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Effect of Vehicles on Percutaneous Absorption. I.[1] Characterization of Oily Vehicles by Percutaneous Absorption and Trans-Epidermal Water Loss Test

Hideo Oishi, Yoichi Ushio, Kazumi Narahara, and Mitsunori Takehara

Shionogi Research Lab.[2]

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Comparative studies of oily vehicles, hydrocarbons (HC), esters (E), and tri-glycerides (TG), were done on percutaneous absorption of salicylic acid (SA), physicochemical parameters, and trans-epidermal water loss (TEWL) in rat. The diffusion concept was supported experimentally; vehicle viscosity was found to be an important restriction factor of drug absorption. In HC, which had low affinity to SA as estimated by solubility and partition coefficient, good correlation was obtained between drug absorption and viscosity, but this correlation could be seen only within the series. In spite of using the same series, the reverse effect was obtained in the lower molecular weight range of TG; absorption decreased according to increase in affinity to SA, and maximum absorption appeared with the medium-chain length TG. In E, the skin-altering effect may have a rather important role in absorption, although the viscosity effect was seen. TEWL was suppressed by HC, promoted by E, and promoted slightly by TG. TEWL values correlated well with SA absorption suggesting the importance of the physiological effect of the vehicle in drug absorption.

An important role of the vehicle in topical preparations is to control the movement of the drug into or through the skin to obtain optimum drug availability. Many have reported about vehicles in percutaneous absorption, but no definite conclusion have been reached.

Salicylic acid (SA) is one of the most popular drugs in topical use and much has been reported about its percutaneous absorption. Absorption of medicaments is known to be better from vegetable and animal oils than from mineral oils.[3] Gemmel and Morrison[4] reported the superiority of lard over emulsifying ointment as the vehicle of SA. Stolar, *et al.*[5] and others[6] reported the better absorption of SA from emulsion bases than petrolatum bases. On the contrary, Nogami, *et al.*[7] stated that absorption of SA from hydrophilic ointment was less than that from other ointment bases involving yellow petrolatum. And recently, Washitake, *et al.*[8] evaluated the mineral oils as a superior vehicle in absorption for SA compared with isopropyl myristate (IPM), hexadecyl alcohol, and oleic acid. These conflicting reports may be due to differences of experimental technique and conditions involving the animals. Another reason may be the complexity of composition and ingredients of the topical preparations.

Theoretical analysis of the percutaneous absorption related with the vehicle was presented by Higuchi,[9] Wagner,[10] and others. An absorption model was presented by Hanano[11] in

1) This work was presented at the 95 th Annual Meeting of the Pharmaceutical Society of Japan, Nishinomiya, April 1975.
2) Location: *5-chome, Sagisu, Fukushima-ku, Osaka-shi.*
3) J.J. Eller and S. Wolf, *Arch. Derm. Syph.*, **40**, 900 (1939); R.G. Harry, *Brit. J. Derm.*, **65**, 82 (1941); G. Valette, *Pharm. J.*, **170**, 461 (1953).
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8) M. Washitake, T. Anmo, I. Tanaka, T. Arita, and M. Nakano, *J. Pharm. Sci.*, **63**, 397 (1975).
9) T. Higuchi, *J. Soc. Cosm. Chem.*, **11**, 85 (1960).
10) J.G. Wagner, *J. Pharm. Sci.*, **50**, 379 (1961).
11) M. Hanano, *Chem. Pharm. Bull. (Tokyo)*, **7**, 300 (1959).

which the absorption process of SA and benzoic acid in human subjects were treated by steady state diffusion model. Arita, *et al.*[12] and Washitake, *et al.*[13] adopted first order kinetics on percutaneous absorption of SA and carbinoxamine in guinea pig. Kakemi, *et al.*[14] adopted diffusional model, based on the concentration, partition coefficient, and diffusion coefficient. Drug transport through the skin may controlled by the diffusion and thus application of first order kinetics may require some restrictions.

