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Effect of Vehicles on Percutaneous Absorption. III.[1] Simulation and Measurement of Input Data

Mitsunori Takehara, Toshio Nakagawa,[2a] Yoichi Ushio, Kazumi Narahara, and Hideo Oishi[2]

Shionogi Research Lab.[2]

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Diffusion coefficients of salicylic acid (SA) in the vehicles and the skin and partition coefficients of SA between the intact or stripped skin and a saline solution were measured, the simulation of drug absorption from the vehicles, based on the theory in Part II, was carried out, and the proportionalities between the calculated and the experimental absorption values were sufficient for all vehicles. It was found that the skin layer has an unknown nondiffusional resistance by an absorption experiment through the stripped skin. Volume effect of the drug phase on the percent absorption was interpreted by an accumulation of the vehicle at the circumference of the cell caused by an interfacial tension between the vehicle and the cell.

Part I reported percent absorption (Q) of salicylic acid (SA), trans-epidermal water loss (TEWL) factors (F), volume and concentration effects of drug phase on the absorption, and partition coefficients (Pa) of SA in the vehicle-water systems.

Part II reported the theory of percutaneous absorption.

The F value is related to the effect of vehicles on the skin, and Pa to the chemical potential of SA in the vehicles. Due to existence of the honey layer, non-diffusional resistance (X) may exist between the drug phase (vehicle) and the skin, drug absorption may be restricted, and the percent absorption of SA from the vehicles may increase when the honey layer is removed.

In simulation, infinite or minimum quantity cannot be handled by the digital computer, and we must content with approximate quantities. However, the simulated values must not deviate from the original when the simulation parameter is exchanged for another value.

We reported here on the diffusion coefficient (D_a) of SA in the vehicles and the skin, partition coefficient (P) of SA in a saline-skin system, simulated values of drug absorption from the vehicles when intact and stripped skins were used, volume effect of drug phase on the Q values, and the effect of separation number or transport coefficient (comparable to the diffusion coefficient) on the simulated values.

Experimental

(I) Diffusion Coefficient (D_a) of Salicylic Acid (SA)——McBain's porous filter method was employed to determine the diffusion coefficient (D_a) in the vehicles and a cell constant was determined using a 0.1 N KCl aqueous solution.

(II) Rat Abdominal Skin——Male rats weighing about 250 g were anesthetized with a 20% urethan aqueous solution by subcutaneous injection. Abdominal hair was removed with an electric shaver (Brown Sixtant®). The skin was called "the intact skin". Next, the honey layer was removed with cellophane tape, the procedure being repeated 10 times. This was called "the stripped skin".

(III) Partition Coefficient (P) of Salicylic Acid (SA) in a Saline-skin System——The intact or stripped skin was cut off and the skin was shaken with a SA-saline solution for 3 hr at 37°; the SA content in the liquid

1) Part II: T. Nakagawa, M. Takehara, and H. Oishi, *Chem. Pharm. Bull.* (Tokyo), **24**, 1774 (1976). This work was presented at the 95 th Annual Meeting of the Phermaceutical Society of Japan, Nishinomiya, April 1975.

2) Location: *5-chome, Sagisu, Fukushima-ku, Osaka-shi*; *a*) Present address: *3-chome, Furue-dai, Suita-shi, Osaka.*

phase was determined by chemical assay.

A volume of the skin was measured with an ordinary solid(skin)-liquid(squalane) system using a picnometer.

$$P = C(\text{saline})/C(\text{skin}) \quad (1)$$

We regarded the P value as being the same as the partition coefficient of the water-skin system.

(IV) Diffusion Coefficient (D) of Salicylic Acid (SA) in the Skin——Ring-shaped art paper with a 50 mm inner diameter was pasted on the intact or stripped skin with adhesive (Alon alpha®) and then the skin was cut off. The cut off skin was held between two cups (see Fig. 1), the skin protruding from the cups was removed, and the skin edge was fastened with adhesive. SA-saline solution was poured into the outer side cup and saline solution into the other cup. The unit was left standing for 4 hr at 37°. Next, the SA content was determined by chemical assay, and D was calculated by the two-compartment diffusional barrier model according to the theory described in Part II.

