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Model Studies on Percutaneous Absorption and Transport in the Ointment. II.[1] Hydrophilic Ointment of NaI[2]

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In order to verify the applicability of the mathematical models that were proposed in the preceeding paper to simulate the percutaneous absorption of drug and its transport in the ointment, experiments on release and percutaneous absorption of NaI from hydrophilic ointment were carried out. Agreement of calculated and observed values was reasonable.

Factors influencing the percutaneous absorption, namely, vehicles, surfactants, pH, water content, temperature, *etc.* have been studied actively and reported[4] by many authors on various medicaments such as radioactive NaCl,[5] iodine,[6] corticosteroid,[7] sulfonamides,[8] salicylates[9] and so on.

On the other hand, mathematical interpretation of drug release from ointment base[10] and kinetic representation of the percutaneous absorption mechanism[11] have also been reported from a physicochemical view point.

In the preceeding paper, a mathematical model was proposed in which ointment, skin and blood compartment were taken into account. In order to verify the applicability of the model proposed, experiments on release and percutaneous absorption of NaI from hydrophilic ointment were carried out. The purpose of this report is to describe the results of experiments and to compare them with theoretical prediction.

Experimental

Drug and Ointment Base——NaI used was reagent grade and obtained from Nakarai Chemical Co., Ltd. $Na^{131}I$ (Daiichi Pure Chemical Co., Ltd.) was used as tracer substance because of its readily detectable activity and its short life time. Detection of radioactive substance was accomplished by the use of well type scintillation counter.

1) Part I: K. Kakemi, H. Kameda, M. Kakemi, M. Ueda and T. Koizumi, *Chem, Pharm. Bull.* (Tokyo), **23**, 2109 (1975).
2) Partly presented at the 93rd Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1973.
3) Location: *3190 Gofuku, Toyama 930, Japan.*
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10) *a*) T. Higuchi, *J. Soc. Cosm. Chem.*, **11**, 85 (1960); *b*) T. Higuchi, *J. Pharm. Sci.*, **50**, 874 (1961); *c*) W.I. Higuchi, *ibid.*, **51**, 802 (1962).
11) R.J. Scheuplein, *J. Invest. Derm.*, **45**, 334 (1965); R.J. Scheuplein, *ibid.*, **48**, 79 (1967); I.H. Blank, R.J. Scheuplein and D.J. MacFarlane, *ibid.*, **49**, 582 (1967).

Hydrophilic ointment was prepared according to JP VIII, except preservative, *p*-aminobenzoate, which was omitted because of *pro re nata* preparation of the ointment.

***In Vitro* Release Rate**——Release rate of NaI from ointment was determined with the apparatus shown in Fig. 1. Whole setup was placed in a thermoregulated water bath (37°). At the predetermined time interval, sample solution (1 ml each) was withdrawn from the sink and the amount of NaI released from the ointment was determined.

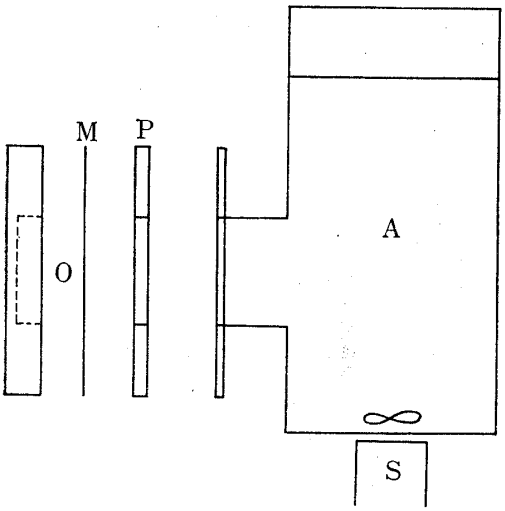

Fig. 1. Schematic Diagram showing the Apparatus used for *in Vitro* Drug Release Experiment

O: ointment, M: membrane, P: packing, S: stirrer, A: sink

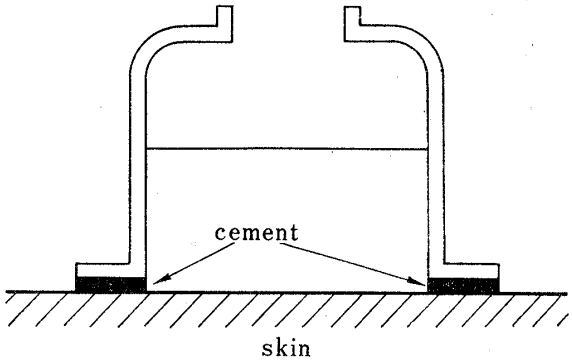

Fig. 2. Schematic Diagram showing the Apparatus used for the Application of Drug Solution

Animal——Unanesthetized male white rabbits weighing 2.5—3.5 kg and male rats (Wistar strain) weighing 180—250 g anesthetized with 1.0 g urethane/kg body weight were used. After animals were fixed on their back, the hair of abdominal skin was cut with an electric hair clipper and then with an electric shave. The exposed skin was wiped cautiously with absorbent cotton soaked in ethyl alcohol.

