Relationship between the Transference of a Drug from a Transdermal Patch and the Physicochemical Properties

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The transferred percentages of 13 drugs to rat skin from transdermal patches were studied to reveal the relationship to their physicochemical properties. The drugs to be tested had melting points of 13.5—234 °C, lipophilic indices of 0.475—5.336, and molecular weights of 122.12—392.45. The transferred percentage of drug to intact skin was lower, the higher the melting point, lipophilic index and molecular weight. The same was true in stripped skin, where the transferred percentage of drug was markedly increased. The difference between transferred drug percentages to stripped and intact skin, which could be regarded as the regulatory contribution of the stratum corneum, tended to be larger, the lower the drug's melting point and lipophilic index.

Keywords transdermal patch; drug transference; melting point; lipophilic index; molecular weight; stripping; stratum corneum

Various transdermal therapeutic systems (TTS) are presently being developed for nitroglycerin, estradiol, isosorbide dinitrate, *etc.* and are currently on the market.[1] The transdermal devices are classified into three groups: (1) reservoir devices, (2) monolithic devices, (3) multi-laminated devices.[2] Transdermal patch is a monolithic device. The patch is comprised of an adhesive matrix containing the drugs, a backing sheet, and a release liner sheet. The release liner sheet is removed when the transdermal patch is applied. The adhesive matrix sticks to the skin and releases the drug. The transdermal patch is a superior device from a manufacturing viewpoint because of its simple form.

It is commonly accepted that the main regulation site of transdermal absorption is not the device but the skin, especially the stratum corneum. Tojo *et al.* reported that the rates of nitroglycerin penetration through skin from various transdermal devices were much lower than the rates of release from the device, and the skin penetration profiles were almost independent of the device structure.[3]

In this study, the stratum corneum's regulation of various drug transference to skin in the case of transdermal patch application was investigated, with the stratum corneum's regulatory contribution being indicated by the difference between the transferred percentages of the drug to stripped and intact skin.

Experimental

Chemicals Nicotinamide (NAM, >98% purity), benzoic acid (BA, 100.3%), salicylamide (SAM, 99.4%), hydrocortisone (HC, 101.8%), ibuprofen (IP, 100.2%), betamethasone (BM, 99.7%), butylparaben (BP, >98%), indomethacin (IM, 99.6%), progesterone (PR, 100.0%) and testosterone propionate (TP, 99.9%) were purchased from Wako Pure Chemical Industries (Osaka, Japan). Methocarbamol (MC, >99%) and isosorbide dinitrate (IS, contains 60% lactose) were purchased from Sigma Chemical Company (U.S.A.). Isosorbide dinitrate was obtained by extraction with ethylacetate, removing lactose by filtration and the solvent by evaporation. Nitroglycerin (GTN) was provided as a 10% solution in ethylacetate by the development section of Sekisui Chemical Co. (Osaka). Other chemicals were of reagent grade. All chemicals and solvents were used without further purification.

Adhesive Copolymer of 2-ethylhexylacrylate and vinylpyrrolidone was used for the adhesive base. It was provided as a 35% solution in ethylacetate by the development section of Sekisui Chemical Co.

Preparation of Transdermal Patches Each drug except for GTN was dissolved in a proper solvent: ethylacetate for IS and BP, ethanol for NAM, and tetrahydrofuran for the others. Concentrations of the solution were 3—30%. The drug solution was mixed with an adhesive solution by use of a Homo disper (Tokushu Kika Kogyo, Osaka). The mixture solution was coated on the release liner sheet (silicon-coated polyethyleneterephthalate (PET) sheet, 38 μm thickness, Fujimori Kogyo, Osaka) and dried at 60 °C for 30 min in a Safety oven (Tabai Espec, Osaka). The thickness of the dried adhesive layer including the drug was about 80 μm. To prepare the transdermal patch, the backing sheet (PET of 6 μm thickness, laminated with ethylene-vinylacetate copolymer of 25 μm thickness) was laminated so as to contact the adhesive layer on the PET side.

The concentration of drug in the transdermal patch was determined by the following equation:

$$\text{conc. of drug}(\%) = 100 \cdot \text{amount of drug (g)} / (\text{amount of drug (g)} + \text{nonvolatile component of adhesive (g)})$$

***In Vivo* Application of Patches** The back hair of a male rat (Wistar strain, 6—7 weeks old, Nippon SLC, Shizuoka, Japan) was removed with clippers and an electrical shaver on the day before the experiment. A circular patch 20 mm in diameter (3.14 cm^2) was applied to the intact or stripped back skin of a rat which had been anesthetized by ethyl ether. The area applied with the patch was then covered with gauze fixed by Silky Tex (Tokyo Eizai, Tokyo, Japan), and the rat was allowed to take food and water. After a 24-h application, the patch was taken off and the amount of drug remaining in the patch was measured as described later.

