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STRATUM CORNEUM RESERVOIR CAPACITY AFFECTING DYNAMICS OF TRANSDERMAL DRUG DELIVERY

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INTRODUCTION

A number of researches [1-5] have reported the observations of reservoir capacity in human stratum corneum since Vickers clearly demonstrated this phenomenon in 1963 [6]. Both lipophilic and hydrophilic drugs may be trapped in the matrix-structure of stratum corneum and diffuse out very slowly due to strong binding and/or markedly low diffusivity (10^{-10}-10^{-11} cm^2/s) [7,8]. Since it affects significantly the dynamics of transdermal drug delivery, the reservoir capacity of the stratum corneum should be thoroughly investigated before a transdermal drug delivery system is developed. In spite of the evidence of the stratum corneum reservoir effect, its mechanism has not yet been fully elucidated. There is no quantitative interpretation reported in the literature which could assist us to gain a fundamental understanding the dynamic characteristics of stratum corneum reservoir capacity.

If a drug is bound in the stratum corneum, the lag time required to reach a steady-state permeation is often observed to

increase, even though the steady-state rate of permeation remains unchanged [9]. Therefore, we should take this rate process into consideration in the analysis of skin permeation profiles generated under in vitro and in vivo conditions.

The drug diffusivity across the stratum corneum has frequently been determined from the Daynes'time-lag method [10] by assuming it as a unilayer membrane :

$$D = \frac{h_{sc}^2}{6\, t_l} \qquad (1)$$

where h_{sc} is the thickness of the stratum corneum and t_l is the lag time, defined as the time intercept of the linear portion of the permeation profile. This diffusivity may be significantly underestimated if the drug is bound to some extent in the stratum corneum. It is rather important to establish the applicability and limitation of Eq. (1) in evaluating the drug diffusivity across the stratum corneum.

In this investigation, we intend to demonstrate the reservoir capacity of the stratum corneum in the skin permeation of steroids. This reservoir capacity is commonly caused by the dissolution of free drug molecules in the stratum corneum as well as their subsequent binding to the stratum corneum. We plan to differentiate the relative contributions of these processes to the skin permeation profiles under the system-off state of transdermal drug delivery. The "system-off" state is defined as the state immediately following the application of a transdermal drug delivery system for a given period of time.

MATHEMATICAL MODEL

In this investigation, mathematical formula has been derived from a bi-layer diffusion model to describe the dynamics of drug permeation across the skin (Fig. 1). This model considers the skin as composed of two layers : the stratum corneum and the viable skin. It is assumed that the drug binding takes place in

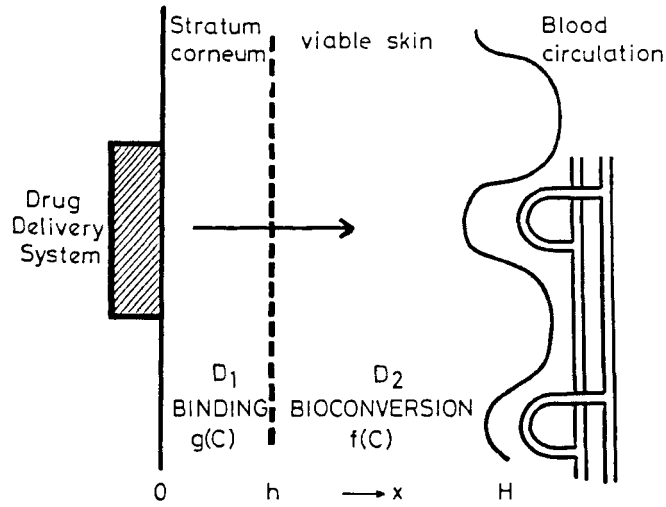

Figure 1

Dynamic Diffusion Model
Skin : bi-layer (stratum corneum and viable skin)
f(C) : enzymatic reaction in the viable skin (Michaelis-Menten Kinetics)
g(C) : drug binding in the stratum corneum (Langmuir Isotherm)

the stratum corneum, while the enzymatic reaction occurs only in the viable skin.

