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Basic Studies on Controlled Transdermal Delivery of Nicardipine Hydrochloride Using Ethylene-Vinyl Acetate and Ethylene-Vinyl Alcohol Copolymer Membranes

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The permeability of a model drug, nicardipine hydrochloride (NC), through ethylene-vinyl acetate copolymer (EVAc) or ethylene-vinyl alcohol copolymer (EVAl) membrane as a rate controlling layer was examined as one step in the development of a well-designed membrane permeation-controlled transdermal therapeutic system (TTS). The membrane permeability of NC from various suspensions in ethanol (EtOH)–methyl ethyl ketone (MEK)–water mixed solvents was affected by the solvent composition as well as the membrane composition. The NC permeation through EVAc membrane increased with increase in the MEK content in the solvent, whereas that through the EVAl membrane showed a convex curve against MEK content. As solvent penetration into the membranes may be important for the NC permeation, the extent of swelling of EVAc or EVAl beads was determined as an index of solvent penetration. The relationship between the solvent composition and degree of swelling of the copolymer was similar to that between the solvent composition and the logarithm of the product of the steady-state permeation rate of NC through EVAc or EVAl membrane and thickness of the membrane. It was found from the results of the permeation and swelling experiments that the permeability of NC through EVAc or EVAl membrane is mainly affected by the solvent penetration into the membrane. Finally, the effect of EVAl membrane on the permeation of NC through the intact or damaged skin was measured. The NC permeation through a piled layer of EVAl membrane and full-thickness skin was similar to that through a piled layer of EVAl membrane and damaged skin. This result suggests that the application of these membranes would be useful in making a well-designed TTS which shows little inter- and/or intra-subject variation in skin permeation of NC.

Keywords——membrane permeation-controlled transdermal therapeutic system; nicardipine hydrochloride; ethylene-vinyl acetate copolymer; ethylene-vinyl alcohol copolymer; rate-controlling layer

During the past three decades, many oral sustained-release dosage forms have been developed. These may reduce the frequency of dosing and improve patient compliance,[1] but the absorption rate of drugs from oral preparations may be affected by several biological factors in patients, *i.e.* the gastric emptying rate and first pass effect, as well as the release rates of drugs from the preparations. These factors may result in marked inter- and intra-subject variations in plasma concentration of drugs. Well-designed transdermal therapeutic systems (TTS) might be one of the alternatives to avoid the shortcomings of oral formulations. Several transdermal systems have been developed,[2] but it is doubtful whether the absorption rate of drugs from these systems is well controlled, because the plasma concentration of drugs varies widely between subjects and also among application sites.[3] TTS is generally useful to treat chronic disease.[2c] However, an application of a TTS at the same site for a long time may cause irritation of the skin surface and a change of the application site may result in different

plasma concentration of the drugs. Therefore, TTS which can maintain a constant blood level independently of both the skin condition and application site may be ideal to treat chronic disease.

In the present study, the permeabilities of nicardipine hydrochloride (NC)[4] through ethylene-vinyl acetate copolymer (EVAc)[5] and ethylene-vinyl alcohol copolymer (EVAl)[6] membrane as rate controlling layers were examined in order to develop a membrane permeation-controlled TTS which can provide zero-order release and a constant skin permeation rate of the drug. In addition, the effect of the membrane on the *in vitro* permeability of NC through excised hairless rat skin was measured.

Experimental

Materials——NC was kindly supplied by Nissan Chemical Industries (Tokyo, Japan). EVAc beads and membranes (vinyl acetate content; 18 and 11 mol%) were supplied by Mitsui Du Pont Polychemical Co. (Tokyo), and EVAl beads and membranes (vinyl alcohol content; 68 and 56 mol%) were supplied by Kuraray Co. (Tokyo). The EVAc beads were about 4 mm in diameter and the membranes were about 0.035 cm in thickness. The EVAl beads were about 3 mm in diameter and the membranes were about 0.002 cm in thickness. The beads were used for the swelling experiments and the membranes were used for NC permeation experiments.

