[Chem. Pharm. Bull. 26(3) 837—841 (1978)]

UDC 615.31.011.4.033 : 612.014.1

Analysis of Permeation Profiles of Drugs from Systems containing Micelles[1]

Kazuhiko Juni, Toshiaki Tomitsuka, Masahiro Nakano, and Takaichi Arita

Faculty of Pharmaceutical Sciences, Hokkaido University[2]

(Received August 2, 1977)

A theoretical model is introduced to describe the permeation of drug through membranes from systems containing micelles. Taking distribution of drug between aqueous and micellar phases into account, an equation is derived which describes the permeation profile of drug from the system. Applicability of the model was experimentally tested employing local anesthetics, one of five surfactants, and silicone or ethylene-vinyl acetate copolymer membrane.

Keywords——sustained release; silicone membrane; ethylene-vinyl acetate copolymer membrane; surfactants; micelle; butamben; benzocaine; membrane permeation; micelle/solution partition

Recently, much effort has been made on the development of controlled drug delivery systems for topical uses.[3–8] Synthetic polymer membranes or matrices have often been employed as rate-controlling barriers in such systems.[3–8] When a solid drug or a drug suspension is enclosed within such a membrane as in a silicone capsule, a zero-order release can be achieved. For the release of a drug dispersed uniformly in a polymer matrix, Q–$t^{1/2}$ relationship (where Q=the amount of drug released at time t) has been reported to follow.[9] When a drug is released from its solution through a membrane, the release rate decreases exponentially with time. To sustain the release rate in such a system, a use of soluble complexes of drug and that of micelles have been proposed previously.[10–12]

In the present communication, the release profiles of drug through membranes from systems containing surfactant micelles were analyzed by the employment of the equation derived for a simplified model.

Theoretical

For sustained release of drugs from systems containing micelles, the following simple model shown in Fig. 1 is considered. 1) In the donor compartment, the drug is distributed between the two phases, *i.e.* a dispersed micellar phase and a continuous aqueous phase and only the drug in the latter phase can permeate through the membrane, 2) distribution of the

1) Part IV of Controlled Drug Permeation. Part III; K. Juni, M. Nakano, and T. Arita, *Chem. Pharm. Bull.* (Tokyo), **25**, 2807 (1977).
2) Location: *Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan.*
3) A.C. Tanquary and R.E. Racey, Eds., "Controlled Release of Biologically Active Agent," Plenum Press, New York, N.Y., 1974.
4) J. Drobník, P. Špaček, and O. Wichterle, *J. Biomed. Mater. Res.*, **8**, 45 (1974).
5) M.L. Rosenblum, D.L. Bowie, and M.D. Walker, *Cancer Res.*, **33**, 906 (1973).
6) A.S. Lifchez and A. Scommegna, *Fertil. Steril.*, **21**, 426 (1970).
7) D.M. Worthen, T.J. Zimmerman, and C.A. Wind, *Invest. Ophthalmol.*, **13**, 296 (1974).
8) K. Juni, M. Nakano, and T. Arita, *Chem. Pharm. Bull.* (Tokyo), **25**, 1098 (1977).
9) T. Higuchi, *J. Pharm. Sci.*, **50**, 874 (1961).
10) M. Nakano and N.K. Patel, *J. Pharm. Sci.*, **59**, 77 (1970).
11) M. Nakano, K. Juni, and T. Arita, *J. Pharm. Sci.*, **65**, 709 (1976).
12) K. Juni, M. Nakano, and T. Arita, *Chem. Pharm. Bull.* (Tokyo), **25**, 2807 (1977).

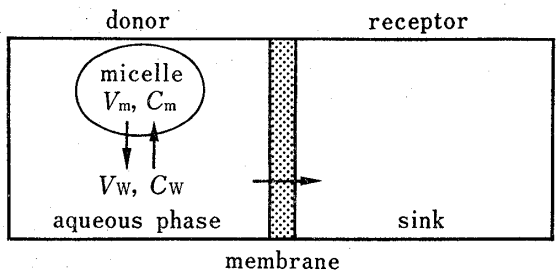

Fig. 1. Schematic Representation of Sustained Release of Drug through Membrane from a System Containing Micelle

drug between the micellar and aqueous phase is instantaneous at any moment, and 3) contribution of the diffusion layer effect at the membrane surface can be neglected.

