

Effect of Skin Surface Lipid on the Skin Permeation of Lidocaine from Pressure Sensitive Adhesives

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Pressure sensitive adhesives (PSA) tapes containing different concentrations of lidocaine were prepared by a general casting method using styrene-isoprene-styrene block copolymer, and the *in vitro* skin permeation of lidocaine from each tape was evaluated using diffusion cell and excised hairless rat skin. The skin permeation was proportionally increased by up to 40% lidocaine in the PSA tape and did not change after this concentration. Although the bending point of the steady-state flux *via* skin concentration curve was found at 40%, saturated concentration or solubility of lidocaine in the tape was estimated to be about 20% by differential scanning calorimetry (DSC) measurement. In addition, the steady-state flux of lidocaine through skin from water or silicone fluid suspension (92 or 120 $\mu\text{g}/\text{cm}^2 \cdot \text{h}$, respectively) was very similar to those of 40, 50 and 60% tapes (105, 101 and 112 $\mu\text{g}/\text{cm}^2 \cdot \text{h}$, respectively). Decrease in the concentration in tapes during the permeation experiment explained only part of these phenomena. To analyze them further, the drug free PSA tape with or without (control) skin surface lipid was affixed to 50% lidocaine PSA tape for 48 h, and the amount of lidocaine crystal in the layered tapes was measured by DSC. The amount was found to be lower in the lipid-containing tape than in the lipid-free tape, suggesting that skin surface lipid can dissolve lidocaine crystal or solid in PSA tape to decrease its thermodynamic activity. Thus it is important to follow the concentration and thermodynamic activity of lidocaine in PSA tape, skin and the interface between the two layers to exactly assess its skin permeation flux.

Keywords skin permeation; lidocaine; pressure sensitive adhesive; skin surface lipid

Discomfort or pain induced by insertion of an injection needle is feared by many patients, especially children. Some formulations for topical skin anesthesia may overcome this,¹⁾ such as a dermal patch.²⁾ In the present study, free lidocaine (lidocaine base) was used as a model drug, due to its small molecular size (mol. weight: 243.3), low melting point (66–69 °C), high skin penetration, quick and strong anesthetic effect, high stability, and other qualities.^{3,4)} Pressure sensitive adhesive (PSA) tapes containing 10 to 60% lidocaine were prepared by a general casting method⁵⁾ using styrene-isoprene-styrene (SIS) block copolymer, and the skin permeation of lidocaine from each tape was evaluated *in vitro* using excised hairless rat skin and diffusion cell. Determinants for the skin permeation rate are discussed from the obtained data.

MATERIALS AND METHODS

Materials Lidocaine was obtained from Wako Pure Chemical Industries, Ltd. (Osaka, Japan) and silicone fluid (360 medical fluid, 20 cs) from Dow Corning Asia Corporation (Kanagawa, Japan). SIS block copolymer (TR-1107) and rosin (KE-311) were gifts from Shell Chemicals, Ltd. (Tokyo, Japan) and Arakawa Chemical Industries, Ltd. (Osaka), respectively. PSA matrix was prepared by mixing SIS block copolymer, rosin and liquid paraffin at a ratio of 28:34.4:2.7 in our laboratory. Other chemicals and solvents were of reagent grade and used without further purification.

Animals and Skin Membrane Preparation Male hairless rats (WBN/IL-Ht) 7–8 weeks old were supplied by Ishikawa Laboratory Animals (Saitama, Japan) and were used in all animal experiments. The abdominal region of hairless rat skin was carefully shaved and excised before an experiment.

Preparation of Lidocaine PSA Tape Lidocaine, PSA matrix and ethyl acetate were mixed in a screw-capped vial and shaken at room temperature to get a homogeneous solution. The general casting method was used to prepare PSA tapes containing 10, 20, 30, 40, 50 and 60% lidocaine of 40–50 μm thickness.⁵⁾ Lidocaine free tape was also prepared.

Determination of Solubility For measurement of lidocaine solubility in water, excess drug was added to distilled water in a screw-capped vial and stirred at 37 °C in a water bath. After equilibration (48 h), a part of the drug suspension was withdrawn and quickly filtered through cellulose acetate membrane (0.2 μm pore size, Advantec Toyo, Tokyo). The filtrate was adequately diluted with water to determine the solubility.