The mass balance of drug molecules over a differential volume element of the skin is expressed as

$$\left\{1 + g(C)\right\} \frac{\partial C}{\partial t} = \frac{\partial}{\partial x}\left(D \frac{\partial C}{\partial x}\right) - f(C) \qquad (2)$$

where g(C) and f(C) are the terms which define, respectively, the drug binding and enzymatic reaction in the skin layers. If we assume the enzymatic reaction follows the Michaelis-Menten kinetics and the binding process obeys the dual sorption model, then

$$f(C) = \frac{k_1 C}{1 + k_2 C} \qquad (3)$$

for the metabolism of drug in the viable skin, and

$$g(C) = \frac{p\ C}{(1 + q\ C)^2} \quad (4)$$

if Langmuir isotherm[11] applies or

$$g(C) = p\ C^q \quad (5)$$

if Freundlich isotherm applies.

Equation (2) can be solved under appropriate initial and boundary conditions. In this study, we apply the same initial and boundary conditions as discussed previously and employ the Method of Lines[12] to solve Equation (2). The accuracy of numerical method was previously tested by comparing the numerical solution with the analytical solution under a simplified condition of unilayer skin permeation[13,14].

EXPERIMENTAL

In vitro skin permeation kinetics studies were carried out using the skin of hairless mouse. The abdominal skin excised freshly was mounted between each pair of two half-cells of a hydrodynamically well-calibrated in vitro skin permeation system (Fig. 2). Progesterone, hydrocortisone and estradiol were used as the test drugs. Excess amount of each drug was homogeneously suspended in the donor solution (aqueous solution of 40% PEG400) to maintain a constant drug concentration gradient during an entire course of permeation experiment. The 40% aqueous PEG400 solution was also used as the receptor solution to provide a sink condition needed, because of its good solubilization effect on steroidal drugs.

At appropriate time intervals after the initiation of skin permeation experiment, an aliquot of 20-50ul was sampled from the receptor solution and assayed for drug concentration by HPLC. These data yielded the "system-on" profiles of transdermal drug delivery. After the drug permeation reached a steady-state, the entire drug reservoir was withdrawn from the donor compartment