The vehicle not only improves drug penetration, but also can have some protective or therapeutic effects on the applied site by itself. Thus, the vehicle should not be an irritant or harm the skin. In this respect, trans-epidermal water loss (TEWL) test is a very significant technique for measuring the barrier function of the skin. Insensible perspiration of the skin, film properties of cosmetics or ointments, whether occlusive or permeable, have been observed by many authers,[15] as well as physiological normality or disorderlines of the skin function caused by diseases,[16] chemicals,[17] or mechanical treatment.[18] The TEWL value may be related to the permeability of drugs into the skin.[17]

We tried to characterize the oily vehicles which play an important part in topical formulations, to establish the optimum application of vehicles in therapy. Related series of hydrocarbons (HC), esters (E), and tri-glycerides (TG) were selected as vehicles, and percutaneous absorption and TEWL in rat were measured. We discuss physicochemical parameters and physiological factors on the basis of the diffusion concept.

Experimental

(I) Vehicles——The vehicles used are in Table I; the listed abbreviations were used through the studies of this series.

(II) Preparation for Animal Experiments——Male Wister rats weighing 260 ± 10 g were anesthetized with 20% urethane aqueous solution by subcutaneous injection. Abdominal hair was removed with an electric shaver (Brown Sixtant®), and the rats were fixed on their backs. The shaved skin was wiped clean with absorbent gauze soaked in 70% ethanol then dried, and a glass cell as shown in Fig. 1 was glued onto the center of the skin with adhesive (Alon alpha®). The area of skin for sample contact was about 10 cm^2.

The skin was rinsed by charging 8 ml distilled water. After discharging the water, soft tissue paper was used to remove the remaining water then the skin was dried with an electric dryer.

(III) Absorption Experiments——Sample solution was charged into the cell which was then closed and kept horizontal for various periods of time. Generally, 2 ml of 0.5% SA-vehicle solution, 0.03% in the case of HC, was charged for 4 hr. The percent absorption (Q) was calculated from the loss of the drug applied. In special cases, concentration, volume, and contact time were varied to investigate the effect of these factors. The technique recovering drug from the vehicle is given below.

(IV) TEWL Test——After a rat was prepared as given above, a water absorption tube containing about 2 g of dried $Mg(ClO_4)_2$ was attached to the top of the cell (see Fig. 1-B).

(IV-1) Initial TEWL Measurements: The initial TEWL value was measured by the following procedure. Air, dried by being passed over $CaCl_2$ and silica-gel, was introduced through the side arm of the cell and the air flow was kept constant at about 35 ml/min. The initial rate of the TEWL in individual rats was measured by periodical weighing of the absorption tube at 10 min. Intervals, and calculated from the slope of the line, given by plotting the cumulative weight gain of the tube against time, when it formed a straight line.

(IV-2) Charged TEWL Value in Air Flow System: The charged TEWL value was measured after initial value measurement using the same rat by putting a 0.2 ml sample in the cell which contained a disk of gauge spread out previously in order to maintain uniform contact with the skin surface.

12) T. Arita, R. Hori, T. Anmo, M. Washitake, M. Akutsu, and T. Yajima, *Chem. Pharm. Bull.* (Tokyo), **18**, 1045 (1970).
13) M. Washitake, T. Yajima, T. Anmo, T. Arita, and R. Hori, *Chem. Pharm. Bull.* (Tokyo), **21**, 2444 (1973).
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15) K. Okamoto and T. Kondo, *Yakuzaigaku*, **29**, 207 (1969); G. R. Berube, M. Messinger, and M. Berdick, *J. Soc. Cosm. Chem.*, **22**, 361 (1971); O.K. Jacobi, *ibid.*, **18**, 149 (1967); M.M. Rieger and D.E. Deem, *ibid.*, **25**, 253 (1974).
16) M. Shahidullah, E.J. Raffle, A.R. Rimmer, and W. Frain-Bell, *Brit. J. Derm.*, **81**, 722 (1969).
17) H. Baker, *J. Soc. Cosm. Chem.*, **20**, 239 (1969).
18) G. Eriksson and L.O. Lamke, *Acta Dermatovener.* (Stockholm), **51**, 169 (1971).

(IV-3) Discharged TEWL Value in Air Flow System: The TEWL after treatment of the sample was measured similarly after removing the sample by absorption with soft tissue paper and allowing the cup to stand open without air delivery for 20 min.

Sample amount and contact time were varied from 25 to 2000 mg to investigate the effect on the TEWL Value. The effect of SA on TEWL was also investigated under the condition shown in Fig. 11 and Table IV.