For measurement in silicone fluid, excess drug was added to silicone fluid in a microtube and shaken at 37 °C. After equilibration, the drug suspension was centrifuged (5 min, 5000 rpm) at 37 °C. Then 0.2 ml of saturated solution was withdrawn and vigorously mixed with 5 ml of 0.01 N HCl. After separating aqueous phase (5 min, 5000 rpm) and adequately diluting, lidocaine was analyzed by HPLC.

Lidocaine solubility in PSA matrix was measured as follows: a known weight of PSA tapes placed in an aluminum pan was measured by differential scanning calorimetry (DSC). Lidocaine solubility was calculated by the relation of the heat of exotherm against the amount of pure lidocaine crystal (see Results).

In Vitro Skin Permeation Procedure A side-by-side diffusion cell set consisting of two half cells⁶⁾ was used for skin permeation of lidocaine from its suspension in water and silicone fluid. Skin membrane was mounted between the two half cells, each 2.70 ml in volume and 0.95 cm^2 in effective diffusion area. The receiver cell was filled with 2.70 ml of distilled water and the donor compartment with

the same volume of drug suspension. Concentration of the drug suspension was 3 to 5-fold its solubility. Both donor and receiver compartment were stirred with a star-head bar driven by a constant-speed synchronous motor (MC-301, Scinics, Tokyo) at about 1200 rpm. The permeation study was conducted at 37 °C. The receiver solution was withdrawn at predetermined times and analyzed by HPLC, and the same volume of distilled water was added to the cell to keep the volume constant.

Each half cell of the side-by-side diffusion cell set as above was used for the skin permeation experiment of lidocaine from PSA tapes. Skin membrane was mounted on the half cell, and a round piece of lidocaine tape (diameter = 1.0 cm) was intimately contact on the skin. Distilled water (2.7 ml) was added to the cell and the experiment was started. Detail procedures were the same as above.

Effect of Skin Surface Lipid on the Dissolution of Lidocaine in PSA Tape Figure 1 shows a diagram of this experimental procedure. A round piece (diameter = 2.0 cm) of lidocaine free PSA tape (F) was first applied on the abdominal skin of hairless rat for 5 h to extract some lipid (L) from the skin surface (Fig. 1a). The resulting tape containing skin lipid (L-F) was then adhered to 50% lidocaine PSA tape (D) of the same size, and the layered tape (D-L-F) was maintained at 37 °C for 48 h. The amount of lidocaine crystal in this layered tape was measured by DSC (Fig. 1b) and the ratio of the crystal against the initial value in the 50% lidocaine PSA tape (Fig. 1d) was calculated. The same size of lidocaine free PSA tape (F) was adhered to 50% lidocaine tape (D) to make another layered tape without skin lipid (D-F) and the ratio of crystal was measured (Fig. 1c) in the same way for comparison. This control was an index for the dissolution of lidocaine crystal by PSA matrix alone.

HPLC Analysis⁷⁾ Lidocaine was determined by HPLC which consisted of a pump (LC-6A, Shimadzu, Kyoto, Japan), an ultraviolet detector (SPD-6A, Shimadzu), a 4.6 mm × 250 mm stainless-steel column packed with Nucleosil 5C18 (Macherey Nagel, Germany) and an integrator (C-R6A, Shimadzu). The mobile phase was 35:65 of acetonitrile: 0.1% phosphoric acid containing 5 mM sodium 1-hexanesulfonate, and the flow rate was 1.0 ml/min. Detection was by UV absorbance at 230 nm, and ethyl *p*-hydroxybenzoate was used as an internal standard in acetonitrile.

DSC Analysis DSC measurement was performed on a Rigaku TAS-200 (Tokyo) using a sample pan made of aluminum. The temperature range was 25 to 100 °C and heating rate was adjusted to 5 °C/min. Samples kept at room temperature and 37 °C for at least 72 h were used.

