EFFECT OF STRATUM CORNEUM STRIPPING ON SKIN PENETRATION OF DRUG

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Introduction

Transdermal administration of systemic drugs has recently received growing attention in the pharmaceutical industry because of its advantages over conventional oral dosage forms.^{2,8)}

For the development of the drug delivery system, not only the drug release from the device but the mechanism of skin penetration should be thoroughly investigated. It is frequently demonstrated that the principal resistance to drug transport in transdermal administration resides in the diffusion process through the stratum corneum, which is outermost layer of the skin.^{5,6)} It is, therefore, essential to understand the barrier function of the stratum corneum for elucidating the mechanism of diffusion, permeation and partitioning of drugs across the skin.

In this communication, we discuss the effect of consecutive strippings of the stratum corneum by adhesive tape on the profile of skin penetration for drugs. The rate of skin penetration of the drugs is measured as a function of number of strippings under *in vitro* conditions using a hairless mouse skin.

1. Mechanism of Skin Stripping

If we have a two-layer skin which consists of the stratum corneum and the viable layer,¹⁰⁾ the overall flux of skin penetration becomes

$$Flux = \Delta C / (R_s + R_v) = (C_d - C_r) / (R_s + R_v) \quad (1)$$

where C_d and C_r are the drug concentrations in the donor and receptor solutions, and R_s and R_v are the resistances to drug transport across the stratum corneum and the viable skin, respectively.

The ratio of drug penetration rate, E , across the stripped skin with various amounts of stratum corneum removed to that across the whole (intact) skin is then given by

$$E = \frac{h_0 / (D_s K_s) + h_v / (D_v K_v)}{h_s(n) / (D_s K_s) + h_v / (D_v K_v)} \quad (2)$$

where h , D and K represent the thickness, diffusivity of drug, and partition coefficient between two phases in intimate contact, respectively, and $h_s(n)$ is the thickness of the stratum corneum after n strippings by adhesive tape. The thickness of intact stratum corneum h_0 and of viable skin h_v are $10 \mu\text{m}$ and $370 \mu\text{m}$, respectively¹⁰⁾ for the hairless mice used in this work. If only the layer which is in contact with the adhesive tape is removed at each stripping, the thickness of the stratum corneum $h_s(n)$ is represented by

$$\begin{aligned} h_s(n) &= h_0(1 - n/n_c) \quad \text{for } n \leq n_c \\ h_s(n) &= 0 \quad \text{for } n > n_c \end{aligned} \quad (3)$$

where n_c is the minimum number of strippings required to remove all layers of stratum corneum. The stratum corneum consists of 8 to 16 layers of keratinized flattened cells,⁴⁾ so the minimum number of strippings should be within this range.

Substitution of Eq. (3) for $h_s(n)$ into Eq. (2) gives

$$E = \frac{h_0 / (D_s K_s) + h_v / (D_v K_v)}{h_0(1 - n/n_c) / (D_s K_s) + h_v / (D_v K_v)} = \frac{k}{(k - n/n_c)} \quad (4)$$

where $k = 1 + (h_v/h_0)(D_s K_s/D_v K_v)$.

The diffusivity and the partition coefficient for each skin layer can be determined by the time-lags and the steady-state penetration rates.¹⁰⁾

2. Experimental

Two well-calibrated *in vitro* skin permeation systems (K-C cell and V-C cell, Fig. 1)⁹⁾ were used in this study. K-C cell was used for the penetration of nitroglycerin (Drug I) from Transderm-Nitro, a reservoir-type transdermal delivery system,⁵⁾ while V-C cell was used for the penetration of progesterone (Drug II) and verapamil (Drug III) with saturated concentrations in the donor solution. The receptor

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Fig. 1. *In vitro* apparatus for skin penetration studies: a) V-C diffusion cell (effective volume of compartment = 3.5 ml, membrane area = 0.64 cm²). For Drug I: Donor compartment contains 20% PEG 400 solution while receptor compartment contains 20% PEG 400 in saline solution. For Drug II: Donor compartment contains silicone fluid (DC360) while receptor compartment contains 40% PEG 400 in saline solution. For Drug III: Donor compartment contains buffer solution (pH = 6.0) while receptor compartment contains buffer solution (pH = 7.4). b) K-C diffusion cell (effective volume of compartment = 12 ml, membrane area = 3.14 cm²)

compartments for both types of diffusion cells were maintained under sink condition⁷⁾ during the entire period of the penetration experiments (about 24 to 48 h). The hydrodynamic characteristics of these diffusion cells were previously determined⁹⁾ and the effect of the boundary layers formed on the skin surfaces on the rate of penetration was negligible under the present experimental conditions.

The penetration profiles of drugs across the abdominal skin of hairless mouse, whose stratum corneum had been stripped *n* times by an adhesive tape (Scotch #810 Tape, 3M), were measured as a function of the number of strippings. The drug concentrations in the receptor solution were assayed by HPLC procedures.