The amount transferred from the patch to the skin was obtained from difference between the dose and the amount of remainder. The dose was calculated from the concentration of the drug in the transdermal patch and the weight of the adhesive layer of the applied patch.

Determination of Drug Amount in Transdermal Patch Each 20 mm diameter transdermal patch was extracted with 50 ml methanol for 24 h. The extraction was analyzed by a high-performance liquid chromatograph (HPLC, LC-6A, Shimadzu, Kyoto) equipped with a UV spectrophotometric detector (SPD-6AV, Shimadzu), an auto injector (SIL-6A, Shimadzu), a column oven (CTO-6A, Shimadzu) and a system controller (SCL-6A, Shimadzu). A column filled with Nucleosil 5C18 (4.6 mm i.d. and 150 mm length, NC packed column, Nippon Kuromato Kogyo, Tokyo) was used in a reversed phase.

HPLC was operated at a column temperature of 40 °C and a flow rate of 0.9—1.0 ml/min. The wavelength of detection and mobile phase for each drug was as follows: 262 nm and 50 mM K_2HPO_4 (pH 7.5 adjusted with H_3PO_4) : methanol = 95 : 5 (v/v) for NAM, 227 nm and 50 mM KH_2PO_4 (pH 2 adjusted with H_3PO_4) : methanol = 60 : 40 (v/v) for BA, 302 nm and water : methanol = 70 : 30 (v/v) for SAM, 274 nm and water : methanol = 60 : 40 (v/v) for MC, 220 nm and water : methanol = 50 : 50 (v/v) for IS, 350 nm and water : acetonitrile : acetic acid = 48 : 48 : 4 (v/v/v) for PX, 220 nm and water : methanol = 60 : 40 (v/v) for GTN, 240 nm and water : methanol = 50 : 50 (v/v) for HC, 220 nm and 50 mM KH_2PO_4 (pH 2 adjusted with H_3PO_4) : methanol = 40 : 60 (v/v) for IP, 240 nm and water : methanol = 40 : 60 (v/v) for BM, 254 nm and water : methanol = 40 : 60 (v/v) for BP, 254 nm 0.1% H_3PO_4 : methanol = 30 : 70 (v/v) for IM, 280 nm and water : methanol = 42 : 58 (v/v) for ES, 240 nm and water : methanol = 30 : 70 (v/v) for PR and TP, respectively. The retention time was between 5 and 20 min.

Solubility of Drug in the Patch The solubility of isosorbide dinitrate (IS) in the patch was determined as follows. The patch (30% IS) in which an IS crystal was observed microscopically was stuck on one side of a

silicone rubber membrane (Silastic 500-3, Dow Corning, U.S.A.). The other side of the membrane was stuck on a patch (15% IS) in which the crystal was not observed. After two weeks of preservation at room temperature, the IS concentration in the patch in which the crystal was not observed was measured.

For other drugs, although the solubilities in the patches were not measured, patches of 2.5, 5, 10, 15, 20% concentration were prepared and the maximum concentration patch in which the crystal was not observed after two weeks preservation at room temperature was used. For the GTN patch, as an exception the maximum concentration was determined by adhesiveness because GTN is liquid at room temperature. The values of drug concentrations in the patches used for this experiment are shown in Table I.

Determination of Lipophilic Index of Drug The lipophilic index was determined in a reverse phase of HPLC[4] as described previously. A mixture of water (30—90%) and methanol (70—10%) was used as the mobile phase. Nucleosil 5C18 was used as the stationary phase, which was packed into a column 4.6 mm i.d. and 150 mm length (NC packed column). A mixture of about 100 μg/ml of the drug and 250 μg/ml formamide in methanol was injected in HPLC, which was operated at a column temperature of 40 °C and a flow rate of 1.0 ml/min, and was detected at a wavelength of 220 nm. The retention times of formamide (t_0) and the drug (t_R) were determined at various water/methanol ratios of the mobile phase.

The log k' value is defined by the following equation:

$$\log k' = \log\{(t_R - t_0)/t_0\}$$

When log k' values obtained for a drug were plotted against methanol concentrations in the mobile phase, they approximated a straight line. The extrapolated log k' value to 0% methanol was obtained by the least squares method, and it was employed as the lipophilic index ($\log k'_0$) of the drug.

Results and Discussion

Relation between Drug Concentration in Adhesive and the Transferred Percentage of Drug from Patch to the Skin The percentage of IS transferred in 24 h from transdermal patches which contained 15% and 3% IS is plotted in Fig. 1 as a function of the number of strippings. Through microscopic examination it was observed that 16 strippings completely removed all layers of the stratum corneum of rat skin. The transferred percentages of IS from both transdermal patches increased with the number of strippings in a similar manner.

