Influence of Isosorbide Dinitrate Concentration on Its Skin Permeability from Adhesive Matrix Devices

Tomomi HATANAKA,[a] Manami OGUCHI,[a] Kenji SUGIBAYASHI[a,b] and Yasunori MORIMOTO*,[a,b]

Faculty of Pharmaceutical Sciences[a] and Life Science Research Center,[b] Josai University, 1–1 Keyakidai, Sakado, Saitama 350–02, Japan.
Received November 20, 1990

Adhesive matrix devices containing a model drug, isosorbide dinitrate (ISDN), were prepared with three different types of pressure sensitive adhesives (PSAs). ISDN permeation through excised hairless rat skin from the different devices was measured *in vitro*. For each PSA type, the steady state permeation rate of ISDN increased proportionally with an increase of ISDN concentration in the PSA and reached a maximum level at a certain concentration. Although the concentrations reaching the maximum skin permeation level varied among PSA types, the maximum rate for each PSA type was largely similar to that for ISDN aqueous suspension. The release rate of ISDN from devices was too fast to influence the skin permeation rate for all devices. In the PSA of devices showing maximum skin permeability, ISDN crystalline was observed by polarizing microscopy and differential scanning calorimetry. These results suggest that the skin permeation of ISDN from adhesive matrix devices was controlled by the thermodynamic activity of the drug in the PSAs.

Keywords adhesive matrix device; skin permeation; pressure sensitive adhesive; drug concentration; thermodynamic activity; isosorbide dinitrate

The objective of this study was to investigate the influence of physical and chemical properties of adhesive matrix devices on the skin permeability of drug. Adhesive matrix devices containing a model drug, isosorbide dinitrate (ISDN), were prepared using three different typical pressure sensitive adhesives (PSAs), namely acrylic, rubber and silicone adhesives. The effect of ISDN concentration and type of PSAs on ISDN permeability through the excised hairless rat skin from the devices was determined. Moreover, the adhesive properties and ISDN release for the devices were also evaluated.

Materials and Methods

Materials ISDN was a gift from Kyukyu Pharmaceutical Co. (Tokyo, Japan). An aqueous emulsion (50% solid content) of acrylic adhesive (methacrylic acid–butyl acrylate copolymer, mole ratio 50 : 1) was kindly supplied from Kyukyu Pharmaceutical Co. A rubber adhesive mixture made mainly from a styrene–isoprene-styrene block copolymer (weight ratio of styrene : isoprene 14 : 86) was supplied from Toko Pharmaceutical Industries Co. (Tokyo). Silicone adhesive (bio-PSA® Q7-2920) was purchased from Dow Corning Co. (Midland, MI, U.S.A.). Other chemicals were of a reagent grade and obtained commercially.

Preparation of Adhesive Matrix Devices The adhesive matrix devices were prepared by a casting method.[1] An appropriate volume of 20% ISDN ethyl acetate solution was added to the adhesive solution or emulsion and thoroughly stirred with a Teflon-spatula. The rubber-type adhesive solution (50% solid content) was formulated by adding chloroform to an additive-mixture containing styrene–isoprene–styrene block copolymer. The adhesive solution or emulsion containing ISDN was applied to a backing sheet, polyethylene terephthalate film. After allowing the solvent to evaporate off at 60 °C for 5 min, the adhesive samples were kept at room temperature for 24 h. The dried adhesive matrix devices were weighed and their thickness was measured with a dial thickness gauge (limit 0.1 μm). The devices with a thickness greater than 600 μm were obtained by laminating the PSA layers. The devices with various concentrations of ISDN (3—288 mg/g) were prepared by varying thicknesses of PSA layers with a constant ISDN content of 800 μg/cm^2. Table I shows the PSA type, ISDN concentration and thickness of the adhesive matrix devices prepared in this study.

Evaluation of Adhesive Properties The adhesive properties of adhesive matrix devices were evaluated after being kept at 23 °C, 60% relative humidity for 24 h. The ball tack test was done according the method of J. Dow.[2] The probe tack was measured with a Nichiban probe tack tester (Nichiban Co., Tokyo). Apparent viscosity and peel adhesion were measured by the shear strength test (PSTC no. 7)[3] and 180° peel test,[4] respectively.