3. Results and Discussion

Typical skin penetration profiles (Drug II) are shown in Fig. 2. For the other drugs, similar profiles were obtained. As can be seen from Fig. 2, the cumulative amount of drug penetrated across the skin increases linearly with increasing duration of penetration, indicating that no significant change in skin structure during the penetration experiments occurred due to skin damage or hydration. However, both the rate of penetration and the lag time were appreciably influenced by the number of strippings. The steady-

Fig. 2. Time course of skin penetration for Drug II. The values by lines are numbers of skin strippings

Table 1. Effect of skin stripping on steady-state rate of penetration

Number of strippings	Steady-state rate of penetration, $\mu\text{g}/\text{cm}^2\cdot\text{h}$ ($\pm$ s.d.)		
	Drug I	Drug II	Drug III
0 (intact skin)	24 (3.0)	0.78 (0.04)	9.1 (0.8)
2	25 (2.2)	0.88 (0.09)	11 (1.4)
4	36 (3.4)	0.86 (0.11)	—
5	—	—	17 (2.8)
6	39 (3.9)	1.15 (0.23)	—
7	—	—	22 (3.7)
8	51 (2.9)	1.28 (0.06)	—
10	74 (8.0)	—	99 (11)
12	71 (2.3)	1.75 (0.24)	—
16	—	1.76 (0.09)	—
20	73 (4.8)	1.87 (0.37)	—
25	72 (5.5)	—	117 (14)

Donor concentration, C_d : 50 mg/ml for Drug I, 0.52 mg/ml for Drug II, 5.2 mg/ml for Drug III.

state rates of penetration are listed in Table 1. The amount of material sticking to adhesive tape during consecutive strippings may be influenced not only by the type of adhesive tape and the pressure applied but also by the skin species. However, the narrow standard deviation of the penetration data shown in Table 1 clearly indicates that the present stripping approach for hairless mouse skin was reproducible. This is probably due to the fact that the stratum corneum consists of protein-rich flattened cells separated from one another by thin-layer intercellular lipid. The diffusivity and the partition coefficient for each skin layer, stratum corneum and viable skin, were calculated on the basis of the two-layer model¹⁰⁾ and are listed in Table 2.

The factor of enhancement in penetration rate, E , is plotted in Fig. 3 as a function of the number of strippings. The enhancement factor increased markedly with increasing number of strippings initially and then reached a plateau at about ten strippings

Table 2. Diffusivity and partition coefficient across hairless mouse skin

	Drug I	Drug II	Drug III
Diffusivity (cm ² /s)			
Stratum corneum	1.92×10^{-10}	1.94×10^{-10}	1.11×10^{-10}
Viable skin	2.22×10^{-7}	3.52×10^{-8}	5.76×10^{-8}
Partition coefficient			
Stratum corneum	1.04	3.76	4.76
Viable skin	0.07	1.02	3.70
Lag-time (h)			
Whole skin	1.1	4.3	3.6
Viable skin	0.3	1.8	1.1

Fig. 3. Enhancement factor E as a function of number of strippings; I: Drug I; II: Drug II; III: Drug III; IVa: methanol¹⁴; IVb: methanol¹⁵; V: phenol¹¹. ●, □, ○, Experimental; — Calculated from Eq. (4). $k = 1.05$ (Drug I), 1.75 (Drug II) and 1.09 (Drug III).

($n_c = 10$).

By substituting the diffusivity and the partition coefficient into Eq. (4), the enhancement factor E was calculated and is compared with the experimental data in Fig. 3. The experimental data appear to be well explained by the present skin-stripping model. In Fig. 3, the literature data on methanol and phenol are also plotted for comparison. Except for the data for Drug IVb, a similar E vs. n relationship was noted for methanol (IVa) and phenol (V). The E vs. n relationship for IVb is somewhat different from all the other results. The reason for this discrepancy is not known by the authors. However, it is interesting to note that the literature data for simple molecules like

methanol and phenol follow similar behavior to that observed for more complicated molecules like the Drugs I, II and III used in this study. It is interesting to see that the E vs. n relationship suddenly changes around the critical stripping number, n_c . This finding implies that the boundary between the stratum corneum and the viable epidermis is fairly distinguishable; in other words, a clear interface probably exists between these two layers. This observation supports the idea of applying the partitioning mechanism to explain transdermal drug penetration across composite layers of skin tissues.

Nomenclature

C	= drug concentration	[mg/ml]
C_d	= drug concentration in donor solution	[mg/ml]
C_r	= drug concentration in receptor solution	[mg/ml]
D	= diffusivity of drug	[cm ² /s]
E	= enhancement factor by Eq. (2)	[—]
h	= thickness of skin layer	[cm]
K	= partition coefficient	[—]
k	= constant defined in Eq. 4	[—]
n	= number of strippings	[—]
n_c	= critical number of strippings (= 10)	[—]
Q	= cumulative amount of drug penetrated	[mg/cm ²]
R	= resistance to skin penetration of drug	[s/cm]
t	= time	[s]
h_o	= thickness of intact stratum corneum	[cm]

<Subscript>

o	= intact stratum corneum
s	= stratum corneum
v	= viable skin
w	= whole (intact) skin

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