Percutaneous Absorption of Drugs IV: Percutaneous Absorption of Drugs from Oily Vehicles

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Abstract □ The percutaneous absorption and retention of salicylic acid and carbinoxamine from four oily vehicles (liquid paraffin, oleic acid, hexadecyl alcohol, and isopropyl myristate) were studied by employing a recirculation apparatus. The absorption followed first-order kinetics, with the exception of the initial period. The vehicle that had a strong affinity to the drug showed a poor drug-releasing effect, and poor absorption and retention of drugs by the skin were observed. Higher absorption rate constants were observed for damaged skin than intact skin. The acceleration of absorption because of skin damage, however, was not so great from liquid paraffin as from the aqueous solution. The amount of drugs retained in the damaged skin declined following the initial increase.

Keyphrases □ Salicylic acid in oily vehicles—correlations between *in vitro* adsorption and *in vivo* percutaneous absorption, physicochemical parameters □ Carbinoxamine in oily vehicles—correlations between *in vitro* adsorption and *in vivo* percutaneous absorption, physicochemical parameters □ Vehicles, oily—percutaneous absorption of salicylic acid and carbinoxamine from liquid paraffin, hexadecyl alcohol, oleic acid, and isopropyl myristate □ Absorption, percutaneous—salicylic acid and carbinoxamine from oily vehicles, intact and damaged skin

In previous studies (1–3), the percutaneous absorption of salicylic acid and carbinoxamine was investigated using the intact and damaged skin of male guinea pigs. The factors involved in the percutaneous absorption from aqueous solutions were examined by measuring the amount of the drugs retained in the skin and the amount lost from the recirculating solutions. Ointment and cream bases are generally used in topical dosage forms. It is, therefore, possible that these vehicles interact with drugs and modify their release rate from the bases. Moreover, vehicles may have effects on the permeability of drugs through the cutaneous tissue barrier and on the barrier itself.

The percutaneous absorption of drugs from vegetable oils and animal fats that tend to penetrate through the skin was reported to be superior to that from mineral oils (4–6). The effects of various oily vehicles on the percutaneous absorption of salicylic acid was studied by measuring the amount of the drug excreted in the urine; the drug was substantially absorbed from lard and lanolin but only slightly absorbed from petrolatum[1] (7, 8). Strakosch (9) reported that the extent of absorption of salicylic acid was not affected by the type of emulsion, but Stolar *et al.* (10) pointed out that the extent of absorption of drugs varies with the type of emulsion.

The absorption of salicylic acid from hydrophilic ointment was less than that from yellow petrolatum, simple ointment, and absorption ointment, although the influence of the ointment base was not great (11).

[1] Vaseline.

Studies on the absorption of salicylic acid from polyethylene glycol 400 and four other hydrophilic vehicles showed that the partition coefficient of the drug between the vehicle and benzene was well correlated with the degree of drug absorption from the vehicle (12). An experimental model for the thermodynamic consideration of the relation between the vehicle and percutaneous absorption was presented (13, 14), but many problems remain to be solved.

In the present study, the authors used oily vehicles to examine the influence of four different types of bases, *i.e.*, liquid paraffin, oleic acid, hexadecyl alcohol, and isopropyl myristate, on the percutaneous absorption of drugs and compared the absorption from the oily vehicles with that from aqueous solutions.

EXPERIMENTAL

Drugs—Salicylic acid (pKa = 3.0) was employed as an acidic drug, and carbinoxamine (pKa = 8.9) was used as a basic drug. These drugs were dissolved in hexadecyl alcohol, oleic acid, or isopropyl myristate to give a concentration of 500 μg/ml. Carbinoxamine was dissolved in liquid paraffin to give concentrations of 250, 500, and 1000 μg/ml; the concentrations of salicylic acid were 75, 150, and 300 μg/ml because of its poor solubility in liquid paraffin.

Oily Vehicles—Light liquid paraffin (specific gravity 0.855, bp 180–190°/5 mm Hg), hexadecyl alcohol (2-hexyl-1-decanol, specific gravity 0.842, bp 195–205°/50 mm Hg), oleic acid (specific gravity 0.895, bp 230–235°/15 mm Hg), and isopropyl myristate (specific gravity 0.850, bp 158–160°/5 mm Hg) were used immediately after distillation of the reagent grade oils.