For the application of ointment, a plastic case (5 cm × 4 cm × 0.2 cm) filled with the ointment (for rabbits) or a piece of aluminum foil (5 cm × 4 cm) on which the ointment was spread (for rats) were attached to the exposed skin. For the application of drug solution, a glass cell shown in Fig. 2 was attached to the exposed and wiped skin using α-cyanoacryrate (Toa Gosei Co., Ltd.) and the solution was introduced into the vessel. Blood samples were taken from marginal ear vein (rabbits) or by cardiopuncture (rats).

Results and Discussion

Release of NaI from Hydrophilic Ointment

Cumulative amount of NaI released into sink are plotted against square root of time and are shown in Fig. 3. A straight line obtained indicates that Eq. 1 holds.[10c]

$$Q = 2C_{in}\sqrt{\frac{D_0 t}{\pi}} \qquad \text{Eq. 1}$$

Where Q is the amount of NaI released per unit area of application, C_{in} is the initial concentration of NaI in the ointment and D_o is the diffusion constant of NaI in the ointment. Least square fit of the data of Fig. 3 to Eq. 1 gave the value of 2.01×10^{-6} cm^2/sec for D_o, which coincides with the value reported by Higuchi.[10c]

Pharmacokinetics of NaI Disposition

Blood concentration of NaI after a rapid intravenous injection was determined and shown in Fig. 4. To some of the rabbits, 0.001M NaI solution was administered for 5 days prior to the injection of NaI for the purpose of blocking iodide uptake by thyroid. Appreciable effect on the disposition of NaI, however, was hardly observed.

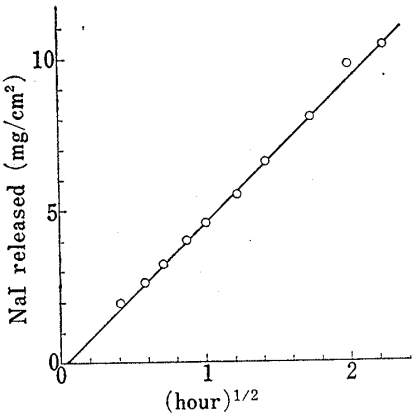

Fig. 3. Release of NaI from Hydrophilic Ointment into Water *vs.* the Square Root of Time

C_{in}=50.0mg/ml, area=4.15 cm²

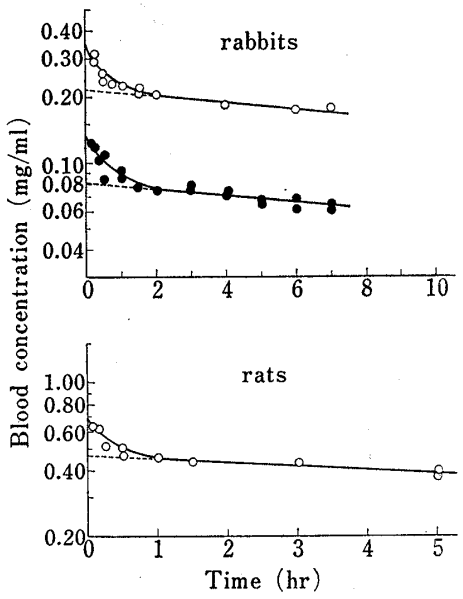

Fig. 4. Blood Concentration of NaI after a Rapid Intravenous Injection to Rabbits and Rats

dose: rabbits ○ 250 mg ● 100 mg
rats ○ 50 mg

An examination of Fig. 4 shows that after attainment of distribution equilibrium, elimination of NaI from blood is expressed by first order rate process, in both species. Rate constants and volumes of distribution calculated from the straight line portion of the curves of Fig. 4 are shown in Table I.

TABLE I. Distribution Volume and Elimination Rate Constants of NaI in Rabbits and Rats

	V_d (ml/kg)	k_{el} (hr^{-1})
Rabbits	5×10^2	0.04
Rats	5×10^2	0.04

Application of NaI Solution

In order to determine apparent thickness L°_s and effective diffusion constant D_s° of the skin, NaI solution was applied to the skin and the concentration of NaI appeared in blood and remained in the cell were determined. Results are roughly divided into two unaccounted-for groups by the rapidity of NaI appearance in blood. Observed values of NaI concentration in blood are plotted against time in Fig. 5. Concentration of NaI remained in the cell after application for 480 minutes to rabbits were 30.1 mg/ml (rapid) and 48.3 mg/ml (slow).