Skin Permeation Procedure The abdominal skin of a male hairless rat (WBN/ILA-Ht, 6 weeks old, Life Science Research Center, Josai University, Saitama, Japan) was excised after being shaven carefully. An adhesive matrix device was applied on the stratum corneum side of the excised skin and the skin with the device was mounted between two half diffusion cells with a water jacket, having a volume of 2.5 ml and a 0.95 cm^2 effective diffusion area.[5] The receiver compartment (dermis side) of each cell was filled with 2.5 ml of distilled water and stirred throughout the experiment with a star-head bar in each half-cell, driven by a constant-speed synchronous motor (MC-301, Scinics, Tokyo) at 1200 rpm. The experiments were done at 37 °C by circulating warm water. At appropriate times, 500 μl samples were withdrawn from the receiver compartment and 500 μl of distilled water was added to keep the volume constant. Other experiments were done by filling the donor compartment (stratum corneum side) with 2.5 ml of ISDN aqueous suspension (3.0 mg/ml) instead of application of adhesive matrix devices.

Release Procedure The diffusion cell described above was employed for determining the release rate of ISDN from adhesive matrix devices. An adhesive matrix device was applied onto a half-cell, and the half-cell was filled with 2.5 ml of distilled water and stirred throughout the experiment. Samples (1 ml) were withdrawn from the half-cell for assay at appropriate times, and 1 ml of distilled water added to keep the volume constant.

ISDN Analysis ISDN was assayed by high performance liquid chromatography (HPLC). The HPLC system consisted of a pump (LC-6A, Shimadzu, Kyoto, Japan), an ultraviolet detector (SPD-6A, Shimadzu),

TABLE I. The PSA Type, ISDN Concentration and Thickness of Adhesive Matrix Devices Prepared in This Experiment

	PSA	ISDN concentration (mg/g)	Thickness (μm)
A-1	Acrylic	288	27.8
A-2		240	33.3
A-3		180	44.4
A-4		90	88.9
A-5		60	133.3
R-1	Rubber	203	39.4
R-2		102	78.4
R-3		68	117.6
R-4		10	800.0
R-5		5	1600.0
S-1	Silicone	165	48.5
S-2		83	96.4
S-3		55	145.5
S-4		5	1600.0
S-5		3	2666.7

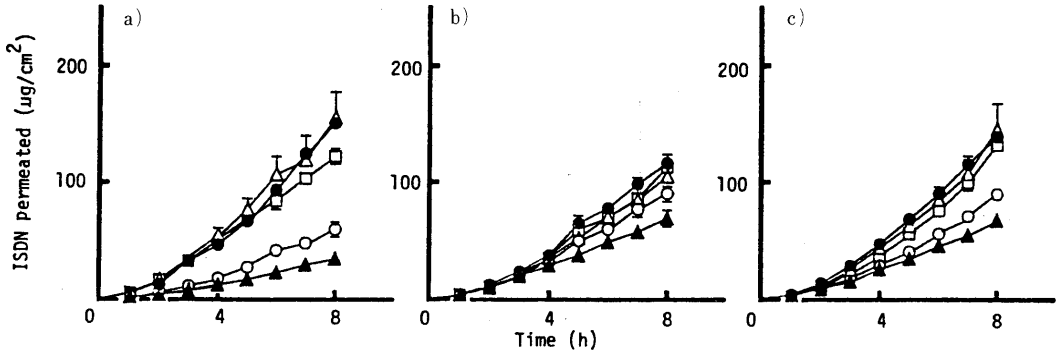

Fig. 1. Skin Permeation Profiles of ISDN from Several Adhesive Matrix Devices

a) Acrylic-type. ●, A-1; △, A-2; □, A-3: ○, A-4; ▲, A-5. *b*) Rubber-type. ●, R-1; △, R-2; □, R-3; ○, R-4; ▲, R-5. *c*) Silicone-type. ●, S-1; △, S-2; □, S-3; ○, S-4; ▲, S-5. Each value represents the mean ± S.E. of 3 experiments.

a 4.6 mm × 250 mm stainless-steel column packed with Nucleosil® $5C_{18}$ (Macherey Nagel, Germany) and an integrator (C-R6A, Shimadzu). Analytical conditions were as follows: mobile phase, water–acetonitrile (45 : 55); flow rate, 1.2 ml/min; detector, UV 254 nm; internal standard, butyl *p*-hydroxybenzoate.