The distribution coefficient, K_p of the drug between these two phases is given by

$$K_p = \frac{C_m}{C_w} = \frac{M_m/V_m}{M_w/V_w} \quad (1)$$

where C, M, and V denote the concentration and the amount of the drug in each phase, and the volume of each phase, respectively, and the subscripts m and w indicate a micellar phase and an aqueous phase, respectively. Under these conditions, if sink conditions are maintained in the receptor side, the permeation rate of drug is given by Fick's law:

$$\frac{dM_r}{dt} = \frac{APC_w}{l} \quad (2)$$

where M_r is the amount of drug in the receptor solution at time t, A the area of the membrane available for permeation, l the membrane thickness and P the permeability. The total amount of drug in the donor solution, M_t is given by:

$$M_t = M_m + M_w = M_t^0 - M_r \quad (3)$$

where M_t^0 is the total amount of drug initially introduced into the system. Rearrangement of Eq. 1—3 leads to:

$$M_r = M_t^0\left[1-\exp\left\{-\frac{APt}{l(K_pV_m+V_w)}\right\}\right] \quad (4)$$

By definition:

$$M_t^0 = V_mC_m^0 + V_wC_w^0 \quad (5)$$

$$C_m^0 = K_pC_w^0 \quad (6)$$

where C_m^0 and C_w^0 are the initial concentration of drug in the micellar phase and that in the aqueous phase, respectively. When the volumes of the donor and receptor compartments are equal and represented by V, rearrangement of Eq. 4—6 leads to Eq. 7.

$$-\ln\left(1-\frac{C_r}{C_t^0}\right) = \frac{APC_w^0}{lVC_t^0}t \quad (7)$$

where C_t^0 denotes the total initial concentration of drug in the donor solution. The ratio C_w^0/C_t^0 is equal to C_s^0/C_s at equiliblium, where C_s^0 and C_s are the solubility of drug in water and that in a surfactant solution, respectively. Then, Eq. 7 becomes:

$$-\ln\left(1-\frac{C_r}{C_t^0}\right) = \frac{APC_s^0}{lVC_s}t \quad (8)$$

In the following experiments, the applicability of Eq. 8 to describe the permeation profile of drugs from micelle containing systems has been tested.

Experimental

Materials——The following chemicals were of reagent grade and purchased from commercial sources: benzocaine (ethyl *p*-aminobenzoate), butamben (*n*-butyl *p*-aminobenzoate) and dodecyltrimethylammonium chloride were from Tokyo Kasei Kogyo Co., Tokyo; polysorbate 80, laurylpyridinium chloride, sodium lauryl sulfate, and sodium dodecylbenzenesulfonate from Wako Pure Chemical Industries, Osaka. They were used without further purification. The membrane used were medical grade silicone membrane (Silastic Sheeting, non-reinforced, Dow Corning Corp., Midland, Michigan) and ethylene-vinyl acetate copolymer membrane (EVAFLEX, vinyl acetate content of 17%, Mitsui Polychemicals Co., Tokyo).

Preparation of Test Solutions——An excess amount of drug was added into distilled water or each surfactant solution in stoppered glass flasks, and the flasks were soaked in a water-jacketed beaker maintained at 30°. The suspension was prepared by stirring the contents for 30 hr. The saturated solution was obtained by filtering the suspension through a sintered-glass disk prior to permeation studies.

Permeation Study——The apparatus used in the present study was the same as the one previously reported.[12] All permeation studies were undertaken at 30°. Immediately after 10 ml of hydrochloric acid solution (pH 1.0, prewarmed to 30°) was pipetted into the receptor compartment and 10 ml of either drug suspension or saturated drug solution into the donor compartment, agitation of both solutions was started. The rotating speed of the magnetic stirrers was set at 500 rpm based on the preliminary study to minimize the effect of the diffusion layer at the membrane surface on the permeation rate. At scheduled time intervals, an aliquot of the receptor solution was pipetted out for determination of drug concentration and the same volume of a fresh hydrochloric acid solution was added. After appropriate dilution with phosphate buffer, pH 6.0, UV absorbance of the solution was measured at λ_{max} of each drug (Hitachi double-beam spectrophotometer, Model 200-20, Hitachi Manufacturing Co., Tokyo). Care was taken to maintain the sink condition so that the concentration of unionized drug (ionized form is considered not to be permeable) in the receptor solution should not exceed one twentieth of that in the donor aqueous phase. All experiments were carried out in duplicate.

Results and Discussion

The following terms which appear in Eq. 8 were determined directly; $A=4.52\ \mathrm{cm}^2$, $l=2.48\times10^{-2}$ cm for silicone membrane (measured thickness whereas the labeled thickness was 2.54×10^{-2} cm) and 1.8×10^{-3} cm for ethylene-vinyl acetate copolymer membrane (labeled thickness), $V=10$ ml, $C_s^0=1.2\times10^{-3}$ M (determined at 30°). In the present experiment, $C_t^0=C_s$ (see Experimental) was determined by solubility measurement in each case. When a drug suspension is placed in the donor compartment, a constant release rate is obtained so that the P value can be calculated from Eq. 2.