This suggests that the concentration of drug does not have any effect on the transferred percentage as far as the solution system is used, because in this experiment the solubility of isosorbide dinitrate is about 16%. Then, transdermal patches containing drugs at the concentrations under solubilities were subjected to the following experiment, and the percentages transferred to the skin were estimated 24 h after application of the patches.

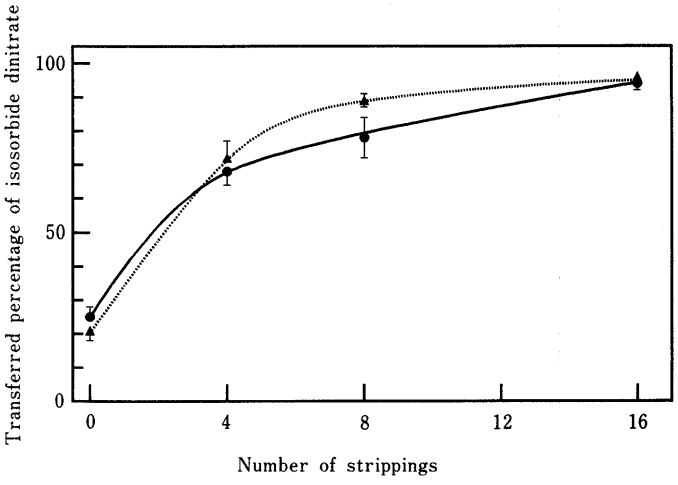

Fig. 1. Effect of the Concentration of IS in the Adhesive on Its Transferred Percentage to Stripped Skin

—●—, 15%; ---▲---, 3%. Plots and bars show the mean and S.E. ($n=4$).

Transferred Percentages of Various Drugs from Patches to the Skin Drugs were used in this experiment with appropriate concentrations and doses, as shown in Table I. The results are shown in Table II. The transferred percentage of each drug increased with variation by stripping. Some drugs showed nearly 100% transference to stripped skin while some showed about 20%, suggesting that the regulation of transference by the stratum corneum was different among drugs.

Difference between Transferred Percentages of Drug to Stripped and Intact Skins, and Its Physicochemical Properties The melting points, the lipophilic indices and the molecular weights of the drugs, as listed in Table III, were introduced to define a relationship between the regulation property of the stratum corneum and the physicochemical properties of drugs. As the melting point is closely related to the intermolecular cohesiveness of the material, it can reflect on the drug's skin permeability.[5] On the other hand, the lipophilicity of a drug was reported to have an effect on its skin permeability,[6-9] and the molecular weight of a material is known to be related to its dif-

Table I. Drug Concentrations in Patches and Doses

Drug (abbr.)	Conc. (%)	Dose (mg/cm^2)
Nicotinamide (NAM)	2.5	0.19
Benzoic acid (BA)	10.0	0.85
Salicylamide (SAM)	10.0	0.82
Methocarbamol (MC)	5.0	0.41
Isosorbide dinitrate (IS)	15.0	1.47
Nitroglycerin (GTN)	18.0	1.06
Hydrocortisone (HC)	2.5	0.20
Ibuprofen (IP)	10.0	0.80
Betamethasone (BM)	2.5	0.23
Butylparaben (BP)	15.0	1.26
Indomethacin (IM)	15.0	1.52
Progesterone (PR)	5.0	0.37
Testosterone propionate (TP)	5.0	0.45

Table II. Transferred Percentages of Drugs to Intact and Stripped Skin, and Their Differences

Drug	Transferred percentage[a]		ΔT (%)[b]
	Intact skin	Stripped skin	
NAM	24.0±3.5	100.0±0.0	76.0
BA	46.1±4.2	99.8±0.1	53.7
SAM	17.7±2.3	98.6±0.6	80.9
MC	2.5±1.0	93.3±1.8	90.8
IS	24.8±3.0	94.3±2.0	69.5
GTN	23.1±3.4	89.1±4.4	66.0
HC	2.2±0.5	38.8±2.0	36.6
IP	5.0±1.2	86.5±2.9	81.5
BM	2.3±0.5	16.9±0.3	14.6
BP	4.3±0.2	40.3±2.3	36.0
IM	0.9±0.2	48.7±2.9	47.8
PR	5.5±0.8	62.5±1.8	57.0
TP	3.8±1.0	25.7±1.4	21.9

a) Each value shows the mean±S.E. ($n=4$). b) Difference between transferred drug percentages to stripped and intact skin.

