Skin Permeability of Water-Soluble Drugs[1)]

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The permeabilities of several water-soluble drugs through excised hairless rat skin from their aqueous suspensions were investigated by using newly designed two-chamber diffusion cells. Disodium cromoglycate, diclofenac sodium, dopamine hydrochloride, isoproterenol hydrochloride, diltiazem hydrochloride and papaverine hydrochloride were selected as water-soluble drugs. Indomethacin, a lipophilic drug, and deuterium oxide (D_2O) were used for comparison. The skin permeability coefficients of these water-soluble drugs were 100—10000 times lower than that of indomethacin. Since these drugs have high solubility in the donor solution (distilled water or lactate buffer), however, the skin permeation rates, which are in general proportional to the product of skin permeability coefficient and solubility of drugs in the drug-donor compartment, were comparable to or higher than that of indomethacin (1.7 $\mu g/cm^2/h$): the skin permeation rate of dopamine hydrochloride (458 $\mu g/cm^2/h$) was about 300 times higher than that of indomethacin. The water-soluble drugs with lower molecular weight and higher solubility in water showed higher skin permeation rates. These results suggest that some water-soluble drugs with low molecular weight and high solubility in water might be good candidates for transdermal drug delivery.

Keywords water-soluble drug; indomethacin; deuterium oxide; skin permeation; excised hairless rat skin

Recently, the use of dermatological preparations has been extended beyond local dermatological treatment to systemic therapy. Lipophilic drugs such as indomethacin (IND), nitroglycerin and isosorbide dinitrate have frequently been used for research on and development of transdermal therapeutic systems (TTS) because of their intrinsic high permeabilities across the skin.[2)] Water-soluble drugs have not generally been administered through the skin, since the skin permeabilities are often low.[3)] However, topical formulation of these drugs has become possible due to the development of strong penetration-enhancing agents such as Azone[4)] and the application of iontophoresis.[5)]

In the present study, the *in vitro* permeation rates of several water-soluble drugs through the excised hairless rat skin were measured by using a newly designed 2-chamber diffusion cell. Disodium cromoglycate (DSCG), diclofenac sodium (DFS), dopamine hydrochloride (DPH), isoproterenol hydrochloride (IPH), diltiazem hydrochloride (DTH) and papaverine hydrochloride (PPH) were selected as model water-soluble drugs (Table I). IND, a lipophilic drug, and deuterium oxide (D_2O) were used for comparison.

Experimental

Materials DSCG, DPH, DTH and PPH were purchased from Sigma Co. (St. Louis, Mo, U.S.A.), Katura Chemical (Tokyo, Japan), Sigma Co. and Wako Pure Chemical Industries (Osaka, Japan), respectively. DFS, IPH and IND were gifts from Hamari Yakuhin Industries (Tokyo), Nikken Chemicals (Tokyo) and Toko Yakuhin Industries (Tokyo), respectively. D_2O (purity 99.8%) was obtained from E. Merck (Darmstadt, West Germany). All other chemicals and solvents were of reagent grade and were used without further purification.

Animals Male hairless rats (WBN/kob strain), weighing approximately 150 g each, were purchased from Saitama Laboratory Animals (Saitama, Japan).

Determination of Solubility and Partition Coefficient For measurement of solubilities of model compounds in water, an excess amount of each compound was added to distilled water (in the case of DSCG, DFS, DTH, PPH and IND) or 0.1 M lactate buffer (pH 4.0) (in the case of DPH and IPH) and incubated over 48 h at 37 °C. The buffer was used to prevent the decomposition of DPH and IPH.[5)] After centrifugation, the concentration of each compound in the supernatant was measured by high performance liquid chromatography (HPLC). The time (48 h) was sufficient for equilibration.

For measurement of the *n*-octanol–water partition coefficients of the compounds, equal volumes (10 ml) of distilled water or lactate buffer and *n*-octanol were added to 10 mg of each drug in a glass-stoppered tube. After equilibration by shaking the mixture for 24 h at room temperature, an aliquot of the *n*-octanol layer was diluted with methanol and 10 μl of this solution was directly injected into the HPLC.