(IV-4) Discharged TEWL Value in Occlusion System (TEWL Factor (F) of Vehicle): The TEWL value after treatment of 2 ml SA-solution for 4 hr in a closed system without air flow was also measured to compare with SA-absorption. But, 0.2 ml SA-solution or vehicle was used in the case of non-volatile vehicles. Other experimental technique was the same as the air flow system.

(IV-5) Comparison of TEWL Rate of Vehicles: The TEWL values were expressed as a ratio of each TEWL rate to the initial rate to quantify the vehicle effect on barrier function of normal skin. These TEWL values measured by three methods are called hereafter "charged", "discharged", and "discharged in occlusion system". The last value was used as the TEWL factor (F) in Part III of this series.

(V) SA Analysis Method——The sample was discharged from the cell, then the skin and cell were rinsed with 5 ml portions of $CHCl_3$ making a total volume of 100 ml. SA-$CHCl_3$ solution was shaken with a $Fe(NO_3)_3$-aqueous solution and SA content was determined by measuring absorbance of SA-Fe## complex at 530 mμ in the aqueous phase.

(VI) Solubility of SA——Solubility of SA in the vehicles was measured at 37°.

(VII) Partition Coefficient of SA in the Vehicle-Water System——SA-vehicle solution was shaken with water at 37° and SA content in each phase was determined by chemical assay.

$$P_a = C(\text{vehicle})/C(\text{water}) \quad (1)$$

(VIII) Partition Coefficient of SA between Vehicle and Powdered Rat Epidermis——

(VIII-1) Dry Rat Epidermis: About 50 mg of dried and powdered epidermis which was prepared from excised back skin was shaken with SA-vehicle solution at 37° and the partition coefficient was calculated from the loss of SA in the solution phase.

$$P = C(\text{epidermis})/C(\text{vehicle}) \quad (2)$$

(VIII-2) Hydrated Rat Epidermis: Dry, powdered epidermis was maintained at 96%-RH for 2 days at room temperature. The hydrated epidermis was shaken with SA-vehicle solution at 37° and the partition coefficient was expressed as

$$P = C(\text{dry epidermis})/C(\text{vehicle}) \quad (3)$$

(IX) Vehicle Viscosity——Viscosity of the vehicle was measured at 37° with an Ubbelohde type viscometer or Ferranti-Shirley cone-and-plate type viscometer.

(X) Water Loss of Agar Gel through the Vehicle Layer——A cup (see Fig. 1-C) was filled with hot 2% agar solution, a filter paper was placed on it, and it was cooled by being held horizontally. The charged volume of agar gel was controlled to maintain a level equal to the rim of the cup. After adding 100 mg, in general, of the vehicle onto the surface of the gel, the cup was stored in a desiccator as shown in Fig. 1-C. The rate of water loss was calculated and compared with the mean control value of the gel itself.

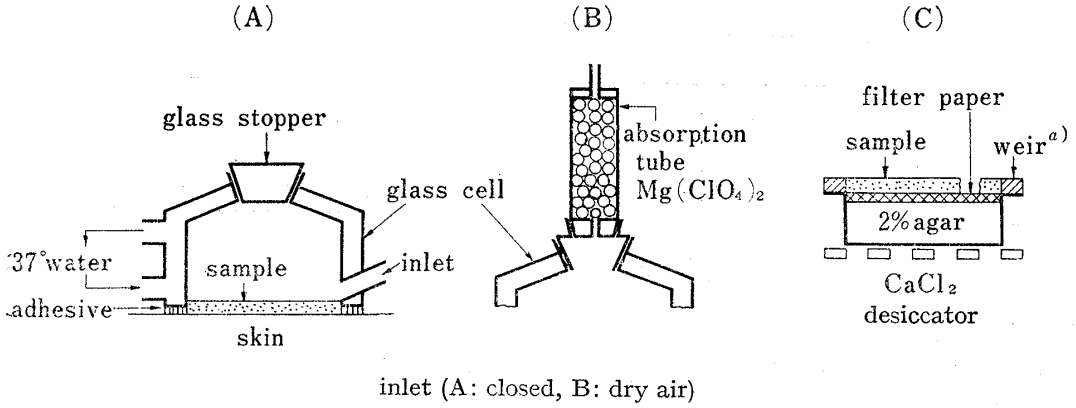

Fig. 1. Schematic Diagram of Apparatus for (A) Percutaneous Absorption and (B) Trans-epidermal Water Loss (TEWL) in Rat, and (C) Water Loss from Agar Gel