SKIN PERMEATION SYSTEM by VALIA & CHIEN

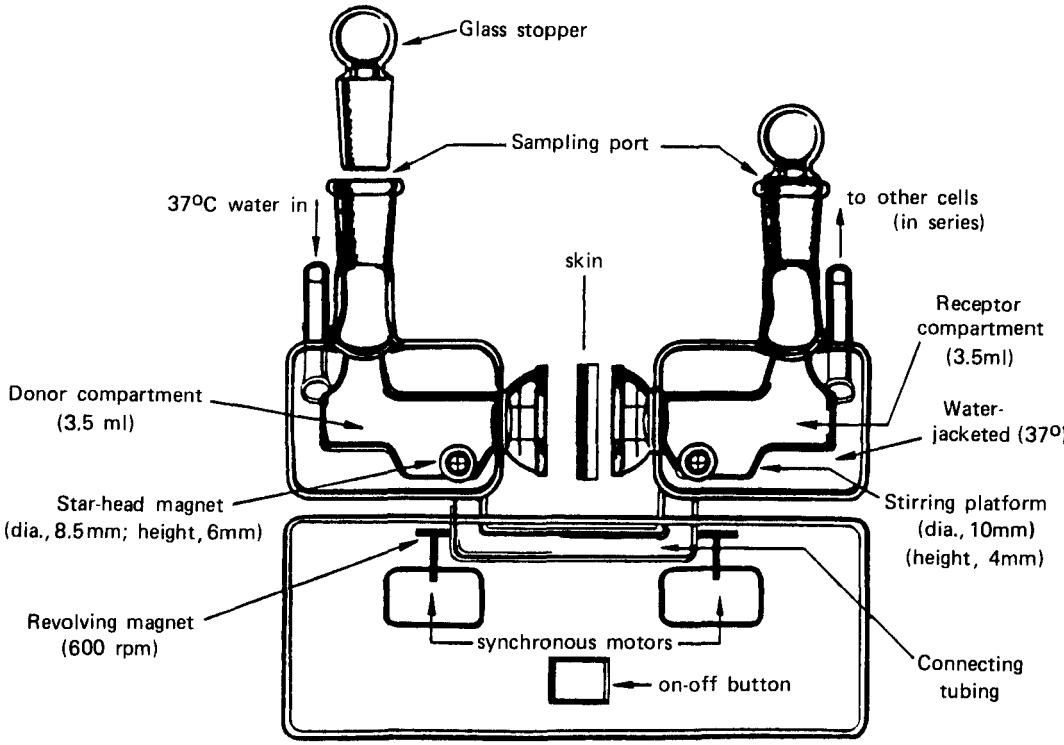

Figure 2

In Vitro Skin Permeation System
Effect volume of compartment = 3.5 ml
Membrane surface area = 0.64 cm^2.
Both donor and receptor compartments contain aqueous 40% PEG-400 solution.

and the surface of the skin was rinsed twice using the same aqueous solution (without drug) to remove the residual drug. Thereafter, the drug concentration profile in the receptor solution, with no donor drug solution, was continuously monitored. This experiment provided the system-off profiles of transdermal drug delivery. The sampling procedure was continued until about 120 hours after the initiation of permeation study.

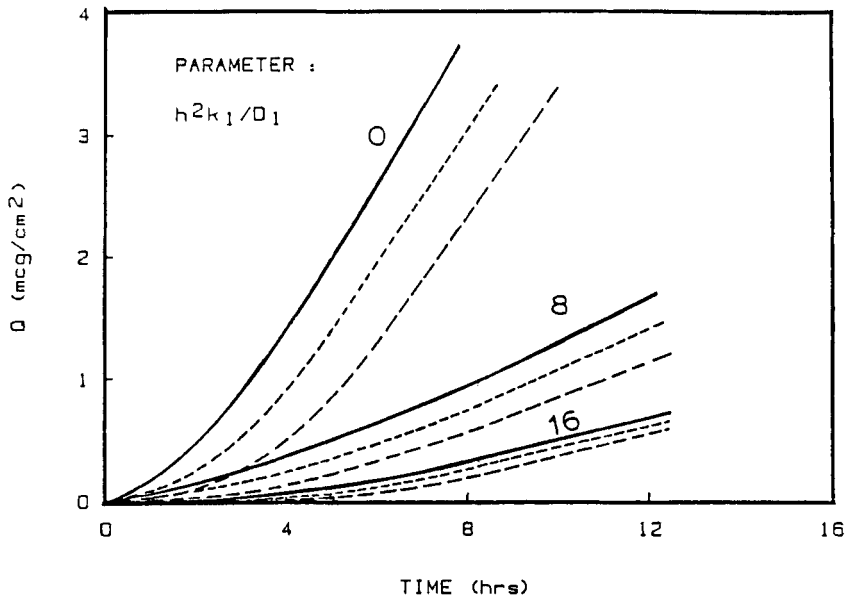

Figure 3

Effect of drug binding in the stratum corneum on the permeation profiles as the parameter of enzymatic reaction rate constant (k_1 , k_2 = 0) under system-on (permeation) condition.
Key : (——) p = q = 0; (·····) p = 4, q = 1; (-----) p = 8, q = 1

RESULTS AND DISCUSSION

Figure 3 shows the effect of drug binding in the stratum corneum on the skin permeation profiles of drug, where various rate constants of enzymatic reaction under "system-on" conditions were assumed. In this simulation, Langmuir isotherm (Eq. 4) has been assumed to be the mechanism of drug binding. It is noted that the binding of drug to the stratum corneum appreciably increases the duration of time-lag to reach a steady-state, while the steady-state rate of permeation remains unchanged. On the other hand, the enzymatic reaction in the viable skin only slightly reduces the duration of time-lag but significantly decreases the steady-state rate of permeation.