Absorption Experiments—A recirculation apparatus, described previously (1), was fixed to the abdominal skin of a male guinea pig, 300–400 g, after removal of the abdominal hair with an electric hair clipper. The abdominal skin from which the stratum corneum was removed by stripping 20 times with cellophane adhesive tape was used as a damaged skin. During the recirculation of test solutions at a constant flow rate, an aliquot of the test solution was pipetted at fixed time intervals and the amount of the drug absorbed was calculated from the decrease in the concentration of the drug in the recirculating solution. Experimental conditions were the same as reported previously (1–3): area of skin, 2.25 π cm^2; temperature of solutions, 31 ± 1°; recirculating flow rate, 15 ± 5 ml/min; solution volume, 25 ml; and room temperature, 23 ± 2°.

Measurement of Cutaneous Retention of Drugs—Male guinea pigs were killed immediately after recirculation of a drug solution for a given time, and the area of the abdominal skin to which the apparatus was fixed was wiped with absorbent cotton to remove the drug solution. The skin of the area was then excised to the corium, and the drug in the skin was determined by the analytical methods described previously (2, 3).

Determination of Partition Coefficients—Ten milliliters of an isotonic solution of sodium chloride was added to 10 ml of the oily vehicles containing the drug at the same concentrations as the test solutions in the absorption experiment. The mixtures were immersed in a thermostated water bath at 31°, and the container was shaken in the bath for 30 sec every 10 min. When equilibrium was attained (approximately 4 hr), the oily phase was separated by centrifuging and the drug concentration was determined spectro-

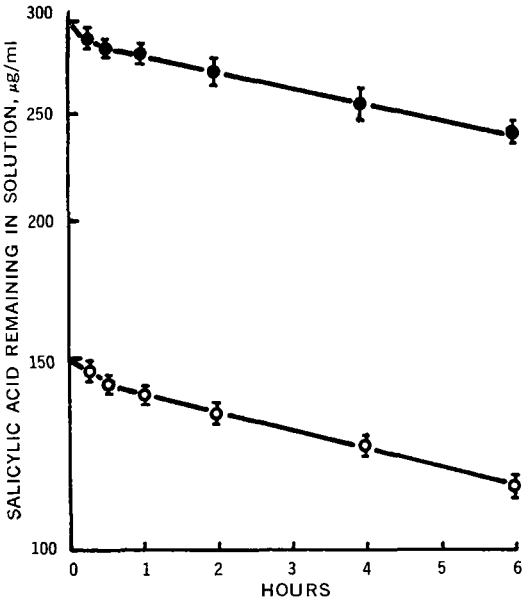

Figure 1—*Logarithmic plots of salicylic acid remaining in the recirculating liquid paraffin solution against time. Initial concentrations of salicylic acid were 300 (●) and 150 (○) μg/ml (mean ± standard error of five experiments).*

photometrically. The partition coefficient was calculated by comparison of the equilibrium concentration with the initial concentration of the drug in the oily vehicle.

Determination of Solubility of Salicylic Acid—Each oily vehicle was placed in a glass-stoppered test tube, and excess salicylic acid was added. The tubes were then shaken in the thermostated water bath. An aliquot of the supernate was pipetted at fixed time intervals until the equilibrium concentration was obtained. The equilibrium value was taken as the solubility of drug in the oily vehicles.

Experiment on Adsorption of Drugs to Excised Skin *In Vitro*—Twenty milliliters of each oily vehicle containing a known amount of drug was placed in a glass-stoppered 50-ml test tube, and a section of abdominal skin (2.25 π cm^2 in size) of the guinea

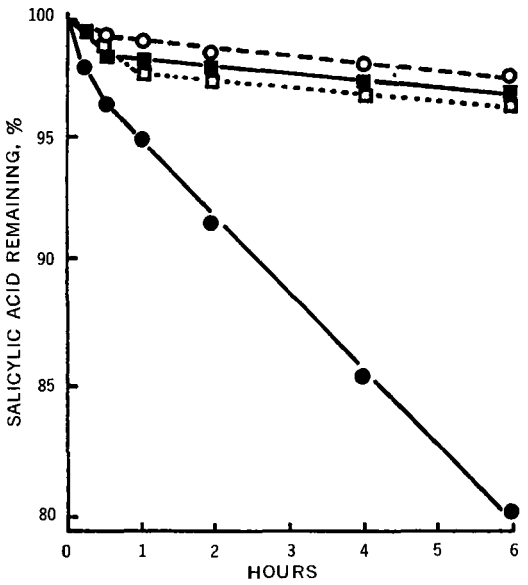

Figure 2—*Logarithmic plots of salicylic acid remaining in various oily vehicles against time. Key: ●, liquid paraffin; ○, oleic acid; ■, hexadecyl alcohol; and □, isopropyl myristate. Initial concentrations of salicylic acid were 300 μg/ml in liquid paraffin and 500 μg/ml in the rest. Each plot represents the mean of three to six experiments.*