The concentration of NaI in the solution did not decrease too much, besides blood concentration was around 0.1 mg/ml, which is negligible compared with that of the solution. The boundary conditions referred to as the special case in the preceeding paper is roughly satisfied. Assuming that k_{el} is equal to zero, the amount of NaI released into blood is approximated by Eq. 2, when t is sufficiently large.

$$V_d \cdot C_b = \frac{C_{in} \cdot D_s^\circ \cdot A}{L_s^\circ}\left(t - \frac{L_s^{\circ 2}}{6D_s^\circ}\right) \qquad \text{Eq. 2}$$

Approximate values of L_s° and D_s° are evaluated from the slope and intercept of the resulting straight line portion of the curves of Fig. 5.

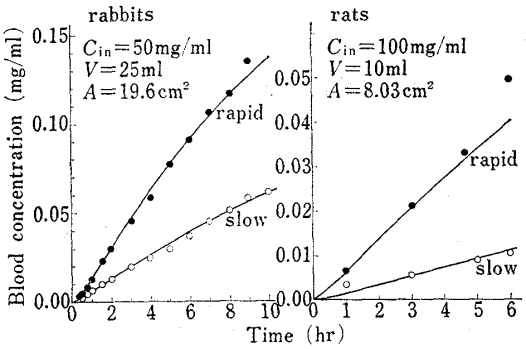

Fig. 5. Blood Concentration of NaI after the Application of NaI Solution to Rabbits and Rats

Smooth lines are theoretical values simulated by Model 1 with parameters shown in Table I and Table II.

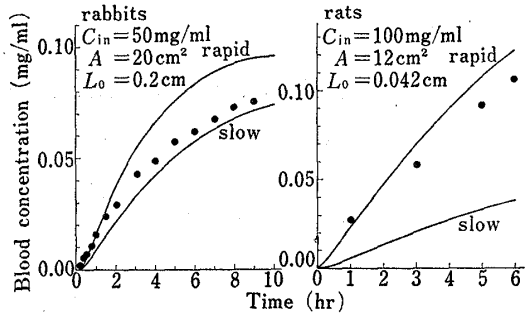

Fig. 6. Blood Concentration of NaI after the Application of Hydrophilic Ointment to Rabbits and Rats

Smooth lines are theoretical values simulated by Model 2 with parameters shown in Table I and Table II.

TABLE II. Apparent Thickness $L_s°$ and Effective Diffusion Constant $D_s°$ of NaI in the Skin

		$L_s°$ (cm)	$D_s°$ (cm²/sec)
Rabbits	rapid	5.12×10^{-2}	3.46×10^{-7}
	slow	2.23×10^{-2}	0.633×10^{-7}
Rats	rapid	8.79×10^{-4}	2.23×10^{-10}
	slow	5.04×10^{-4}	0.375×10^{-10}

Theoretical values of concentration of NaI in the solution and in blood were calculated with various values of $L_s°$ and $D_s°$ by the algorithm of Model 1 described in the preceeding report and compared with the observed values. $L_s°$ and $D_s°$ values finally obtained by the trial and error procedure are shown in Table II. Smooth lines of Fig. 5 are the theoretical curves calculated with $L_s°$ and $D_s°$ values of Table II.

Application of Hydrophilic Ointment

Blood concentration of NaI after an application of hydrophilic ointment are shown in Fig. 6. By utilization of the parameters obtained by the individual experiments described so far, theoretical blood concentrations were calculated with the algorithm of Model 2 described in the preceeding paper. The value of $P°$ was assumed as 2.5 because the volume fraction of water in hydrophilic ointment is about 0.31 and marojity of NaI is expected in water phase. Fig. 6 shows the comparison of calculated and observed values. Agreement of these values varify the model proposed in the preceeding paper.

For the purpose of pharmacokinetic understanding of the mechanism of percutaneous absorption on the application of ointment, mathematical model was defined. The prediction by that was reasonable. This fact proves that the assumptions employed in the preceeding paper for construction of the model were reasonable ones.

Morphologically, skin is never a single layer but it is composed of several layers that are dissimilar in physicochemical nature. Therefore the assumption adopted in the preceeding paper that the skin is a single homogeneous layer, is not free from criticism. Discrimination of the transport route, transfolicular and transepidermal, is another problem. The farther refinement of the model would be necessary.