a) adhesive tape

Table I. Vehicles used and Physicochemical Properties

Vehicle		Viscosity (cp)	Solubility of SA (%)
Hydrocarbons	HC		
Squalane	Sq	16.45	0.075
Drakeol 7[a]	D7	12.76	0.081
Drakeol 35[a]	D35	68.85	0.071
D7 (70%)+D35 (30%)	mix(7:3)	19.37	0.079
D7 (50%)+D35 (50%)	mix(5:5)	26.34	0.076
White petrolatum	WP	156.6	—
Esters	E		
Ethyl butylate	EB	0.53	16.07
Ethyl hexanoate	EH	0.81	12.77
Ethyl octanoate	EO	1.17	10.40
Ethyl decanoate	ED	1.67	8.45
Ethyl laurate	EL	2.35	7.49
Ethyl myristate	EM	3.24	6.85
Ethyl palmitate	EP	4.31	5.62
Isopropyl butylate	IPB	0.62	14.00
Isopropyl myristate	IPM	3.64	5.75
Isopropyl palmitate	IPP	4.66	5.29
Butyl myristate	BM	4.11	5.44
Isostearyl isostearate[b]	Is. Is.	174	1.76
Tri-glycerides	TG		
Tri-acetine	TA	9.45	10.54
Tri-butyrin	TB	6.45	8.68
Tri-caproin	T C6	8.87	7.17
Tri-caprylin	T C8	13.31	6.01
Tri-caprin	T C10	19.56	6.07
Octyl decyl TG[c]	ODO	15.44	6.27
Miglyol 812[d]	MIG	15.81	5.60
Tri-olein	TO	41.95	5.21
Coconut oil	Co. O	27.46	4.76
Olive oil	Ol. O	38.85	2.79
Water		0.69	0.35

a) D7=light liquid pet. NF; D35=heavy liquid pet. USP; Pen. Drake (USA)
b) Nissan Kagaku Co. Ltd.
c) Toshin Kagaku Co. Ltd.
d) Chemische Werke Witten (Ger.)

Table II. Variation of Percent Absorption (Q) with Vehicle Volume

Vehicle volume (ml)	Q (%)
0.2	70.76
1.0	33.09
2.0	19.07
5.0	8.07

Results and Discussion

(I) Viscosity and Solubility

The viscosity of the vehicles and the solubility of SA in the vehicles are listed in Table I.

(II) Mode and Physicochemical Parameters in Percutaneous Absorption

(II-1) Effect of Drug Concentration, Sample Volume, Time Course, and Vehicle Viscosity ——When percutaneous absorption is considered on the grounds of diffusion, the concentra-

Table III. SA Partition to the Skin

Vehicle	Dry epidermis	Hydrated epidermis
Sq	207.2± 1.7	
D7	128.3± 8.9	
D35	156.9± 3.5	
Mix(7:3)	200.5±14.1	
EB	7.3± 0.9	12.5±0.3
EH	6.0± 0.6	11.1±0.5
ED	7.1± 0.2	14.5±0.2
EM	8.7± 0.6	17.1±0.3
IPM	10.1± 1.1	17.6±1.2
TA	4.0± 1.9	7.6±0.6
TB	7.6± 1.3	16.6±1.7
T C6	9.0± 2.5	18.0±2.1
MIG	7.8± 1.5	19.0±0.3
TO	4.3± 0.2	15.1±0.9
Co. O	6.0± 0.1	23.3±0.9

tion of the drug may not affect the percent absorption, and an increasing of the vehicle volume on the skin may decrease the percent absorption. This assumption was suported experimentally as shown in Fig. 2 and Table II.

The time course of drug absorption is relatively linear between the percent absorption and the square root of contact time as shown in Fig. 3.

log-log plots between percent absorption (Q) and viscosity (η) of the vehicle are shown in Fig. 4. Good correlations among them were obtained, except for the low molecular weight range of E and TG where interactions between TG and SA were different from the other cases because double interactions between a vehicle molecule and a SA molecule may occur and dissociation energy is twice that of the other cases. In the case of EB, EH, and IPB, volume of the drug phase was decrease considerably by penetration of vehicle into the skin and percent absorption (Q) may increase by volume effect, but IPB could not explain by the volume effect. A deviation of TA from the extraporated line of low molecular weight range of TG may be explained by a self-association of TA, which have an absormally high viscosity and flow-activation energy, and a deviation of Is.Is. may attributes to a character of it, which may possesses an intermediate character between HC and E estimated from solubility of SA and molecular structure of it.