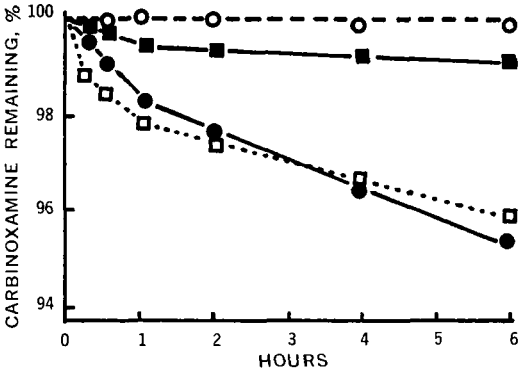

Figure 3—*Logarithmic plots of carbinoxamine remaining in various oily vehicles against time. Key: ●, liquid paraffin; ○, oleic acid; ■, hexadecyl alcohol; and □, isopropyl myristate. Initial concentrations of carbinoxamine were 500 μg/ml.*

pig was added. The tube was placed in the thermostated water bath at 31° and shaken occasionally. An aliquot of the solution was withdrawn at suitable time intervals over 96 hr to determine the equilibrium amount of drug adsorbed by the excised skin.

Change in Solution Volume—The change in the solution volume during the experimental period was determined because absorption of the oily vehicle through the skin was expected. The volume of the test solution at the starting point of this experiment was compared with that after recirculation for 6 hr. The absorption of the oily vehicles through both the intact skin and the damaged skin during the experimental period was negligible.

Determination of Salicylic Acid in Oily Vehicles—Salicylic acid in oleic acid was determined by the colorimetric method using ferric nitrate (15). Determination of salicylic acid in the other oily vehicles was carried out by partly modifying the method used for determination of the drug in an aqueous solution (1). One milliliter of the test solution was placed in a glass-stoppered test tube, and 2 ml of chloroform and 8 ml of 0.2 *N* NaOH were added. After shaking for 20 min, the tube was centrifuged and 2 ml of the aqueous layer was transferred to another test tube. To this tube was added 5 ml of chloroform. After shaking for 20 min and centrifuging, sali-

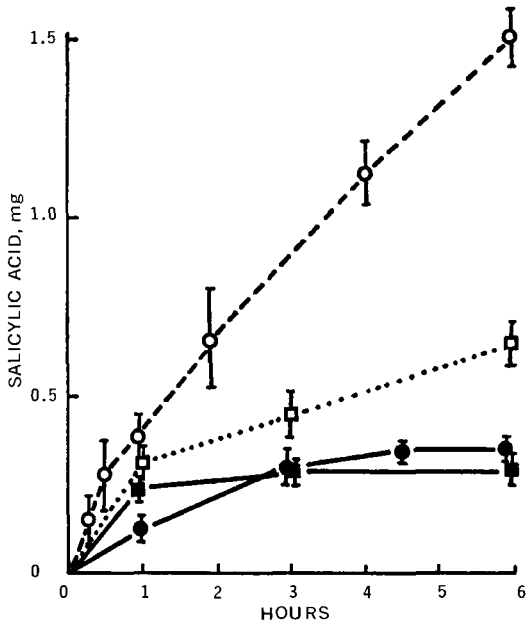

Figure 4—*Percutaneous absorption and retention patterns of salicylic acid. Key: ●, amount retained in the skin from liquid paraffin; ○, amount absorbed from liquid paraffin; ■, amount retained in the skin from buffer solution, pH 3.0; and □, amount absorbed from buffer solution, pH 3.0. Initial concentrations of salicylic acid were 300 μg/ml in liquid paraffin and 500 μg/ml in the buffer solution.*

Table I—Relationship between Percutaneous Absorption and Physical Properties of Drugs