RESULTS

Among PSA tapes containing 10, 20, 30, 40, 50 and 60% lidocaine, only 10 and 20% tapes were transparent with a light yellow color, and lidocaine crystal began to appear in the 30% lidocaine tape. The higher lidocaine concentrations showed weaker adhesive property. Since there was little or no effect of the adhesive property on the *in vitro* skin permeation procedure, the following experiments

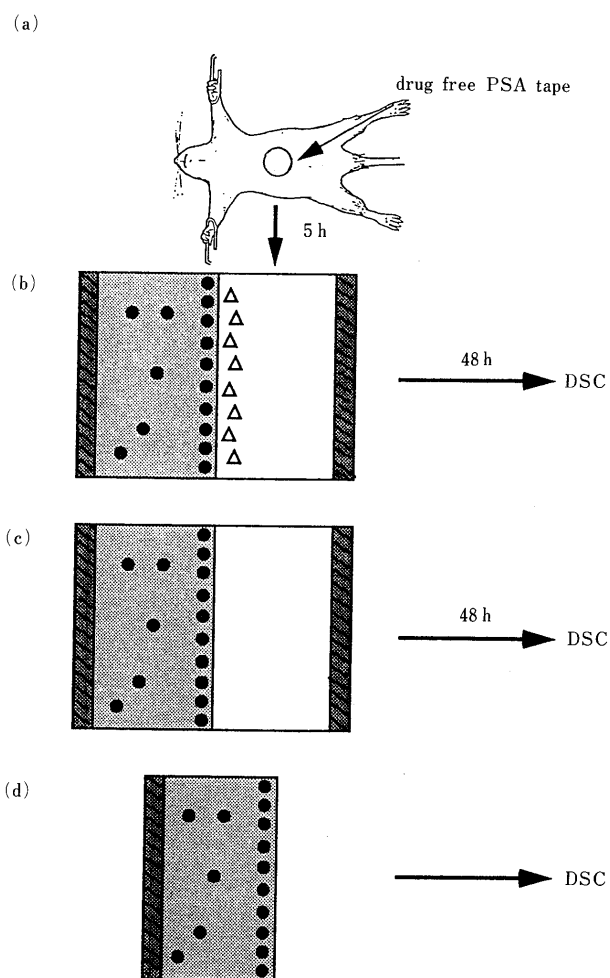


Fig. 1. Schematic Diagram of Experimental Design and Process

■, backing; □, PSA matrix with drug (D); □, PSA matrix without drug (F); ●, drug crystal; △, skin lipid (L).

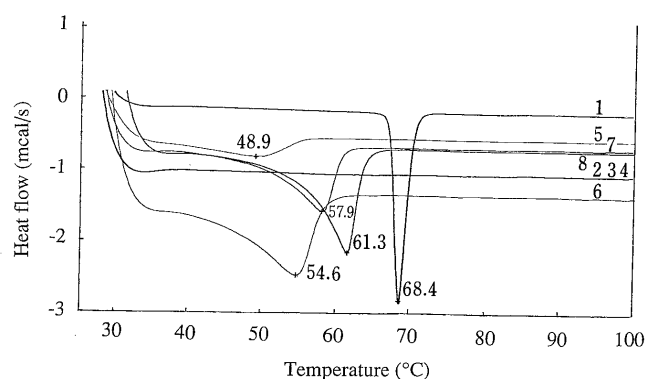


Fig. 2. DSC Thermograms of Pure Lidocaine and 0 to 60% Lidocaine PSA Tapes

All samples were kept at room temperature before DSC measurement. 1, pure lidocaine crystal; 2, 0% lidocaine PSA tape; 3, 10% lidocaine PSA tape; 4, 20% lidocaine PSA tape; 5, 30% lidocaine PSA tape; 6, 40% lidocaine PSA tape; 7, 50% lidocaine PSA tape; 8, 60% lidocaine PSA tape.

were done without modification of the tape preparation.