Table III. Physicochemical Properties of Drugs

Drug	mp (°C)[a]	$\log k'_0$[b]	MW[a]
NAM	131.0	0.48	122.12
BA	122.4	1.04	122.12
SAM	140.0	1.16	137.13
MC	94.0	1.54	241.24
IS	70.0	1.55	236.14
GTN	13.5	1.93	227.09
HC	213.0	2.78	362.47
IP	77.0	3.07	206.27
BM	234.0	3.29	392.45
BP	69.0	3.35	194.22
IM	162.0	3.46	357.81
PR	131.0	4.17	314.45
TP	122.0	5.34	344.48

a) The values of mp (melting point) and MW (molecular weight) were taken from the Merck Index. *b*) $\log k'_0$ (lipophilic index) was measured by the method described in the Experimental section.

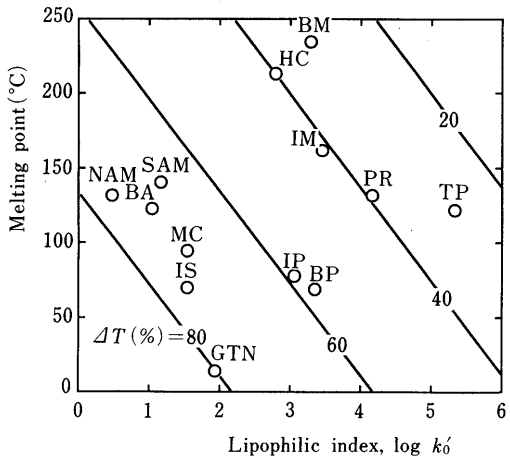

Fig. 2. Two-Dimensional Drug Map and Contours of the Difference between Transferred Percentages of Drugs to Stripped and Intact Skin

Solid lines indicate ΔT (%) calculated from Eq. 4. Plots indicate drugs' location determined by melting points and lipophilic indices.

fusion coefficient.

Next, multiple regression analysis was carried out in a model that had the three parameters mentioned above as independent variables and the transferred drug percentage as a dependent variable. The results were derived from the following Eqs. 1 and 2.

$$T(\%)_{\text{intact skin}} = 37.5 - 0.0059\,\text{mp} - 3.56\log k'_0 - 0.061\,\text{MW} \quad (1)$$
$$r = 0.746$$

$$T(\%)_{\text{stripped skin}} = 139.4 - 0.16\,\text{mp} - 13.15\log k'_0 - 0.069\,\text{MW} \quad (2)$$
$$r = 0.910^*$$

where $T(\%)_{\text{intact skin}}$ or $T(\%)_{\text{stripped skin}}$ show transferred drug percentages to intact skin or stripped (16 times) skin respectively, mp is the melting point (°C), $\log k'_0$ is the lipophilic index, MW is molecular weight and r is the multiple correlation coefficient of which superscript * means that the regression is significant at $p < 0.01$. Equations 1 and 2 indicated that the transferred percentages of drug to the skin tended to be lower, the higher the melting point, lipophilic index and molecular weight.

To consider the regulation property of the stratum corneum, Eq. 3 was obtained by subtracting Eq. 1 from Eq. 2. The difference between the transferred percentages of the drug to stripped and intact skin could be regarded as the regulatory contribution of the stratum corneum.

$$\Delta T(\%) = 101.9 - 0.15\,\text{mp} - 9.95\log k'_0 - 0.008\,\text{MW} \quad (3)$$

where $\Delta T(\%)$ is the difference between transferred percentages of the drug to stripped and intact skin. Equation 3 suggests that molecular weight made little contribution to $\Delta T(\%)$ for the drugs with molecular weights of 122.12—392.45 used in this study.

Next, multiple regression analysis was again carried out, assigning independent variables to the melting point and lipophilic index, and a dependent variable to the difference between transferred percentages of the drug to stripped and intact skin. Equation 4 was formed as a result.

$$\Delta T(\%) = 101.5 - 0.16\,\text{mp} - 9.94\log k'_0 \qquad r = 0.772^* \quad (4)$$

where superscript * of r value means the regression is significant at $p < 0.05$. Equation 4 is shown as contour lines in the two-dimensional drug map (Fig. 2). From these results, it was suggested that the regulatory contribution of the stratum corneum against transference to skin tended to be larger, the lower the melting point and the lipophilic index. This finding might be helpful in the search for drug enhancers, as the regulatory contribution of the stratum corneum could be estimated from the drug's melting point and lipophilic index.

Conclusions

The difference between transferred percentages of drug of stripped and intact skin, which could be regarded as the regulatory contribution of the stratum corneum, tended to be larger, the lower the melting point and lipophilic index of the drug. This finding might be helpful in the search for drug enhancers.

References and Notes

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