(V) Simulation——Based on the theory in Part II, a Fortran program was coded and the simulation of drug absorption was carried out using a Facom 270—30® digital computer (Fuji Electric Co., Ltd).

On the other hand, a Fortran protran program of the two-compartment diffusional barrier model was coded and the diffusion coefficient of salicylic acid in the skin was simulated using the digital computer.

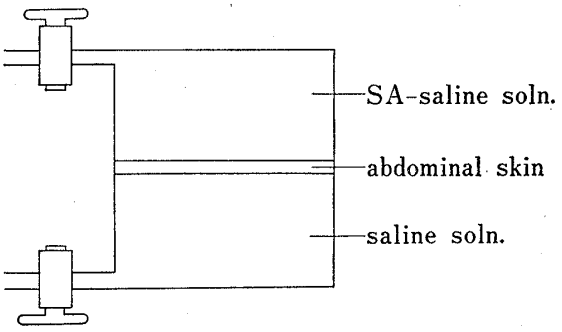

Fig. 1. Diffusion Cell
20 mm×35 mmϕ, about 25 ml

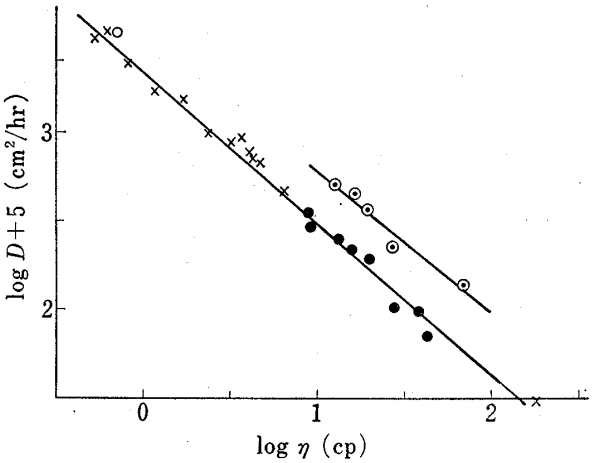

Fig. 2. Double log. Plot of D against η at 37°
⊙: HC; ×: E; ●: TG; ○: H_2O

Results and Discussion

(I) Diffusion Coefficient (D_a)

Double linear relationships with a slope of about −1 between log (D_a) and log (η) were obtained for the hydrocarbons (HC), esters (E), and triglycerides (TG) (see Fig. 2).

These results agree approximately with the Stokes-Einstein theory. Because SA became a dimer in HC and combined with the vehicle's molecule in E or TG, the linear relationships separated into two straight lines. The large diffusion unit results in the low diffusion coefficient.

(II) Partition Coefficient (P)

Partition coefficients (P) of sallcylic acid (SA) between the intact or stripped skin and a saline solution are shown in Table I. Obviously, much of the SA is distributed in the thin honey layer and P of this layer is fairly large.

Table I. Skin Parameters

	Thickness (mm)	D(cm²/hr)	P
Intact skin (cut off)	0.55	15.1×10^{-5}	3.89
Stripped skin (cut off)	0.51	171.3×10^{-5}	3.51

Table II. Simulation Parameters, Experimental and Calcd. Q Values

Vehicle[a)]	P_a	α	γ[b)]	F	Q (calcd.)	Q (exp.)
Sq	0.0527	0.01914	91×10^{-6}	1.17	69.60	63.42
D7	0.0540	0.02111	97	1.24	72.34	69.37
D35	0.0377	0.00580	52	0.98	40.67	32.39
Mix(7:3)	0.0519	0.01541	86	1.16	63.70	71.14
Mix(5:5)	0.0481	0.00890	72	1.11	49.73	51.13
EB	5.988	0.18152	667	7.57	30.29	55.31
EH	4.831	0.13142	438	4.89	28.08	42.31
EO	4.785	0.09273	506	5.68	30.43	26.18
ED	4.762	0.06635	319	3.54	22.63	21.78
EL	4.329	0.04857	318	3.52	23.99	20.78
EM	4.184	0.03937	265	2.92	21.49	20.34
EP	3.876	0.03011	231	2.55	20.53	22.49
IPB	5.952	0.19322	472	5.28	24.94	26.73
BM	3.745	0.03327	183	2.00	17.97	15.91
IPM	4.167	0.04008	241	2.66	20.31	19.07
IPP	3.861	0.02867	193	2.12	18.08	20.58
Is. Is.	2.058	0.00123	109	1.28	11.64	7.16
TA	5.348	0.01257	81	0.88	6.47	1.78
TB	6.329	0.01937	110	1.20	7.34	3.26
T C6	4.525	0.01469	157	1.72	12.92	5.72
T C8	3.831	0.01056	156	1.72	14.30	6.90
T C10	4.926	0.00823	156	1.72	11.42	7.13
ODO	4.546	0.00925	112	1.23	9.60	8.62
MIG	4.115	0.00930	133	1.46	11.86	7.59
TO	2.732	0.00282	125	1.40	12.91	7.56
Co. O	4.082	0.00525	156	1.72	12.48	6.72
Ol. O	3.268	0.00470	118	1.30	12.03	7.88
Water	1.000	0.20000	126	1.37	42.46	42.50