Drugs	Oily Vehicles	Amount Absorbed during 1–6 hr, %	Solubility at 31°, mg/ml	Water–Oil Partition Coefficient at 31°	Amount Adsorbed by Excised Skin *In Vitro*, mg
Salicylic acid	Liquid paraffin	14.6	0.495	41.5	3.56
	Isopropyl myristate	1.7	43.1	0.17	2.26
	Hexadecyl alcohol	1.6	79.2	0.17	1.57
	Oleic acid	1.5	45.2	0.24	0.73
Carbinoxamine	Liquid paraffin	2.8	Very soluble	0.49	0.92
	Isopropyl myristate	1.7		1.09	1.18
	Hexadecyl alcohol	0.0		0.51	0.16
	Oleic acid	0.0		1.02	0.001

cylic acid in the chloroform layer was determined spectrophotometrically at 310 nm.

Determination of Carbinoxamine in Oily Vehicles—Carbinoxamine in oily vehicles was determined by partly modifying the previously reported method (1) for the determination of the drug in an aqueous solution. One milliliter of test solution was placed in a glass-stoppered test tube, and 2 ml of chloroform and 8 ml of 0.2 *N* HCl were added. After shaking for 20 min, the tube was centrifuged, 3 ml of the aqueous layer was transferred to another test tube, and 1 ml of 2 *N* NaOH and 6 ml of chloroform were added. After shaking the tube for 20 min, it was centrifuged and carbinoxamine in the chloroform layer was determined spectrophotometrically at 262.5 nm.

The calibration curves of both salicylic acid and carbinoxamine in oily vehicles were obtained in the 75–1000-μg/ml concentration range prior to the determination of both drugs in oily vehicles. The standard deviation of these data was 1.3%, and these methods were able to determine the drugs with sufficient precision.

Determination of Drug Contents in Skin—Salicylic acid and carbinoxamine in the skin were determined by the method described previously (2).

RESULTS AND DISCUSSION

Absorption of Drugs through Intact Skin—*Percutaneous Absorption of Drugs from Oily Vehicles*—When the logarithmic concentrations of salicylic acid in liquid paraffin were plotted against time, straight lines were obtained except for the initial period (Fig. 1). The slopes of the lines were independent of the initial concentration of drug. Similar straight lines also were obtained with carbinoxamine. Therefore, the disappearance of the drugs from liquid paraffin followed first-order kinetics as was the case from the aqueous solution (1).

From the measurement of salicylic acid concentrations in the recirculating medium at 1 and 6 hr of perfusion for three initial concentrations of 75, 150, and 300 μg/ml, the percentage of salicylic acid absorbed during the 5-hr period was calculated for each initial concentration. The values were around 15% irrespective of the initial concentration. Similarly, the percentage of carbinoxamine absorbed during the same period was around 2.8 for three initial concentrations of 250, 500, and 1000 μg/ml. These observations indicate no saturation phenomenon in the concentration range and thus tend to suggest that the percutaneous absorption of both drugs from liquid paraffin is a simple passive transport.

Figure 2 shows the time course of absorption of salicylic acid from hexadecyl alcohol, oleic acid, and isopropyl myristate together with that from liquid paraffin. The corresponding plots for carbinoxamine are presented in Fig. 3. Little carbinoxamine was absorbed from oleic acid, whereas some carbinoxamine disappeared from hexadecyl alcohol only during the 1st hr. For all salicylic acid systems and carbinoxamine in liquid paraffin and isopropyl myristate, the drug concentration of the recirculating solutions de-

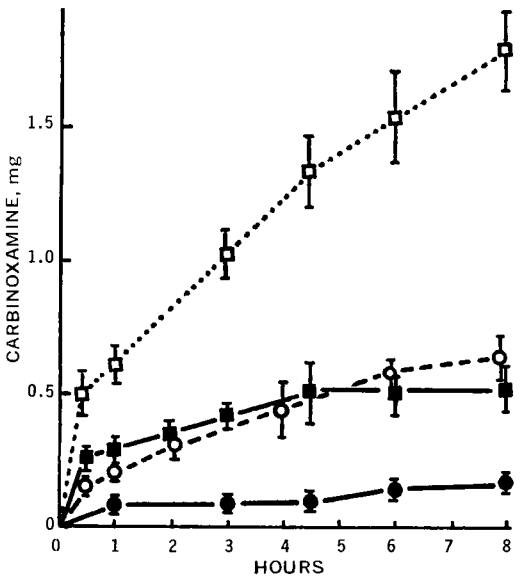

Figure 5—*Percutaneous absorption and retention patterns of carbinoxamine. Key: ●, amount retained in the skin from liquid paraffin; ○, amount absorbed from liquid paraffin; ■, amount retained in the skin from buffer solution, pH 9.0; and □, amount absorbed from buffer solution, pH 9.0. Initial concentrations of carbinoxamine were 500 μg/ml.*