It has been realized that the presence of diffusion layer should be taken into account when drug permeation through membrane is considered.[13] In fact, diffusion layer-effects have been reported for permeation of phenylbutazone through silicone membrane.[14] In particular, the contribution of diffusion layer becomes apparent when the membrane is thin and the agitation of solution is mild.[14] In the present investigation, the solutions on both sides of the membrane were vigorously agitated. Therefore, the aforementioned assumption 3 may not cause a significant error when analyzing the data.

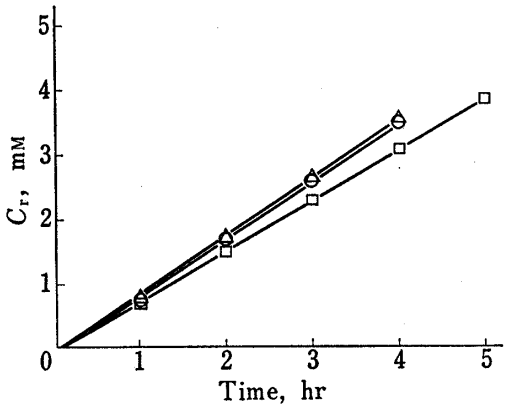

Fig. 2. Release Profiles of Butamben through the Silicone Membrane from Its Suspensions in □, Water; △, 0.5% Dodecyltrimethylammonium Chloride and ○, 0.5% Sodium Lauryl Sulfate at 30°

Fig. 2. shows release profiles of butamben from suspensions in water as well as surfactant solutions. In both cases, linear profiles are obtained during the experimental period. A slight increase in the release rate was observed in the permeation from the suspension containing a surfactant. In addition, increase in the concentration of surfactant in the suspension showed a tendency to give a greater release rate of butamben. These observations may be attributed to the fact that the surfactant either wets the membrane surface better or promotes dissolution of the drug.[15] Further investigation concerning this point is now being continued. The

13) G.L. Flynn and S.H. Yalkowsky, *J. Pharm. Sci.*, **61**, 838 (1972).
14) E.G. Lovering and D.B. Black, *J. Pharm. Sci.*, **63**, 1399 (1974).
15) P. Singh, S.J. Desai, D.R. Flanagan, A.P. Simonelli, and W.I. Higuchi, *J. Pharm. Sci.*, **57**, 959 (1968).

P value was therefore determined in each case using a drug suspension containing a corresponding surfactant.

In Fig. 3 are shown the results for butamben in the presence of three types of surfactants; anionic, cationic and nonionic. Data are presented by plotting $-\ln(1-C_r/C_t^0)$ against time t according to Eq. 8. Data thus treated gave approximately linear profiles as were expected from the model introduced. Experimental data points fitted on theoretical lines fairly well.

Two other surfactants, anionic and cationic, were also employed to examine the applicability of the model to these systems (Fig. 4). Fit similar to that in Fig. 3 was observed. Slight deviation from theoretical lines may be attributed to a certain error in determining P value from suspension data or to an unidentified factor which was not taken into account in the model.

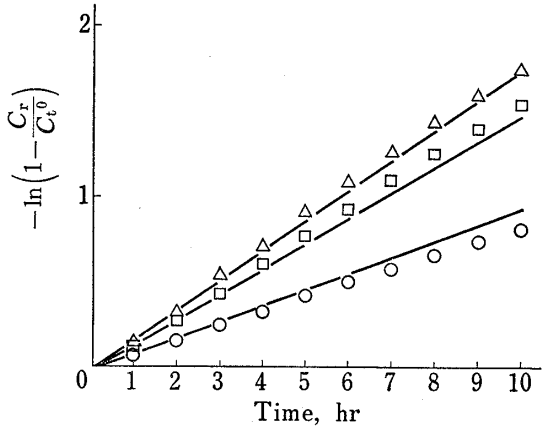

Fig. 3. Release Profiles of Butamben through the Silicone Membrane from Its initially Saturated Solutions in ○, 0.5% Sodium Lauryl Sulfate; □, 0.5% Polysorbate 80 and △, 0.4% Dodecyltrimethylammonium Chloride Solution at 30°

——, theoretical profile.