Polarizing Microscopy The PSA layer of adhesive matrix devices was observed by polarizing microscopy (Transmitted Light Nomarsky System Microscope, model BHS-N, Olympus, Tokyo) at 35×.

Differential Scanning Calorimetry (DSC) The PSA layer of adhesive matrix devices was studied by a differential scanning calorimeter (DSC-8240B, Rigaku Co., Tokyo). A weighed sample (about 9 mg) was packed in an aluminum pan. An empty pan was used as a reference. Each sample was heated at a rate of 10 °C/min from −100 to 100 °C.

Analysis of Release Profiles The solubility and diffusion coefficient of ISDN in PSAs were estimated by computer fitting the release profiles of ISDN in dissolved and suspended devices using W. I. Higuchi's (Eq. 1)[6] and T. Higuchi's (Eq. 2)[7] equations, respectively.

$$Q = hC_0\left\{1 - 8/\pi^2 \sum_{m=0}^{\infty} 1/(2m+1)^2 \exp(-D(2m+1)^2\pi^2 t/4h^2)\right\} \quad (1)$$

$$Q = \sqrt{D(2C_0 - C_S)C_S t} \quad (2)$$

where Q is the amount of drug released per unit area, h is the thickness of the PSA layer, D is the diffusion coefficient of the drug in the PSA, C_0 and C_S represent the total drug concentration and solubility in PSA, respectively, and t is time.

Results and Discussion

Evaluation of Adhesive Properties Table II shows the adhesive properties of adhesive matrix devices prepared without ISDN and commercial products, Frandol® tape and Frandol® tape S. Several adhesive properties, such as ball tack and peel, of devices prepared in this study were higher than those of commercial products, except for probe tack. Although the adhesive strength was lowered by adding ISDN, the value was high enough to maintain an intimate contact with the skin surface by comparison to the following standards: Ball tack, No. 16; $\log\eta$, 6; bakelite peel, 200 g/15 mm.[8]

Influence of ISDN Concentration in PSAs on Skin Permeation Figure 1 shows the time course of the cumulative amount of ISDN which permeated excised hairless rat skin from several devices. The cumulative amount of ISDN which permeated increased linearly with time after a short lag time (about 1 h), and the slope of linear portion, namely the steady state permeation rates, varied markedly dependent on the ISDN concentration of the devices (Fig. 2). For each type of PSA, the permeation rate increased proportionally with an increase of ISDN concentration in PSAs and reached a constant maximum level above a concentration. The concentrations reaching the maximum level were about 200, 10 and 5 mg/g for acrylic, rubber and silicone adhesives, respectively. But, the maximum level for each PSA type was largely similar to that for ISDN aqueous suspension (about 23 μg/cm² h), ass shown by the broken line in Fig. 2.

TABLE II. Evaluation of Adhesive Properties of Several Adhesive Matrix Devices

Device	Ball tack	Probe tack (g/5 mm i.d.)	$\log\eta$	Peel (g/15 mm)	
				Bakelite	Steel
Acrylic-type	No. 29	754 ± 13[a)]	7.93	1202 ± 127[a)]	696 ± 17[a)]
Rubber-type	No. 32<	643 ± 26[a)]	8.13	584 ± 11[a)]	584 ± 14[a)]
Silicone-type	No. 26	115 ± 13[a)]	7.96	920 ± 5[a)]	885 ± 8[a)]
Frandol® tape	No. 27	495	6.55	390	340
Frandol® tape S	No. 20	215	7.88	390	290

Each value represents the mean of 2 experiments. *a*) Each value represents the mean ± S.E. of 3 experiments.