Figure 4 demonstrates the effect of enzymatic reaction rate constant k_1 (dimensionless) on the ratio of time-lag

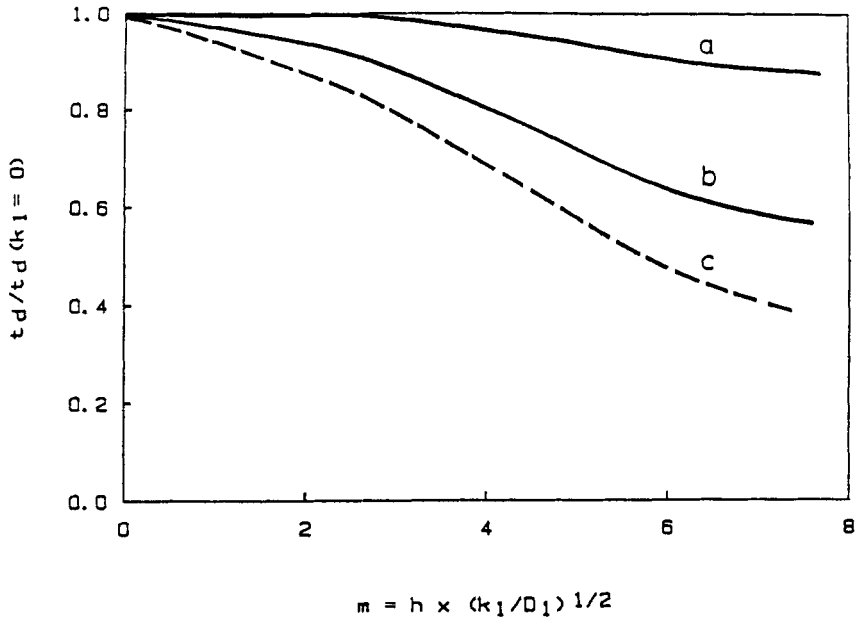

Figure 4

Effect of enzymatic reaction rate constant on the time-lag
Key : (a) Partition coefficient (stratum corneum/viable skin) = 5 $D_2/D_1 = 10^3$, D_2 (diffusivity in viable skin); D_1 (diffusivity in stratum corneum) = 5×10^{-11} cm^2/sec.
(b) Partition coefficient = 5; $D_1 = 5 \times 10^{-10}$ cm^2/sec; $D_2/D_1 = 10^2$
(c) Single-layer membrane.

(dimensionless) as a parameter of drug diffusivity. The dashed line was previously obtained for the uni-layer membrane[13]. The result indicates that drug binding increasingly affects the ratio of time-lag as the diffusivity across the stratum corneum increases. This simulation points out that the time-lag should be carefully analyzed by taking into account the drug binding in the stratum corneum as well as the enzymatic reaction in the viable skin.

The experimental permeation profiles of lipophilic progesterone and hydrophilic hydrocortisone across hairless mouse skins are shown, respectively, in Figures 5 and 6. In these illustrations, the solid line and the dashed line represent,