Diffusion Cells A diffusion cell, consisting of two half-cells with a water jacket connected to a water bath at 37 °C was newly developed. Each half cell has a volume of 2.0 ml and an effective diffusional area of 1.13 cm^2 (Fig. 1). A star-head bar was driven in each half cell by a constant-speed

TABLE I. Physicochemical Properties of Water-Soluble Drugs, IND and D_2O

Substance	Molecular weight	Solubility (mg/ml)	log $K^{a)}$
DSCG	512.3	195.30	−3.21
DFS	318.1	32.40	−1.21
DPH	189.6	508.00	−3.37
IPH	247.7	335.06	−2.84
DTH	451.0	557.06	−2.82
PPH	357.8	32.44	−29.4
IND	357.9	0.01	2.99
D_2O	20.0	—	—

a) Partition coefficient (*n*-octanol/water or *n*-octanol/lactate buffer). Values of solubility and log K are the means of 3 measurements.

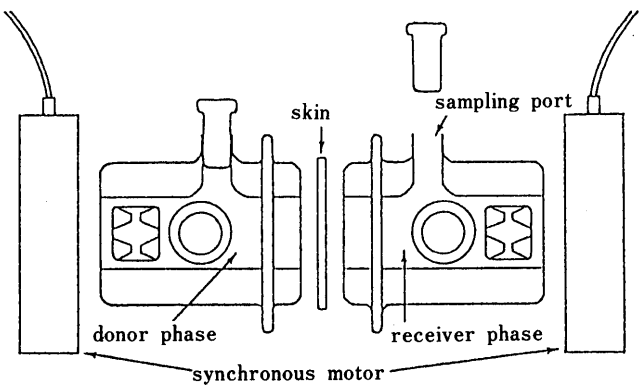

Fig. 1. Schematic Diagram of the Newly Developed 2-Chamber Diffusion Cell Apparatus

synchronous motor (MC-301, Scinics, Tokyo) at about 600 rpm. The diffusion cell is very compact and convenient to measure the skin permeation of drugs.

Skin Membrane Preparation The abdominal region of hairless rats was carefully shaved. About 4 cm^2 (2 cm square) of the left and right abdominal skin was excised and mounted between two half diffusion cells by using a spring clamp.

***In Vitro* Permeation Procedure** The dermis of the skin was in contact with the receiver compartment and the stratum corneum with the donor compartment. The receiver compartment of each cell was filled with 2.0 ml of 0.9% NaCl solution or pH 4.0 lactate buffer and the donor compartment with 2.0 ml of drug suspension (drug amount; about twice the solubility) in distilled water or the same buffer. Initial pHs in the donor compartment were 5.7, 7.7, 3.7, 3.8, 3.3, 3.0 and 4.9 for DSCG, DFS, DPH, IPH, DTH, PPH and IND, respectively, and these values remained almost the same throughout the experiments. D_2O was also used instead of drug suspension. At appropriate times, a 200 μl sample was withdrawn from the receiver compartment and the same volume of fresh buffer was added to keep the volume constant. The skin permeation rate (flux) and permeability coefficient were mainly used to evaluate the skin permeability of drugs.[4c]

Analysis of Drug Concentrations The concentration of drugs was determined by HPLC (LD-6A, Shimadzu, Kyoto, Japan) by using a 4.6 mm × 250 mm stainless steel column packed with Nucleosil $5C_{18}$ (Yamamura Chemical Laboratories, Tokyo). Other conditions are listed in Table II. D_2O was assayed by the method reported previously.[7]