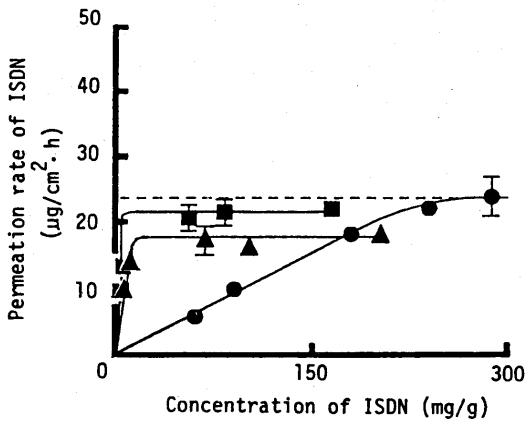

Fig. 2. Influence of ISDN Concentration in PSA on the Skin Permeation Rate of ISDN

●, acrylic-type; ▲, rubber-type; ■, silicone-type. Each value represents the mean ± S.E. of 3 experiments. The broken line represents the skin permeation rate from an ISDN aqueous suspension.

Release of ISDN from Adhesive Matrix Devices In order to evaluate the diffusivity of ISDN in PSA layers, the release of ISDN from several adhesive matrix devices was studied. Figure 3 illustrates the results of the release experiments. The release rate of ISDN for rubber adhesive was lower than that for acrylic and silicone adhesives. The release

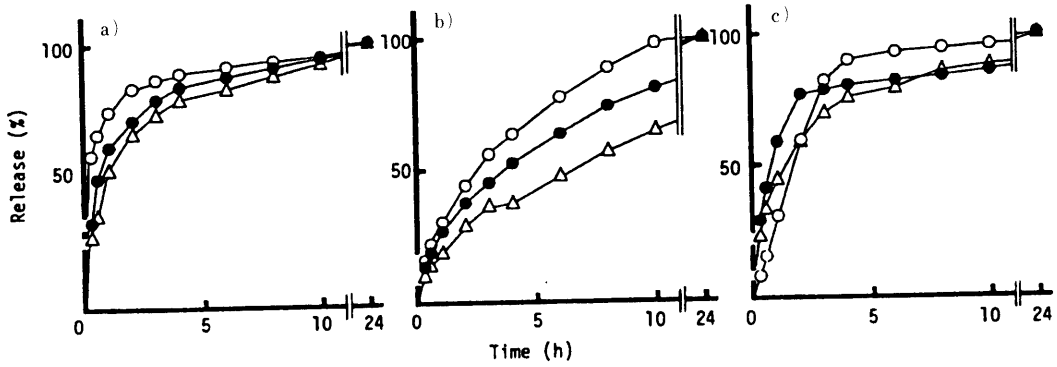

Fig. 3. Release Profiles of ISDN from Several Adhesive Matrix Devices

a) Acrylic-type. ○, A-3; ●, A-4; △, A-5. b) Rubber-type. ○, R-1; ●, R-2; △, R-3. c) Silicone-type. ○, S-1; ●, S-2; △, S-3. Each value represents the mean of 2 experiments.