Figure 2 shows a DSC thermogram of pure lidocaine crystal and 0 to 60% lidocaine PSA tapes; (these samples were stored at room temperature for 72 h before DSC measurement). The exothermic peak was found due to the presence of the crystal in the tapes, except for the 10 and

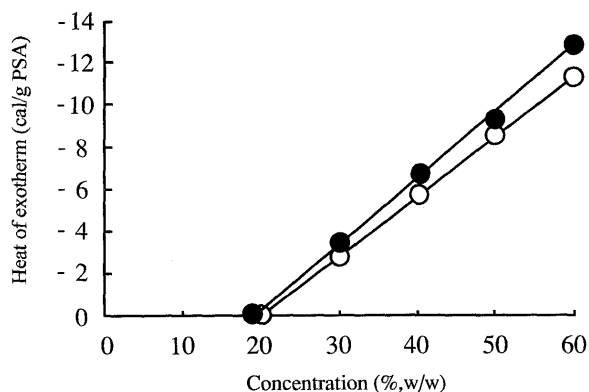


Fig. 3. Relation between the Heat of Exotherm and the Lidocaine Concentration in PSA Tape

○, room temperature; ●, 37°C before DSC measurement.

20% tapes, which were similar to those of PSA matrices without the drug (0% lidocaine tape). In the 30 to 60% lidocaine PSA tapes, the higher drug concentration showed higher exothermic transition per unit weight of tapes, which suggests that the amount of drug crystal increased with increase of the drug concentration.

Figure 3 shows the relationship between the heat of exotherm and the concentration of lidocaine in PSA tape. Data are for two kinds of sample which was kept at room temperature and 37°C for 72 h. A good linearity was found for both cases (regression coefficient > 0.99). The x-axis intercept should be the solubility or saturated concentration (19.96 and 18.65% at room temperature and 37°C, respectively) of lidocaine in the tape. Such an unusual result that the solubility of lidocaine in the PSA tape decreased as the temperature increases is similar to that in water.⁸⁾ Lidocaine crystal appeared in the PSA tape when the drug concentration was beyond this concentration. The solubilities of lidocaine in water and silicone fluid were 3.91 and 21.9 mg/ml at 37°C, respectively, so in PSA the solubility was, respectively, about 40 and 10 times higher.

The time courses of the cumulative amount of lidocaine permeated through the excised skin from PSA tapes with different concentrations of lidocaine are shown in Fig. 4. Permeation increased with increase of the drug concentration up to 40% in PSA tape, but little change in permeation was found with more than 40% lidocaine especially up to 12 h. It is very interesting that permeations from 20 and 30% tapes were lower than those from 40 to 60% tapes, although each tape was saturated at the beginning of the permeation experiment. From a thermodynamic point of view skin permeation rate of a drug is dependent on its thermodynamic activity and that rate becomes maximum when a saturated solution is administered.^{9,10)}

Figure 5 illustrates the time course of the cumulative amount of lidocaine permeated through skin from a water or silicone fluid suspension. The result of 40% lidocaine PSA tape is shown for comparison for each skin permeation profile from 0 to 12 h. The three curves are very similar; the skin permeation rates were 92, 120 and 105 $\mu\text{g}/\text{cm}^2 \cdot \text{h}$ for water and silicone fluid suspension and 40% PSA tape, respectively. This phenomenon obeyed T. Higuchi's theory that the skin permeation rate from

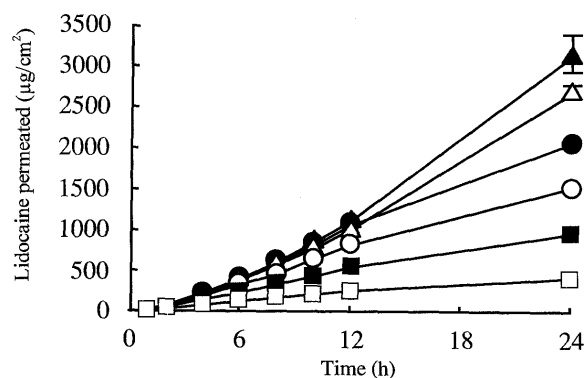


Fig. 4. Time Course of the Cumulative Amount of Lidocaine Permeated through Hairless Rat Skin from 10 to 60% Lidocaine PSA Tapes

□, 10%; ■, 20%; ○, 30%; ●, 40%; △, 50%; ▲, 60% lidocaine PSA tape. Each point represents the mean \pm S.E. of at least three experiments.