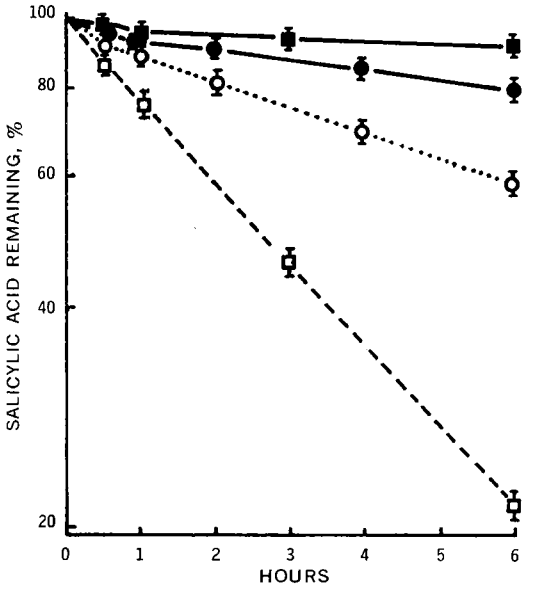

Figure 6—*Logarithmic plots of salicylic acid remaining in the recirculating solution against time. Key: ●, liquid paraffin on intact skin; ○, liquid paraffin on damaged skin; ■, buffer solution, pH 3.0, on intact skin; and □, buffer solution, pH 3.0, on damaged skin. Initial concentrations of salicylic acid were 500 μg/ml in the buffer solution and 300 μg/ml in liquid paraffin.*

Table II—Relationship between Percutaneous Absorption of Salicylic Acid and Composition of Vehicle

Composition of Vehicle, %		Amount Absorbed during 1–6 hr, %	Solubility at 31°, mg/ml	Water–Oil Partition Coefficient at 31°
Liquid Paraffin	Isopropyl Myristate			
100	0	14.6	0.495	41.5
90	10	5.7	3.21	1.73
75	25	3.9	7.97	0.75
50	50	2.8	17.6	0.39
25	75	2.6	29.5	0.27
0	100	1.7	43.1	0.17

creased, following first-order kinetics after a lapse of the initial period.

The solubilities of salicylic acid in these vehicles and the water–oil partition coefficients of both drugs were investigated to examine the cause of the difference in the percutaneous absorption among these vehicles (Table I). The solubility of salicylic acid in liquid paraffin was lower than that in other solvents, whereas the water–oil partition coefficient was higher. These physical properties of salicylic acid may account for its greater absorption from liquid paraffin than from other oils. For carbinoxamine, however, the difference in the amount absorbed among these vehicles was not so great because its partition coefficients were all small and of similar magnitude.

The amount of drug adsorbed by the excised skin *in vitro* from the four different vehicles (Table I) seems to be related to absorption in the initial period from the recirculating solution (Fig. 2). Only a trace of carbinoxamine was adsorbed from oleic acid, while the amounts absorbed from liquid paraffin and isopropyl myristate were as large as about 1 mg. This finding is also reflected by absorption of carbinoxamine in the initial period (Fig. 3).

To examine the correlation between the affinity of a drug to vehicles and the amount absorbed, liquid paraffin and isopropyl myristate, which differ widely from each other in solubility and absorption characteristics of salicylic acid, were mixed in different proportions, and the variation of percutaneous absorption of salicylic acid with solvent composition was investigated (Table II). The solubility of salicylic acid in the vehicles increased and the water–oil partition coefficient decreased as the proportion of isopropyl myristate was increased. Thus, it became evident that the amount of the drug absorbed tends to decrease as the affinity of drug to the vehicle is increased.