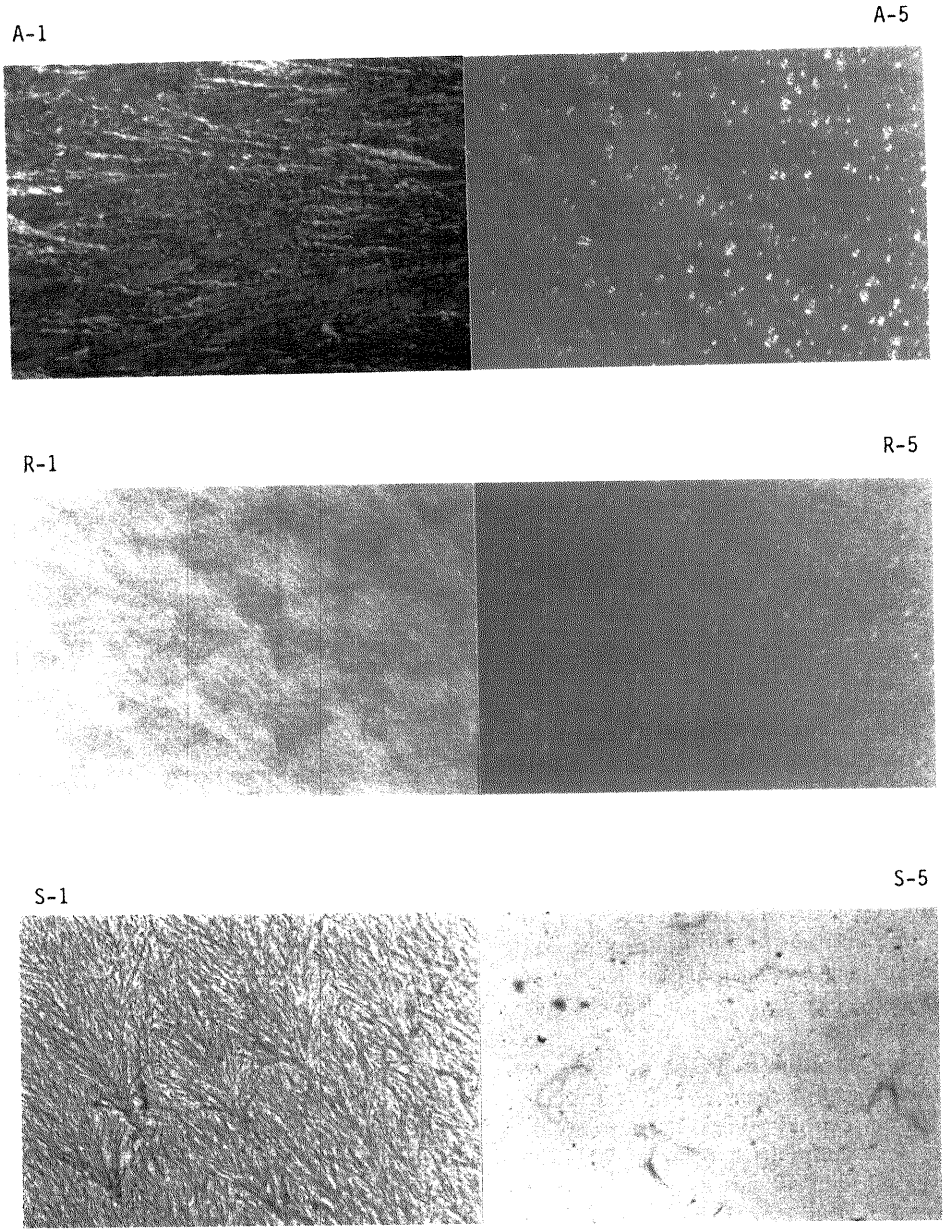

Fig. 4. Polarizing Micrographs of Several Adhesive Matrix Devices (Acrylic-Type A-1, A-5; Rubber-Type R-1, R-5; Silicone-Type S-1, S-5)

A-1, R-1 and S-1 were the typical devices which showed a maximum skin permeation rate, and A-5, R-5 and S-5 were the typical devices which didn't show a maximum permeation rate.

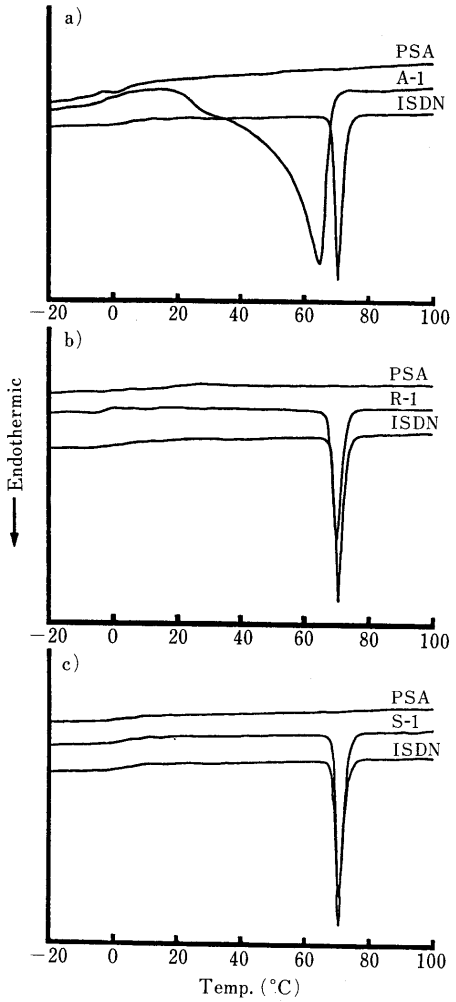

Fig. 5. DSC Thermograms of Several Adhesive Matrix Devices

a) Acrylic-type. b) Rubber-type. c) Silicone-type. A-1, R-1 and S-1 were the typical devices which showed a maximum skin permeation rate, and A-5, R-5 and S-5 were the typical devices which didn't show a maximum permeation rate.

rate of ISDN from each type of device had a tendency to increase with increasing ISDN concentration. The rate was too high to affect the skin permeability of ISDN. The swelling of the acrylic adhesive (2.34±0.21% after 24 h) was ignored in this study.