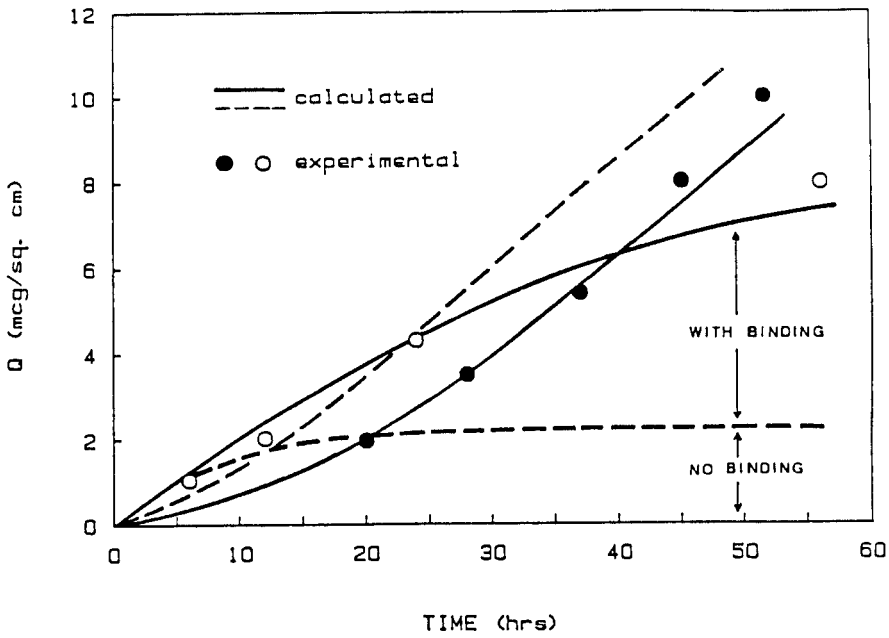

Figure 5

Stratum corneum reservoir capacity of progesterone permeation
Key : D_2/D_1 = 528; D_1 = 7.75 x 10^{-11} cm^2 /sec; P = 55;
p = 8; q = 0.5; h = 10 um; H = 380 um.
● (Data with device on skin)
○ (Data after device removal)

respectively, the predicted permeation profiles with and without stratum corneum binding. If we ignore the drug binding in the stratum corneum, the calculated profile under the system-off condition deviated markedly from the experimental data since only the free drug molecules in the stratum corneum contribute to the reservoir capacity. If the contribution of drug binding is also taken into account, the calculated permeation profile (solid line) agrees fairly well with the experimental observation. It was also found that the fraction of drug bound to the stratum corneum affects very significantly to the system-off profile.

Figure 7 shows the experimental permeation profile of estradiol across the skin of hairless mouse. Based on the system-

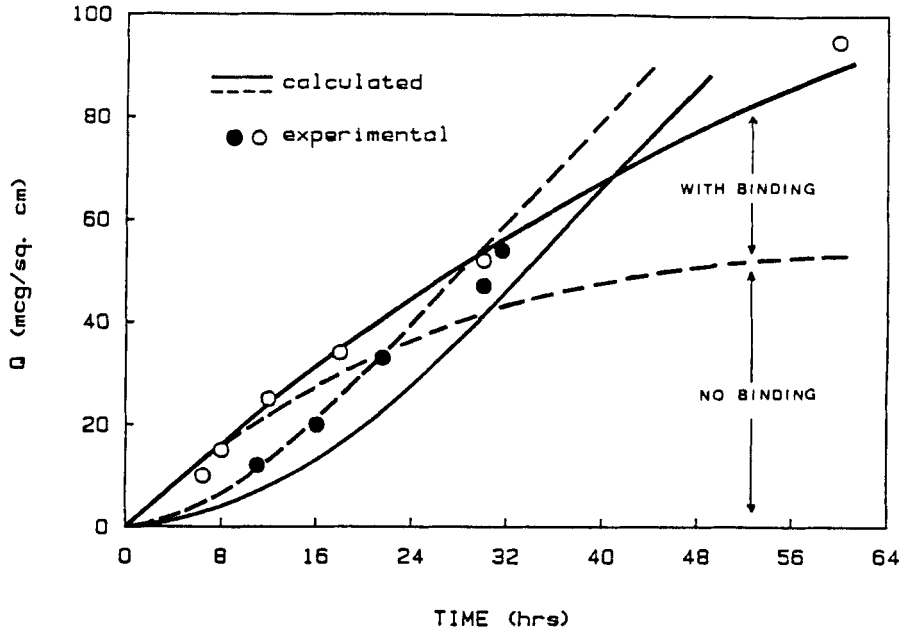

Figure 6

Stratum corneum reservoir capacity of hydrocortisone permeation
Key : D_2/D_1 = 1100; D_1 = 3.87 x 10^{-11} cm^2/sec; P = 0.105;
p = 8; q = 0.5; h = 10 um; H = 380 um.
● (Data with device on skin)
○ (Data after device removal)