(II-2) Effect of Solubility and Partition Coefficient——Both solubility and partition coefficient are physicochemical parameters reflecting affinity between SA and vehicle molecule. The plots of SA-absorption (Q) against physicochemical parameters shows an analogous pattern (see Fig. 5 and 6).

Absorption of SA from TG was generally small and no clear difference appeared in the series, but the tendency of lower absorptions which had higher solubility and partition coefficient was obtained.

On the contrary, in series of E and HC, reversed relations were obtained as shown in the figures. But in HC, the solubility and partition coefficients were so small that the interactions are negligible and vehicle viscosity may play a role as the rate-limiting factor.

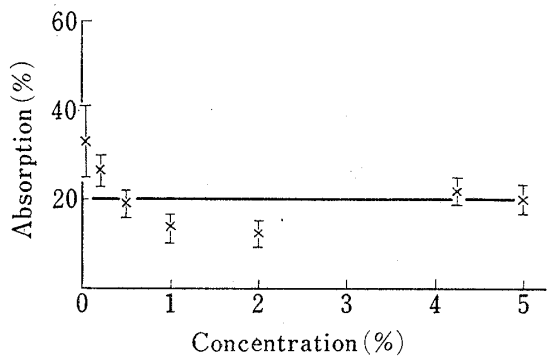

Fig. 2. Effect of Drug Concentration on Percutaneous Absorption of Salicylic Acid from Isopropyl Myristate Solution

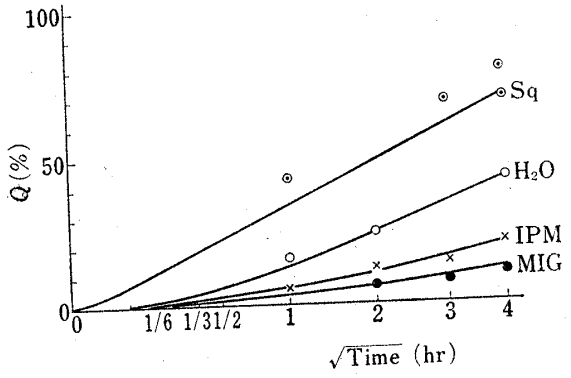

Fig. 3. Variation of Q with $\sqrt{\text{Time}}$

——: theoretical curve
⊙: Sq
×: IMP
●: MIG
○: H_2O

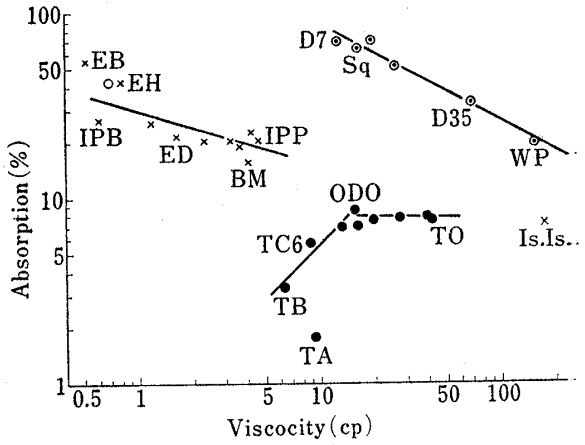

Fig. 4. Effect of Vehicle Viscosity on Percutaneous Absorption of Salicylic Acid

⊙: hydrocarbon
×: ester
●: triglyceride
○: water

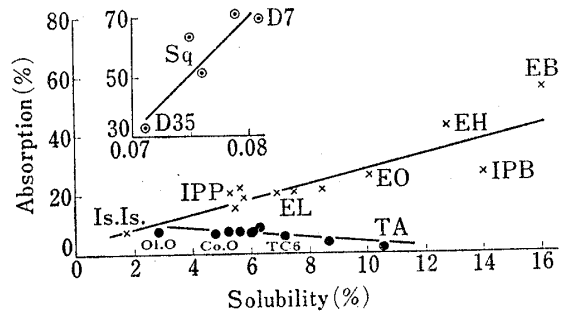

Fig. 5. Relationship between Salicylic Acid Solubility in Vehicle and Its Percutaneous Absorption