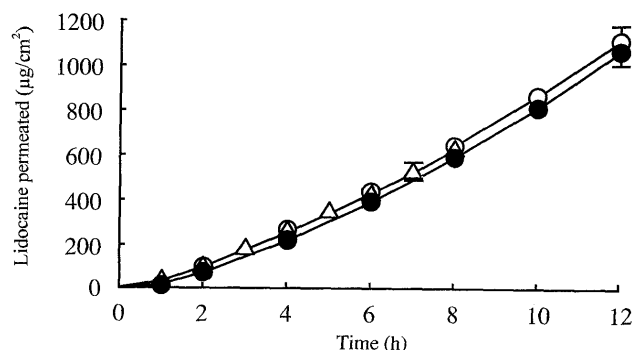


Fig. 5. Time Course of the Cumulative Amount of Lidocaine Permeated through Hairless Rat Skin from Water and Silicone Fluid Suspensions and 40% Lidocaine PSA Tape

△, water suspension; ○, silicone fluid suspension; ●, 40% lidocaine PSA tape. Each point represents the mean \pm S.E. of at least three experiments.

drug suspensions is independent of the vehicle.⁹⁾

Figure 6 shows the relationship between the pseudo steady state flux (average for 4–12 h) of lidocaine and its concentration in water and in PSA tapes. In PSA tape (Fig. 6b) a good positive linearity was found (regression coefficient, 0.9991) when the concentration was below 40%. The highest steady-state rate (plateau level, 105, 101 and 112 $\mu\text{g}/\text{cm}^2 \cdot \text{h}$ for 40, 50 and 60% PSA tape, respectively) of lidocaine was obtained above a drug concentration of 40%. A similar curve was obtained from aqueous solution and suspensions (Fig. 6a). The plateau level (119 and 92 $\mu\text{g}/\text{cm}^2 \cdot \text{h}$ for 0.8 and 2.0% aqueous suspensions) was very close to that of PSA tapes.

To clarify why the flux was maximum at more than 40% lidocaine tape (not 20%) although the saturated concentration of lidocaine in PSA matrix was about 20%, the effect of skin surface lipid on the skin permeation was investigated by the method shown in Fig. 1. Table I shows the results. D1 to D6 (see Fig. 1d for the experimental method and Table I for detail results) indicate 50% lidocaine PSA tape. The amount of lidocaine crystal in each tape was calculated by its exothermic transition. D1-F1 to D3-F3 (Fig. 1c and Table I) represent 50% lidocaine tape layered with skin lipid free tape. Lidocaine PSA tape was adhered to drug free tape for 48 h at 37°C.

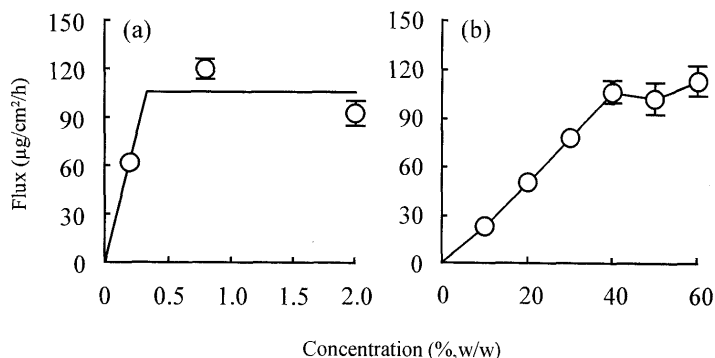


Fig. 6. Effect of Lidocaine Concentration on Steady-State Rate of Skin Permeation from (a) Water and (b) PSA Tapes
Each point represents the mean \pm S.E. of at least three experiments.