on data, the diffusivity and solubility of estradiol across each skin layer were calculated. The solid line and the dashed line show the calculated profiles with and without drug binding, respectively. It is interesting to note that the extent of binding of estradiol in the hairless mouse skin is less significant than progesterone and hydrocortisone. This finding suggests that the permeation profile of estradiol can be analyzed without consideration of the binding.

In summary, the drug binding capacity of stratum corneum depends on the drug species. The permeation profile across the skin can be better analyzed after a thorough understanding of the stratum corneum reservoir capacity.

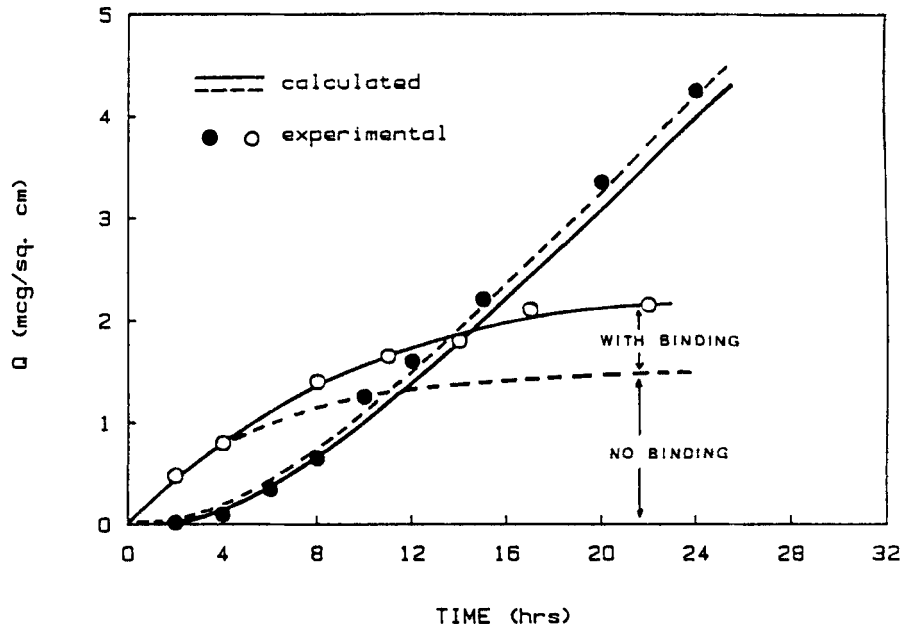

Figure 7

Stratum corneum reservoir capacity of estradiol permeation
Key : D_2/D_1 = 3000; D_1 = 3 x 10^{-11} cm^2 /sec; P = 5;
p = 1; q = 1; h = 10 um; H = 380 um;
● (Data with device on skin)
○ (Data after device removal)

CONCLUSION

The results have led us to conclude that the reservoir-capacity of the stratum corneum can be quantitatively explained by a bi-layer dynamic skin model. This reservoir capacity is caused by the combined effects of free drug diffusion and bound drug desorption. The enzymatic reaction in the viable skin may appreciably reduce the duration of time-lag. The applicability of the time-lag method for the determination of drug diffusivity across the skin depends on the binding capacity of the drug in the stratum corneum. It is important to note that the studies of the dynamic characteristics of skin permeation of drugs, both at system-on and system-off conditions, could provide useful data to

gain some fundamental understanding of the mechanism of transdermal drug delivery.

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