⊙: hydrocarbon
×: ester
●: triglyceride

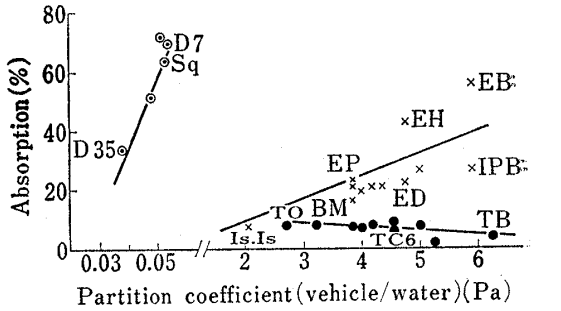

Fig. 6. Relationship between Vehicle/Water Partition Coefficient of Salicylic Acid and Its Percutaneous Absorption

⊙: hydrocarbon
×: ester
●: triglyceride

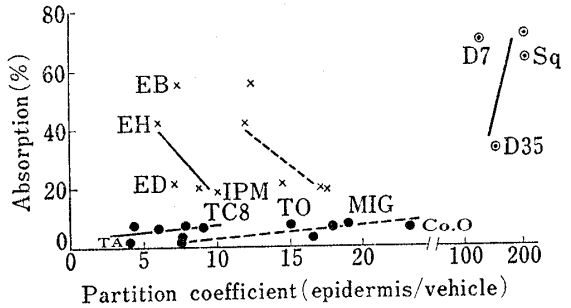

Fig. 7. Relationship between Epidermis/Vehicle Partition Coefficient of Salicylic Acid and Its Percutaneous Absorption

⊙: hydrocarbon
×: ester
●: triglyceride
——: dry skin
------: hydrated skin

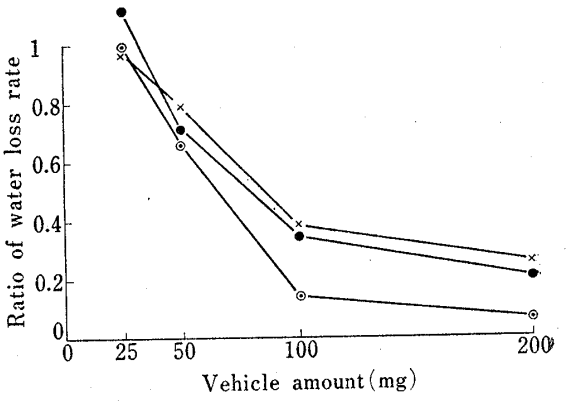

Fig. 8. Effect of Vehicle Amount on Water Loss from Agar Gel

⊙: D35
×: IPM
●: MIG

Table IV. TEWL Values in Air Flow System and Water Loss through Vehicle

Vehicle	TEWL Charged			Ratio of water loss rate
	Charged	Discharged	Exp. Cond.[a]	
Sq	0.50±0.06	1.10±0.16	A	0.06±0.02
D7	0.66±0.08	1.20±0.17	A	0.14±0.04
D35	0.47±0.07	1.07±0.26	A	0.14±0.04
D35	0.43±0.04	1.05±0.11	B	
WP	0.23±0.02	0.85±0.10	A	0.11±0.05
EB	1.66±0.17[b]	2.09±0.36	D	
EH	10.22±1.40[b]	7.59±0.72	D	
EO	5.00±1.05[b]	4.37±0.54	C	0.74±0.05
EO	4.57±1.35[b]	5.98±1.51	D	
ED	3.95±0.32	7.36±0.46	D	0.64±0.03
EL	3.04±0.71	7.82±2.21	D	
EM	2.82±0.38	8.01±0.21	D	0.61±0.05
IPB	3.15±0.09[b]	4.21±0.09	D	1.08±0.03
IPM	2.20±0.48	5.50±1.68	D	0.39±0.08
IPM	2.01±0.18	4.87±0.56	C	
IPP	1.87±0.24	4.64±0.67	C	0.32±0.03
BM	1.62±0.07	5.21±0.24	D	0.44±0.04
Is. Is	0.70±0.00	1.28±0.17	D	
TA	1.12±0.09	1.08±0.10	D	1.01±0.04
TA	1.14±0.10	1.04±0.12	A	
TB	1.38±0.08	2.10±0.18	D	0.73±0.05
TB	1.18±0.08	1.56±0.12	A	
T C6	1.40±0.17	2.94±0.28	D	
T C8	1.30±0.21	2.34±0.30	D	
MIG	1.05±0.06	1.95±0.18	D	0.35±0.05
MIG	0.89±0.11	1.61±0.25	A	
TO	0.84±0.07	1.40±0.08	D	0.23±0.03
Ol. O	0.93±0.18	1.78±0.37	D	