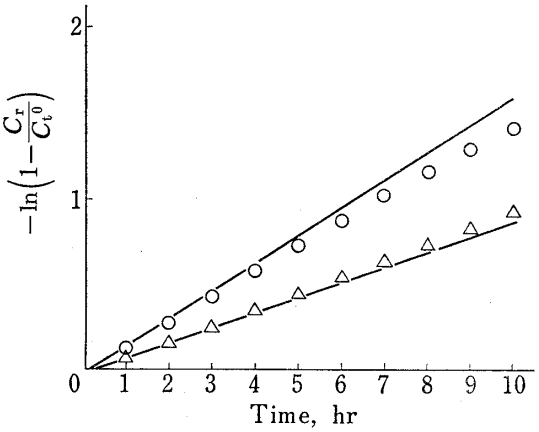

Fig. 4. Release Profiles of Butamben through the Silicone Membrane from Its initially Saturated Solutions in △, 0.5% Laurylpyridinium Chloride and ○, 0.5% Sodium Dodecylbenzenesulfonate Solution at 30°

——, theoretical profile.

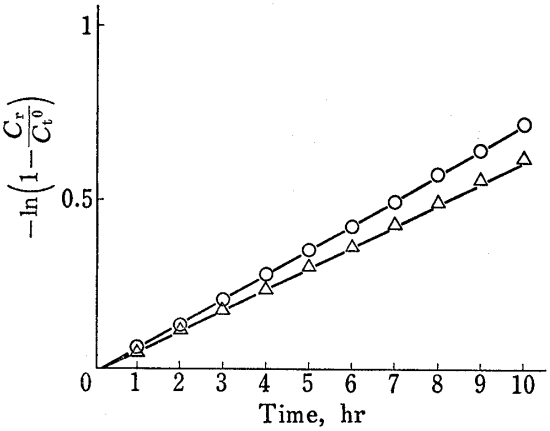

Fig. 5. Release Profiles of Benzocaine through the Silicone Membrane from Its initially Saturated Solutions in △, 0.5% Dodecyltrimethylammonium Chloride and ○, 0.2% Sodium Lauryl Sulfate Solution at 30°

——, theoretical profile.

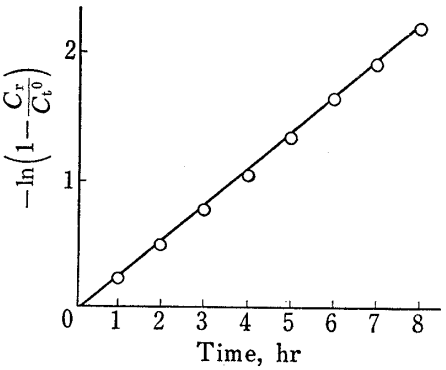

Fig. 6. Release Profiles of Butamben through the Ethylene-Vinyl Acetate Copolymer Membrane from Its initially Saturated Solution in 0.2% Sodium Lauryl Sulfate Solution at 30°

——, theoretical profile.

Benzocaine, an analog of butamben, was also employed to test the applicability of the model. Benzocaine has a higher solubility in water and lower partition tendency to silicone membrane than butamben. Fig. 5 shows the release profiles of benzocaine in the presence of two types of surfactants. Theoretical and experimental profiles coincided, indicating that the drug release in this case can be satisfactorily described by Eq. 8.

Fig. 6 represents data obtained with the ethylene-vinyl acetate copolymer membrane which is also classified as a partition membrane. Release of butamben through the ethylene-vinyl acetate copolymer membrane also followed the theoretical line.

When a suspension is employed as a donor solution, dissolution step is involved as well as partition and diffusion steps. In such a drug as butamben which has rather large (membrane/water) partition coefficient, dissolution may become a rate-determining step in some instances. If such be a case in the butamben-silicone membrane system, a calculated P value from permeation studies in the presence of suspension may not represent a "true permeability". Slight deviation of the observed profile from the theoretical profile in the butamben-silicone membrane system may be attributed, in part, to this phenomenon. On the other hand, the permeation profile of butamben through ethylene-vinyl acetate copolymer membrane and that of benzocaine through silicone membrane can be adequately described by the model (Fig. 5 and 6), indicating that partition-controlled process is dominant in these systems. These observations may be rationalyzed in the following way. Since benzocaine has a lower partition coefficient than butamben and ethylene-vinyl acetate copolymer membrane has lower permeability than silicone membrane (roughly, one half, unpublished data), partition of the drug into the membrane may become a rate-limiting step in these two systems.

Based on the present investigation, it may be concluded that the model shown in Fig. 1 may thus adequately describe the release of drug through partition membrane from systems containing micelles. Equation 8 would provide one a means by which one can control the release of drug by selecting a membrane which gives proper permeability for a drug and adjusting area and thickness of the membrane.

Acknowledgement This work was supported in part by the Grant-in-Aid for Scientific Research from The Ministry of Education, Sciences and Culture, Japan.