Kakemi *et al.* (16) postulated two mechanisms for rectal absorption of sulfonamides from oils: the drug dissolved in the oil is absorbed into the rectal mucosa either directly or through the mucosal secretion. When the latter mechanism prevails over the former, the water–oil partition coefficient of the drug between the aqueous

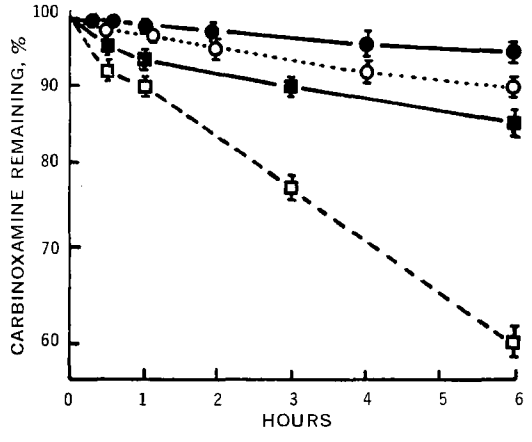

Figure 7—*Logarithmic plots of carbinoxamine remaining in the recirculating solution against time. Key:* ●, *liquid paraffin on intact skin;* ○, *liquid paraffin on damaged skin;* ■, *buffer solution, pH 9.0, on intact skin; and* □, *buffer solution, pH 9.0, on damaged skin. Initial concentrations of carbinoxamine were 500 μg/ml.*

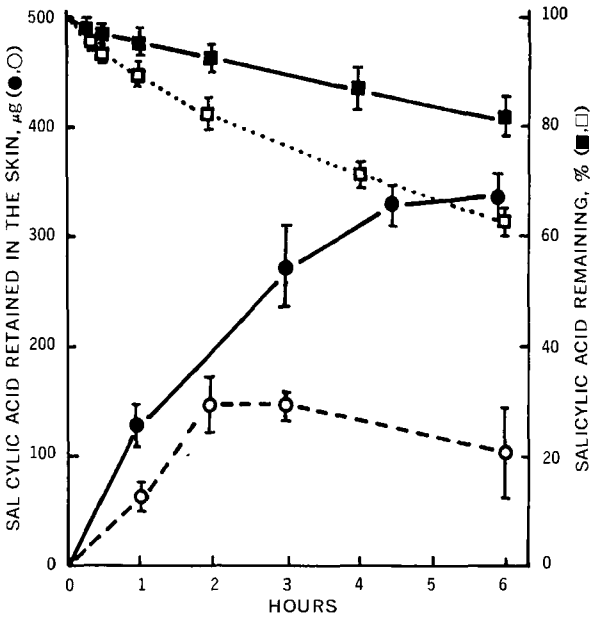

Figure 8—*Percutaneous absorption pattern of salicylic acid from liquid paraffin. Key:* ●, *amount retained in intact skin;* ○, *amount retained in damaged skin;* ■, *percent remaining in liquid paraffin applied on intact skin; and* □, *percent remaining in liquid paraffin applied on damaged skin. Initial concentrations of salicylic acid were 300 μg/ml.*

and oily phases is expected to influence greatly the absorption rate of drugs. In the reverse situation, this would not be true.

As in the case of rectal absorption of drugs from oils, these two mechanisms may be considered for percutaneous absorption, *i.e.*, direct absorption and absorption *via* the aqueous secretion (secreted by the skin). The second mechanism is more likely to be predominating in the percutaneous absorption of salicylic acid from oils. This proposition is based on the fact that the amount of salicylic acid absorbed from liquid paraffin, which has a large drug-releasing ability (high partition coefficient), was much larger than that from other oils having a strong affinity to salicylic acid and very poor drug-releasing power (low partition coefficient). The absorption of carbinoxamine, on the other hand, cannot be interpreted similarly and requires further consideration.

Time Course of Cutaneous Retention of Drugs from Oily Vehicles—Figure 4 shows the comparison of the amount of salicylic acid absorbed and that retained in the skin when two different vehicles (*i.e.*, liquid paraffin and an aqueous solution) were used. A similar comparison is presented for carbinoxamine in Fig. 5. The amount retained in the skin and that absorbed from the aqueous vehicle increased with time in a similar manner during the initial stage of the experiment with salicylic acid as described previously (2). But the former quickly approached a plateau value.

From the liquid paraffin, however, the amount absorbed during the initial period was much larger than the amount retained. After 6 hr of recirculation, the ratio of the amount of the drugs retained to that absorbed from liquid paraffin was lower than that from the aqueous vehicle, *i.e.*, 0.20 and 0.25 from liquid paraffin for salicylic acid and carbinoxamine, respectively, and 0.45 and 0.35 from the aqueous solution for the same drugs, respectively. A similar trend was observed for the other three oily vehicles.