Results and Discussion

Table I shows the molecular weight, solubility in water,

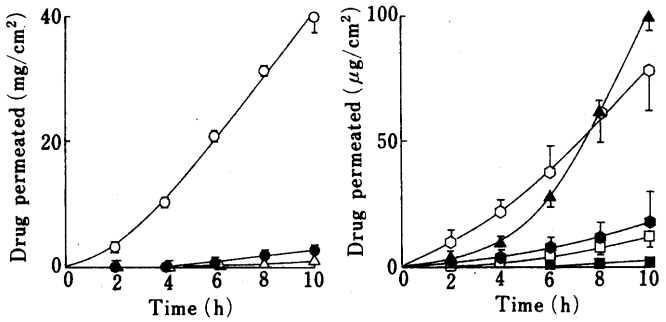

Fig. 2. Skin Permeation Profiles of Several Drugs through Excised Hairless Rat Skin

D_2O (○), DPH (●), IPH (△), DFS (▲), DTH (○), PPH (●), DSCG (□) and IND (■) were used. Each point represents the mean ± S.E. of 3—6 experiments.

TABLE II. HPLC Conditions for the Measurement of Several Drugs

Substance	Wavelength (nm)	Mobile phase	Flow rate (ml/min)	Internal standard
DSCG	254	0.005 M tetrabutyl ammonium hydroxide	0.7	*p*-Oxybutyl benzoate
DFS	278	1% phosphoric acid/methanol (1/99)	1.0	*p*-Oxybutyl benzoate
DPH	280	0.05 M phosphate buffer (pH 2.3)/methanol (97/3)	1.4	Gallic acid
IPH	280	0.05 M phosphate buffer (pH 2.3)/methanol (97/3)	1.4	Gallic acid
DTH	240	0.05 M phosphate buffer (pH 2.3)/acetonitrile (60/40)	1.0	—[a]
PPH	254	0.05 M phosphate buffer (pH 2.3)/acetonitrile (70/30)	1.4	*p*-Oxymethyl benzoate
IND	260	Water/methanol (40/60)	1.0	—[a]

a) Absolute calculation method was used.