a) experimental condition; A=vehicle, 200 mg, 2 hr, B=0.03% SA soln., 0.2 ml, 4 hr, C=vehicle, 0.2 ml, 4 hr, D=0.5% SA soln., 0.2 ml, 4 hr
b) Vehicle loss in the cell was observed.

Table V. Examples of Discharged TEWL Value in Occlusion System (*F* Value)

Vehicle	*F*	Vehicle	*F*
Sq	1.17±0.08	BM	2.00±0.35
D7	1.24±0.07	IPM	2.66±0.38
D35	0.98±0.07	Is. Is.	1.28±0.34
EB	7.57±1.30	TA	0.88±0.08
EH	4.89±1.19	TB	1.20±0.09
EO	5.68±0.46	T C6	1.72±0.28
ED	3.54±0.38	T C10	1.72±0.30
EL	3.52±0.61	MIG	1.46±0.21
EM	2.92±0.86	Co. O	1.72±0.16
EP	2.55±0.10	Ol. O	1.30±0.21
IPB	5.28±0.62		
		Water	1.37±0.19

(II-3) Partition of SA into the Epidermis——Drug affinity for the skin was investigated by partition of SA to the epidermis (see Table III and Fig. 7).

HC possessed a high affinity for partitioning SA to the epidermis and may have promoted absorption in spite of its rather high viscosity compared with E and TG.

In TG, absorption differences in the series were small but proportional to the partitioning ability to the epidermis.

In E, reverse effects were found, but the relation between absorption rate and skin-partition is difficult to explain.

(II-4) Effect of Hydration on Partition——The large increase of partition coefficients obtained with hydrated skin, may have been caused by swelling of the skin and increasing of the sorption site.

The individual physicochemical parameters studied here could not be understood fully from these absorption phenomena of SA.

(III) Characterization of Oily Vehicles by TEWL Test

(III-1) Water Loss through the Vehicle Layer——The effect of vehicle's film on water loss was varied by the properties of the vehicles, but all vehicles acted as restricting film. The greater the film thickness, the lower the loss rate (see Fig. 8). The restriction ability increased according to viscosity (see Fig. 9 and Table IV), but TG had a rather small effect compared with E and HC with the same viscosity, and the ability of TG was about one-half the value of the other series. TA especially had almost no barrier effect and was not different from the control up to about 100 μm in thickness. This may be caused partly by the hydrophilic property of this vehicle.

(III-2) TEWL Test under Air Flow——We developed a new method for the TEWL test, and used this technique to investigate the alteration effect of the vehicles on the physiological function of the skin.

TEWL values varied with the vehicle as shown in Fig. 10, but did not change much with vehicle volume variation.

In the case of HC, D35 had a high occlusive effect, and the TEWL value was recovered after discharge.

In the case of TG, MIG had no barrier effect, but had a somewhat promotive effect after discharge.

In the case of E, IPM acceralated the TEWL even when in contact with the skin by increasing the sample amount from 25 to 2000 mg. This means that E has an alterating power on the barrier function of the skin.

The time course of TEWL in each vehicle is shown in Fig. 11. A somewhat increasing tendancy was observed in all the series, but in HC, the change was negligible. In the case of IPM, the value rose rapidly in the initial 3 hr and then reach a plateau. Incorporation