TABLE I. Effect of Skin Surface Lipid on the Behavior of Lidocaine Crystal in 50% Lidocaine PSA Tape

	Weight (mg)	cal/g	Crystal amount		Weight (mg)	cal/g	Crystal amount (mg)	Decreasing ratio of crystal (%)	Mean (%)	S.E. (%)
D1 ^{a)}	61.5		5.5136	D1-F1 ^{b)}	78.2	-1.643	4.9225	10.72		
D2	61.9		5.5494	D2-F2	79.3	-1.667	5.0647	8.73	11.40	1.45
D3	57.2		5.1281	D3-F3	71.0	-1.607	4.3714	14.76		
		-2.340								
D4	60.1		5.3881	D4-L-F4 ^{c)}	80.9	-1.195	3.7039	31.26		
D5	59.6		5.3432	D5-L-F5	80.4	-1.009	3.1081	41.83	35.61	2.61
D6	60.2		5.3970	D6-L-F6	80.6	-1.158	3.5759	33.74		

a) D1 to D6 represent 50% lidocaine PSA tape. b) D1-F1 to D3-F3 represent the layered tape of 50% lidocaine PSA tape on drug-free PSA tape. c) D4-L-F4 to D6-L-F6 represent the layered tape of 50% lidocaine PSA tape on drug-free PSA tape containing skin surface lipid.

Comparing the crystal amount in each piece of 50% lidocaine PSA tape with its layered tape, the average rate of decrease of lidocaine crystal due to migration of lidocaine molecules from the 50% tape to the drug free tape was calculated to be 11.4%.

D4-L-F4 to D6-L-F6 (Fig. 1b and Table I) show 50% lidocaine tape layered with PSA tape with skin surface lipid. The lipid was extracted by applying the drug free tape to the hairless rat skin for 5 h. The easy extraction was due to high affinity of the PSA matrix to skin lipid. Comparing the crystal amount in each piece of layered tape, the amount of drug crystal was remarkably decreased and the average rate of decrease was 35.6%. Migration of the drug from 50% lidocaine tape to drug free tape as well as dissolution of the drug crystal in PSA tape by skin surface lipid was the reason for this decrease in the drug crystal in D4-L-F4 to D6-L-F4. The difference between 11.4 and 35.6% (-24.2%) would be the contribution of skin surface lipid. It is suggested from these results that the skin surface lipid dissolves the lidocaine crystal or solid in PSA tape, and this effect may account for why 40% lidocaine tape rather than 20 or 30% showed the highest flux.

DISCUSSION

It is of great interest that the highest steady-state flux of lidocaine skin permeation was obtained from the PSA tape containing more than 40% lidocaine (Fig. 6b) although its saturated concentration was about 20% in this tape (Fig. 3), and a good linearity was also found between the

flux and lidocaine concentration over 0 to 40% of its concentration. To understand what happened after application of lidocaine PSA tape on the skin, the amount of lidocaine in tape and permeated through skin was determined. We noted the skin permeation data for 0 to 12 h obtained by sampling at frequent intervals, so the pseudo steady-state flux was calculated for 4–12 h; (the period 0–4 h was assumed to be a lag time).

Lidocaine was just saturated at about 20% in the PSA tape (1121 µg/cm²). As soon as it was released and penetrated the skin from the 20% PSA tape, its concentration became less than saturation in the PSA tape, e.g. lidocaine concentration changed from 20 to 18% in the PSA matrix over the first 4 h. The skin permeation rate from the 20% tape thus was not the maximum value. In the 40 to 60% lidocaine PSA tapes (with lidocaine of 2613 to 5197 µg/cm²), a great deal of the compound (1059 to 1109 µg/cm²) was permeated through skin over 12 h. The amount remaining in the tape was above solubility in the PSA tapes at 12 h. The skin permeation rate from these tapes thus should be kept at maximum. The skin permeation curves, especially those from 4 to 12 h, were very similar to each other as shown in Fig. 4, and skin permeation reached a plateau (Fig. 6). These data were similar to those of lidocaine suspension in water and silicone fluid (Fig. 5). The above phenomenon can be explained very well by T. Higuchi's theory that the skin permeation rate from drug suspensions becomes maximum independent of the vehicles. From a thermodynamic point of view, the activity of a drug is the same in various suspensions to the neat drug crystal, and that of the drug