$P_b=3.51$, $\beta=0.0072$, $\delta=0.0144$, D(water)$=4760\times10^{-5}$ (cm²/hr); $l_a=0.2$ cm, $N=N_o=60$; $l_b=0.02$ cm, $M=M_o=6$; $\Delta x=0.0033$ cm $(=l_a/N_o=l_b/M_o)$, $X/\Delta x=10808$ (hr/cm²).

a) The abbreviated names were presented in Part I.

b) The γ values were calculated as $P_b=1$.

Table III. Effects of Separation Number and Transport Coefficient on Calculated Q Value

Vehicle	Layer number		
	$N_o=60$, $N=60$ Original	$N_o=60$, $N=60$ Trans. coeff. $=1/2$ of original value	$N_o=60$, $N=120$ $\gamma=$calcd. with eq. (4)
Water	42.46	42.44	42.43
D35	40.67	40.63	40.63
IPM	20.31	20.26	20.26
MIG	11.86	11.82	11.81

(III) Diffusion Coefficient (D) of Salicylic Acid (SA) in the Skin

Diffusion coefficients of the intact and stripped skin are shown in Table I. D of the stripped skin is 10 times greater than that of the intact skin because the diffusional resistance depends mainly upon the honey layer.

(IV) Simulation

Transport coefficients, α, β, γ, (comparable to the diffusion coefficients) were determined as follows. The γ value for the water vehicle was determined by trial and error and the

non-diffusional resistance (X) of the vehicle-skin interface was calculated from the γ value. The non-diffusional resistance (Y) of the skin-blood interface was taken as zero for a simplification of the model. The water vehicle case was chosen as a standard because water is a component of the skin and may exert a slight influence upon it.

The following equations were used to calculate α and β values.

$$D_a(\text{vehicle})/D(\text{water}) = \alpha/0.2 \quad (2)$$

$$D(\text{stripped skin})/D(\text{water}) = \beta/0.2 \quad (3)$$

The γ values for the other vehicles were calculated using Equation (4):

$$\frac{1}{\gamma} = \frac{1}{2\alpha P_a} + \frac{1}{2\beta P_b} + \frac{X/\Delta x}{F}\frac{N}{N_o} \quad (4)$$

Where P_a=partition coefficient of SA to the vehicle, P_b=3.51 from Table I, β=0.0072 from Eq. (3), $X/\Delta x$=10808 calcd. by trial error method, N=separation number, and N_o=original separation number.

The F values were obtained by TEWL experiments reported as an occlusion method in Part I. We thought that the escaping tendency of water through the skin was proportional to the diffusion of SA through it, and the effect of the vehicles on the skin resulted in a decrease of the non-diffusional resistance (X).

The effective thickness of the skin was taken as 0.2 mm because the dermis contains the capillary.

Calculated absorption values (Q) were plotted against the experimental ones (see Fig. 3) and the proportionalities among them were sufficient for all vehicles. In addition, calculated Q values were plotted against time (see Fig. 3 of Part I) and the experimental Q values agreed sufficiently with the theoretical curve.

Simulation parameters and experimental and calculated Q values are listed in Table II.