State of ISDN in PSAs Polarizing microscopy and DSC were employed to find out how the drug exists in PSAs. Comparison of the typical polarizing micrographs of three kinds of devices, with and without showing the maximum skin permeation rate, is shown in Fig. 4. ISDN crystalline was observed in devices with a maximum skin permeation rate, but no crystalline was found in the other devices for all types of PSA. It was suggested that the concentration of ISDN in a PSA was greater than the solubility for the devices having a maximum permeation rate, whereas only the dissolving ISDN existed in PSAs for the other devices.

The fact described above was further supported by the typical DSC thermograms of PSAs for devices having a maximum permeation rate (Fig. 5). A sharp endothermal peak was found at the melting point of ISDN (70 °C) in the rubber and silicone adhesives, suggesting the existence of ISDN crystalline in PSAs. A broad peak between 20 to 70 °C observed in the acrylic adhesive may be due to the influence of binding water and/or overlapping of the melting endotherm of ISDN neat crystalline and a solid solution.

TABLE III. Diffusion Coefficient and Solubility of ISDN in Several PSAs

Adhesive type	D ($cm^2/h \times 10^{-5}$)	C_s (mg/g)
Acrylic-type	3.583±0.576	156.1±18.21
Rubber-type	3.019±0.542	8.846±0.982
Silicone-type	24.44±0.333	1.931±0.294

Each value represents the mean±S.E. of 4 experiments.

Solubility and Diffusivity of ISDN in PSAs Analysis of the release profiles of ISDN was carried out to quantitatively evaluate the difference in solubility and diffusivity of ISDN among several PSAs. The estimated solubility and diffusion coefficient of ISDN in several PSAs is shown in Table III. The estimated solubilities were almost the same as the concentration reaching the maximum skin permeation rate for each type of PSA (Fig. 2). The diffusion coefficient in silicone adhesive was higher than in acrylic or rubber adhesives. The difference might reflect that the glass transition temperature of silicone adhesive (−116 °C) was remarkably lower than for acrylic or rubber adhesives (−41 and −48 °C).[9]

Conclusion

It was suggested from results in the present study that the skin permeation of ISDN from adhesive matrix devices was controlled by the thermodynamic activity of the drug in PSAs similar to the cases of solutions and ointment.[10] In the devices containing excess drug over solubility, the thermodynamic activity of the dissolving drug is generally the same as that of the solid (crystalline) drug. Whereas, in devices containing only the dissolving drug, the activity was proportional to the concentration. Therefore, the skin permeation rate reaches a maximum in the drug-suspended devices, and it is proportional to the concentration of the drug in the drug-dissolved devices. When the skin permeabilities of ISDN from several devices were compared under the same ISDN concentration, the higher permeation rate was obtained in the devices having a lower ISDN solubility. In order to develop novel adhesive matrix devices producing excellent skin permeability of drugs, PSAs with a low affinity against drugs (high thermodynamic activity of drugs) should be selected.

References and Notes

1) M. C. Musolf, "Transdermal Controlled Systemic Medications," eds. by Y. W. Chien, Marcel Dekker, Inc., New York, 1987, pp. 93—112.
2) JIS Z0237.
3) C. A. Dahlquist, "Handbook of Pressure Sensitive Adhesive Technology," eds. D. Satas, Van Nostrand Reinhold, New York, 1989, pp. 97—114.
4) JIS C2107.
5) M. Okumura, K. Sugibayashi, K. Ogawa and Y. Morimoto, *Chem. Pharm. Bull.*, **37**, 1404 (1989).
6) W. I. Higuchi, *J. Pharm. Sci.*, **51**, 802 (1962).
7) T. Higuchi, *J. Pharm. Sci.*, **50**, 874 (1961).
8) Private communication.
9) E. R. Cooper and G. Kasting, *J. Controlled Release*, **6**, 23 (1987).
10) T. Higuchi, *J. Soc. Cosmetic Chemists*, **11**, 85 (1960).