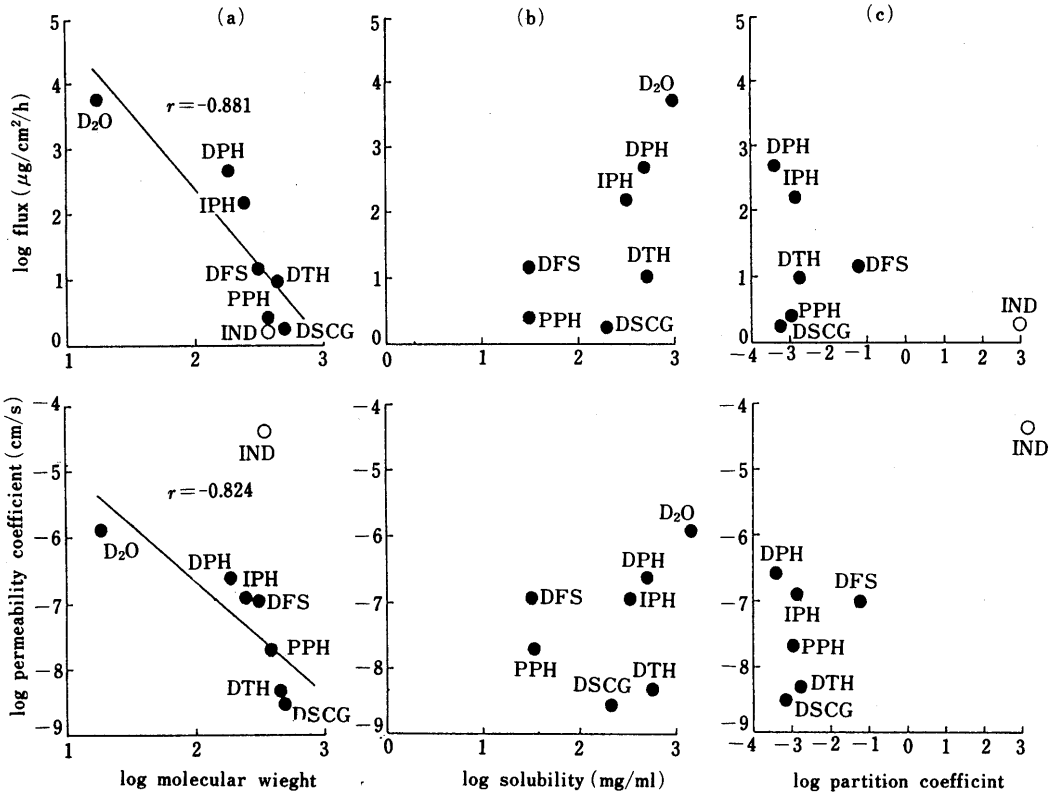

Fig. 3. Relationships between the Skin Permeability and Molecular Weight (a), Solubility (b) and Partition Coefficient (c) of Drugs

Correlation lines were drawn without IND. Each point represents the mean of 3—6 experiments. The S.E. in each case was smaller than the symbol.

and partition coefficient (*n*-octanol/water) of water-soluble drugs used in this experiment. The values for IND and D_2O are also included in the table.

Figure 2 shows the skin permeation profiles of water-soluble drugs, IND and D_2O. The average permeability coefficient was calculated in each case to compare the skin permeability of drugs by dividing the average permeation rate (flux) between 4—10 h by the solubility in water (or lactate buffer).[4b,c] The permeability coefficient of D_2O was calculated by using the flux and its specific gravity (1.10). The skin permeation rate of D_2O was the highest. DPH and IPH showed significantly higher flux than IND. Other water-soluble drugs, DFS, DTH and PPH showed a slightly higher flux than IND. The skin permeation rate of DSCG was lower than that of IND.

As regards the permeability coefficient, IND showed the highest value ($4.27 \pm 2.53 \times 10^{-5}$ cm/s). DPH ($2.51 \pm 0.13 \times 10^{-7}$ cm/s), IPH ($1.24 \pm 0.14 \times 10^{-7}$ cm/s) and DFS ($1.18 \pm 0.13 \times 10^{-7}$ cm/s) have 20—40 times lower permeability coefficient compared to that of IND. The skin permeability coefficient of D_2O ($1.19 \pm 0.08 \times 10^{-6}$ cm/s) was between those of IND and water-soluble drugs. From the relatively high skin permeation of D_2O, water might play a role in the transport of water-soluble drugs. So called "solvent drag" and "convective flow" might operate in the skin permeation of water-soluble drugs from aqueous bases.[7]

Figure 3a shows the relationship between the skin permeability (permeation rate and permeability coefficient) and molecular weight. There were good relationships between log(skin permeation rate) and log(molecular weight) ($r = -0.881$), and log(permeability coefficient) and log (molecular weight) ($r = -0.824$). These results supported Flynn *et al.*'s proposal[8] that membrane permeation rates would be proportional to the cubic or square root of molecular size.

Figure 3b shows the relationship between log(skin permeation rate) and log(solubility of drugs in water or lactate buffer). Although the flux had a tendency to be proportional to the solubility, the correlation coefficient was not so high ($r = 0.688$). Drugs with relatively high molecular weight are below the line, whereas drugs with low molecular weight are above it. This result showed that there are some effects of molecular size on the skin permeation. There was no relationship between log(permeability coefficient) and log(solubility in water) of the water-soluble drugs.

Figure 3c shows the relationship between the skin permeability and partition coefficient of drugs (*n*-octanol/water). There was no relationship between them. Skin permeation of water-soluble drugs was not dependent on the partition of the drugs to the skin.

These results indicate that some water-soluble drugs with low molecular weight and high solubility in water might possess high skin permeability even though the partition of the drugs from topical formulations to the skin is low. Appropriate skin permeation rate (flux) and total clearance of drugs are most important to obtain therapeutic effects. Even though the permeability coefficients are not so high, many drugs with high solubility in aqueous vehicles could be candidates for transdermal drug delivery. Not only lipophilic drugs, which show high skin permeability coefficient, but also hydrophilic drugs, which show high skin permeation rate (flux), might be worthy of feasibility studies for transdermal delivery.

References and Notes

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