(V) Effects of Separation Number of Drug or Skin Phase and Transport Coefficients

The interfacial transport coefficient (γ) is affected by the separation number (N) of the drug or skin phase as shown in Eq. (4). On the other hand, the smaller the transport coefficient (α, β, γ), the nearer the value is to the actual case. A large N and a small transport coefficient prolongs the calculation time.

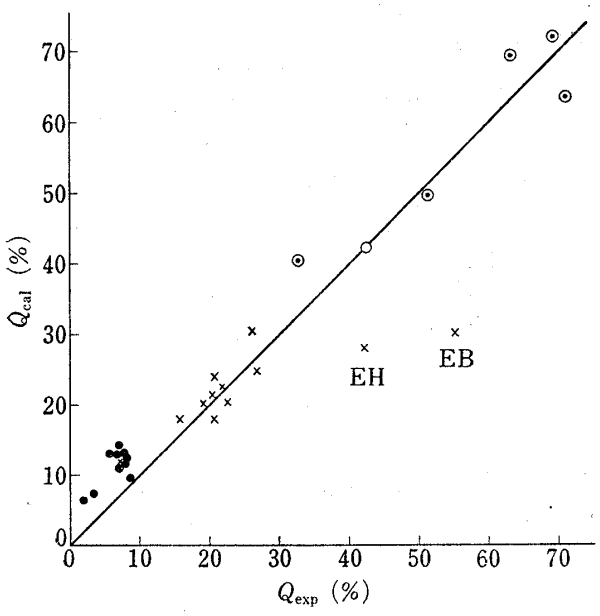

Fig. 3. Q_{cal} *vs.* Q_{exp}
⊙: HC; ×: E; ●: TG; ○: H_2O

The calculated Q values are shown in Table III; the separation number and transport coefficients were exchanged for other values as shown in the table. Obviously, the original separation number and transport coefficients were appropriate values.

(VI) Drug Absorption through the stripped Skin

SA absorption through the stripped skin was compared with the calculated Q values when X=0 (see Fig. 4) and the experimental values agreed closely with the theoretical curve, except at the 20-min point. This result means that the skin layer has an unknown non-diffusional resistance (X) on the surface.

(VII) Effect of the Vehicle Volume

In simulation, an alteration of the vehicle volume corresponds to an altera-

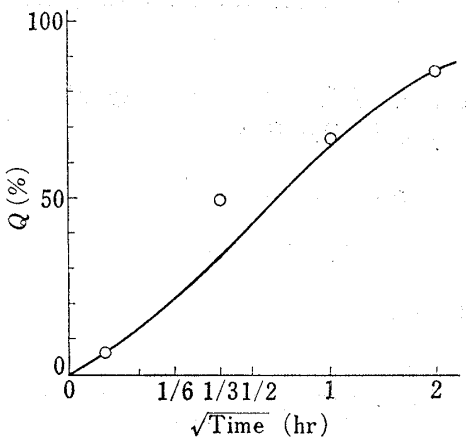

Fig. 4. Drug Absorption through the Stripped Skin

○: H_2O

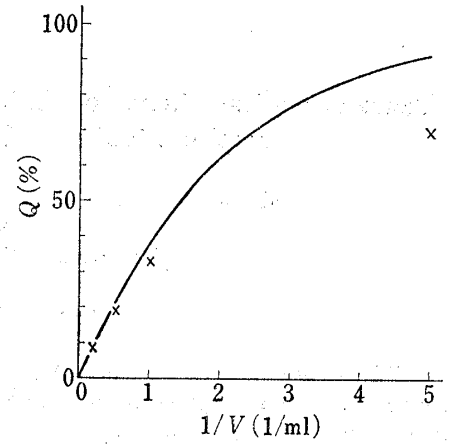

Fig. 5. Variation of Q with Vehicle Volume, 4 hr

×: IPM

tion of N number of the drug phase only and calculated Q value decrease with vehicle volume increase (see Fig. 5). The experimental values (see Table II of Part I) agreed sufficiently with the theoretical curve in the large-volume range, but separated considerably from the curve in the small-volume range. In the small-volume range, a large part of the vehicle accumulated at the circumference of the cell because of an interfacial tension between the vehicle and the cell, and the experimental Q value was lower than that of the theoretical curve.