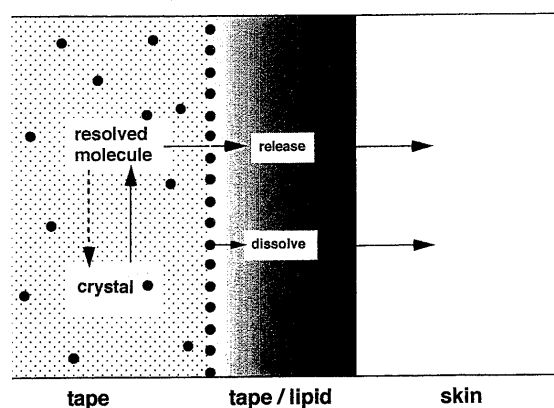


Fig. 7. Schematic Diagram of Lipid on the Skin Surface and Its Effect on the Skin Permeation of Lidocaine

in a solution under saturation will be lower.

In the 30% lidocaine PSA tape, lidocaine was saturated ($1872 \mu\text{g}/\text{cm}^2$) and the skin permeation rate should be similar to those of 40 to 60% lidocaine PSA tapes at least prior to 10 h, because its concentration should still be over the solubility. The skin permeation rate of lidocaine, however, was lower than the maximum. T. Higuchi's theory does not directly explain this result. We then focused on the role of skin surface lipid. Skin possesses sebaceous glands that secrete a mixture of lipid which forms an irregular $0.4\text{--}4 \mu\text{m}$ thick film on the skin surface.¹¹⁻¹⁴ We designed the experiment shown in Fig. 1 to learn the effect of skin surface lipid. Our result proved that the lipid layer between the skin surface and PSA tape dissolved lidocaine crystal from tape (Table I).

If there is a lipid layer between the PSA tape and the skin surface, the drug must enter the lipid layer from the tape first before permeating the actual skin. A drug has its own solubility in the lipid layer and the skin permeation rate will be highest if the drug concentration maintains a saturated state. Even if the drug is initially saturated in the PSA matrix, it may migrate to the lipid layer and both PSA matrix and lipid layer may become under saturation. This can explain the results for the 30% tape in the present experiments. The same kind of effect by skin surface lipid must take place in each tape. A good positive linearity both for the cumulative amount over a certain period (e.g., amounts of lidocaine permeated were about 210, 430 and $640 \mu\text{g}/\text{cm}^2$ for 10, 20 and 30% lidocaine tapes, respectively, over 10 h) and the pseudo steady state flux (about 22, 49 and $77 \mu\text{g}/\text{cm}^2 \cdot \text{h}$ for the same tapes) supports the above explanation. In the PSA tapes containing lidocaine beyond 40%, however, the drug in the lipid layer was saturated throughout the permeation experiments over 24 h. In other words, the question of whether the drug is saturated or not in the lipid layer is dependent upon the degree of saturation in the PSA tape. A similar explanation can be used for skin permeation of lidocaine from water or silicone fluid suspension.

To explain the behavior of lidocaine crystal and the

relationship among PSA tape, lipid layer and actual skin, we simplified the problem as shown in the schematic diagram in Fig. 7. When applying a saturated lidocaine PSA tape on the skin, some skin surface lipid may be extracted into the PSA matrix. Although the borderline is unclear excess lipid still exists between the skin surface and the tape. Lidocaine crystal on the surface of PSA tape, in contrast, first dissolves and migrates from the tape to the lipid layer, and permeates through the actual skin. In the interior of the lidocaine PSA tape, a part of the lidocaine molecules dissolved may be released into the lipid layer, and a part of the lidocaine crystal may be dissolved in the PSA matrix to maintain the dissolution balance of lidocaine.

It is difficult, however, to dynamically follow the effect of skin surface lipid on the dissolution of lidocaine in PSA tape on skin *in vivo*, since lidocaine moves from the formulation to skin and skin lipid may migrate oppositely at the same time and dynamically. Direct evidence will be needed to fully understand this phenomenon.

CONCLUSION

Lidocaine PSA tape may be a potential candidate for topical skin anesthesia. The highest steady-state flux was found at 40% lidocaine PSA tape, not at the saturated concentration (20%) of the compound in tape. T. Higuchi's theory can explain most data except for the phenomenon of 30% lidocaine PSA tape. A skin surface lipid layer may exist which dissolves the lidocaine crystal, and this could explain all the *in vitro* skin permeation data in these experiments.

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