane thickness. It is also interesting to observe that the mean solubility values (567μg/ml for progesterone and 186μg/ml for testosterone) are in good agreement with the solubilities determined independently in the silicone medical fluid (594μg/ml for progesterone[4] and 156μg/ml for testosterone[5]).

CONCLUSION

A simple method for the evaluation of intrinsic time-lag was developed from the three-layer film theory. The diffusivities of progesterone and testosterone through silicone membrane with and without filler were well explained if the filler content is small($\leq$10%). For the membrane with high filler content(23.4%), thin membrane gave a diffusivity which is appreciably lower than that corrected for the thicker membrane. Therefore, this approach should be applied carefully in the membrane with a thickness of greater than 0.16cm and high filler content (>23.4% w/w).

ACKNOWLEDGEMENT

The authors wish to express their appreciation to Dow Corning for providing graduate research fellowships and to Dr. M. Musolf for custom fabrication of the silicone PDMS membrane used in this investigation.

REFERENCES

1. H.A. Daynes, Proc. Roy. Soc. London, A97, 286(1920).
2. J.A. Barrie, J.D. Levine, A.S. Michaels and P. Wong, Trans. Farad. Soc., 59, 869(1963).
3. K. Tojo, M. Ghannam, Y. Sun and Y.W. Chien, J. Cont. Release, (in press).
4. M. Ghannam, K. Tojo and Y.W. Chien, Presented at APhA Academy of Pharmaceutical Sciences 37th National Meeting, IPT-22, Philadelphia, PA, October, 1984.
5. Y. Sun, K. Tojo and Y. W. Chien, Presented at APhA Academy of Pharmaceutical Sciences 37th National Meeting, IPT-24, Philadelphia, PA, October, 1984.