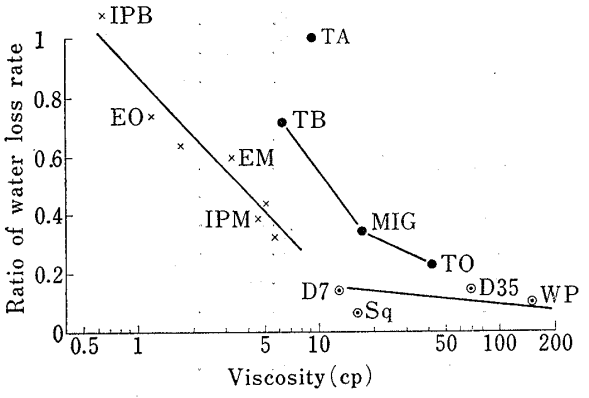

Fig. 9. Effect of Vehicle Viscosity on Water Loss from Agar Gel

⊙: hydrocarbon
×: ester
●: triglyceride

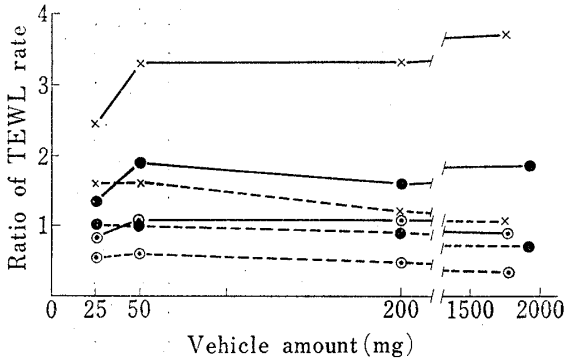

Fig. 10. Effect of Vehicle Amount on TEWL in Air Flow System

⊙: D35
×: IPM
●: MIG
------: charged
——: discharged

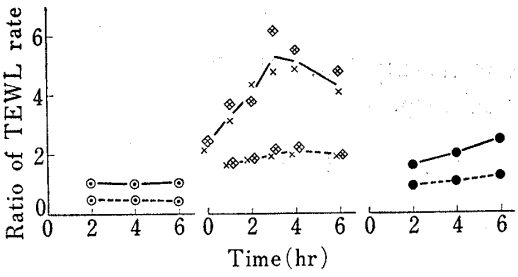

Fig. 11. Effect of Contact Time and Salicylic Acid on TEWL in Air Flow System

⊠: 0.5% salicylic acid soln.,
⊙: D35
×: IPM
●: MIG
------: charged
——: discharged

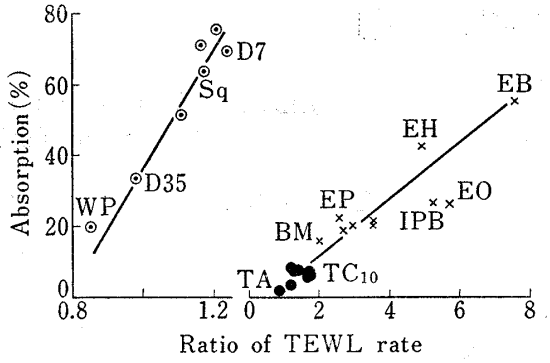

Fig. 12. Relationship between Percutaneous Absorption of Salicylic Acid (Q) and TEWL Value in Occlusion System (F) of Vehicles

⊙: hydrocarbon
×: ester
●: triglyceride

of 0.5% SA in IPM had no effect on the TEWL value, which suggests that SA has no effect on the barrier function of the skin at this concentration, although SA is known to be a keratolytic agent (see Table III).

All HC suppressed the TEWL values and possessed an occlusion effect on the skin. On the contrary, E promoted TEWL even in the charged condition, and TEWL values decreased with increase molecular weight. With TG, a special pattern which gave a peak value at T C6 or T C8 was obtained, and TEWL values were between those of the other series. Charged TEWL values of TG were not very different from those of the control.

Discharged values were about two times greater than the charged values. Decreasing of the TEWL values in the low molecular weight range of E may be due to vehicle loss by evaporation.

(III-3) Discharged TEWL Value in Occlusion System (F Value)——The discharged TEWL values in the occlusion system (see Table V) were found to be somewhat smaller than the discharged TEWL values in air flow system, but an analogous trend was observed. Decreasing of the promotive effect of TEWL value in low molecular weight E was recovered by increasing sample volume and the lower the molecular weight of E, the higher the TEWL value; iso-propyl esters had somewhat lower TEWL values than ethyl esters.

(III-4) Effect of TEWL Factors on SA Absorption——Percent absorption (Q) of SA was plotted against the TEWL factor (F) as shown in Fig. 12. There was relatively good linearity among them, meaning that the alteration effect of vehicles on the physiological function of the skin was a big factor of drug absorption. We found that the TEWL test is a good method for investigating the vehicle effect on barrier function of the skin.

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