These variations in cutaneous retention phenomenon with the nature of the vehicle may be attributed to the fact that the stratum corneum is highly swollen with water when the vehicle is an aqueous solution, whereas no swelling takes place when oily vehicles such as liquid paraffin are employed. The swelling may enhance the retention of drugs because it increases the volume of the stratum corneum.

Absorption of Drugs through Damaged Skin—*Percutaneous Absorption of Drugs from Oily Vehicles*—In Figs. 6 and 7 the percentage of salicylic acid or carbinoxamine remaining in the recirculating solution is plotted against time for the aqueous solution and liquid paraffin. Absorption kinetics are also compared between the

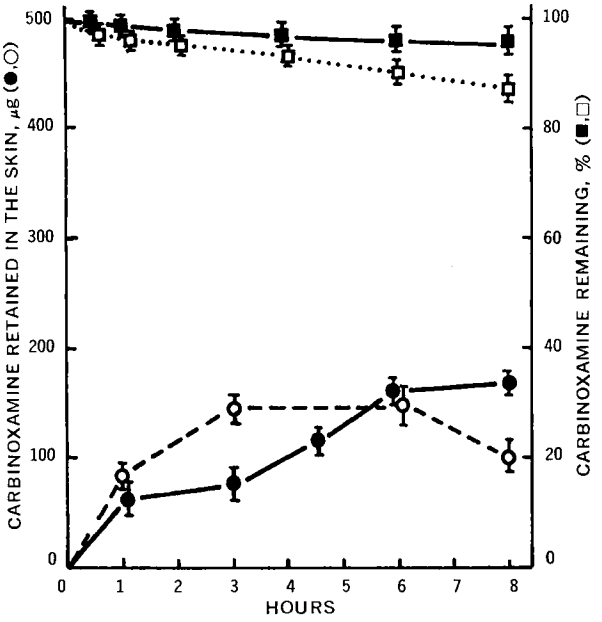

Figure 9—*Percutaneous absorption pattern of carbinoxamine from liquid paraffin. Symbols are the same as in Fig. 8. Initial concentrations of carbinoxamine were 500 μg/ml.*

intact and damaged skins. From the aqueous solution, the absorption rate constant through the damaged skin during the 1–6-hr recirculation period was about 10 times greater for salicylic acid and 3 times greater for carbinoxamine than the corresponding rate constant through the intact skin. However, the absorption rate constant of the drugs through the damaged skin from liquid paraffin was only about twice as much as that through the intact skin.

These results indicated that the damaged skin is particularly permeable to drugs dissolved in water. Drugs dissolved in liquid paraffin may also be absorbed through the damaged skin after being released into an aqueous secretion. Thus, the transfer of the drug into the secretion from oil may be considered the rate-determining step.

Time Course of Cutaneous Retention of Drugs—Figures 8 and 9 show the percentage of the drug absorbed from the recirculating liquid paraffin solution and the corresponding amount retained in the skin for the damaged and intact skins plotted against time. As for salicylic acid (Fig. 8), the amount retained in the damaged skin was less than that in the intact skin and tended to decrease after 2 hr. The absorption of the drug through the damaged skin from the recirculating solution was so rapid that the concentration of the drug remaining in the recirculating solution was decreased to 80% of the original concentration after 2 hr of recirculation and to 60% after 6 hr. Thus, the decrease in salicylic acid concentration in the solution as perfusion continues is most likely to be responsible for the decrease in the amount retained in the skin. Such a decrease was not observed in the intact skin.

As for carbinoxamine, on the other hand, the amount retained in the dámaged skin was larger than that in the intact skin during the 6 hr of recirculation, but the situation was reversed after 6 hr (Fig. 9). The carbinoxamine concentration in the recirculating solution remained at 90% of the initial concentration even after 6 hr of recirculation. The amount of carbinoxamine retained in the damaged skin showed a tendency to decrease only after 6 hr.

These results suggest that the observed difference in cutaneous retention behavior of drug between the intact and damaged skins is attributed to the better absorption of drug through the damaged skin than through the intact skin, whereby the concentration of drug in the recirculating solution falls during the experiment.

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