Preparation of Mixed Solvent——Ethanol (EtOH) and methyl ethyl ketone (MEK) were mixed with water to give a total volume of 100 ml. The resulting solvent was designated as, for example, EtOH : MEK : H_2O = 1 : 2 : 1 mixed solvent (after mixing 25 ml of EtOH, 50 ml of MEK and an appropriate volume of water).[4a]

Permeation of NC through EVAc or EVAl Membrane——An EVAc or EVAl membrane was soaked in several mixed solvents for 14 h at 37 °C. The thickness of the swollen membrane was measured with a micrometer, and each membrane was mounted in a 2-chamber diffusion cell.[7] Each half-cell has a volume of 2 ml and an effective diffusional area of 0.95 cm^2. NC suspension (2 ml) in several mixed solvents was added to the donor-side half-cell. The same solvent system (NC-free, 2 ml) was added to the receiver-side half-cell, in order to prevent the effect of solvent permeation from the donor to the receiver side or the receiver to the donor side on the NC permeation through the membrane. The cell set was kept in a water bath at 37 °C. The cumulative amount of NC which permeated through the membrane per unit area, Q, was determined by using a high performance liquid chromatography (HPLC) system (LC-6A, Shimadzu Seisakusho, Kyoto, Japan). The conditions were as follows: internal standard, quinine hydrochloride; column, 4.6 mm × 250 mm stainless steel column packed with Nucleosil $5C_{18}$ (Nagel, Germany); mobile phase, methanol: 0.02 M KH_2PO_4 (3 : 1); detector, UV 240 nm.

Swelling of EVAc or EVAl——One gram of EVAc or EVAl beads was weighed and added to 10 ml of several mixed solvents. Each sample was incubated in a water bath at 37 °C. At predetermined times, the beads were weighed after wiping the excess solvent from the bead surface.

***In Vitro* Permeation of NC through the Excised Hairless Rat Skin**——Abdominal skin of male WBN/kob hairless rat[7] (Saitama Laboratory Animals, Sugito, Saitama, Japan), weighing 180—200 g, was excised and mounted in a 2-chamber diffusion cell. NC suspension in several mixed solvents was added to the donor-side half-cell. The same solvent was added to the receiver-side half-cell. The cell was kept at 37 °C. The cumulative amount of NC permeating through the skin was determined by HPLC (conditions: same as above).

***In Vitro* Permeation of NC through the Skin with EVAc or EVAl Membrane**——Drug-free gel (25 mg) prepared by adding hydroxypropyl cellulose (HPC-M, Nippon Soda Co., Ltd., Tokyo) to EtOH : MEK : H_2O = 1 : 2 : 1 mixed solvent at a concentration of 3% was applied on 0.95 cm^2 of the stratum corneum side of the excised skin as an

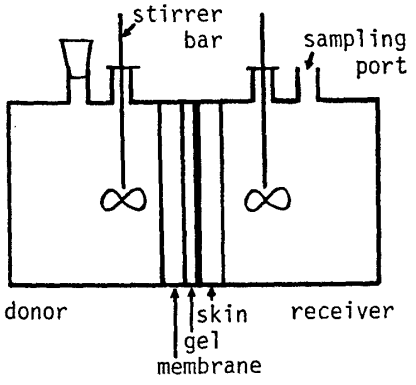

Fig. 1. Assembly of the Excised Skin, Rate-Controlling Membrane and Diffusion Cell in the *in Vitro* Permeation Experiments

adhesive. An EVAl membrane (vinyl alcohol 68 mol%) previously soaked in the same mixed solvent for 14 h at 37 °C was placed on the gel. The skin sample with gel and membrane was mounted in a 2-chamber diffusion cell as shown in Fig. 1. NC suspension in the same mixed solvent was placed in the donor-side half-cell, and drug-free solvent in the receiver-side half-cell. Other conditions were the same in the permeation experiments through the polymeric membranes or the skin. The effect of the membrane was examined by measuring the difference of the NC permeabilities through intact skin and damaged skin which was prepared by removing the stratum corneum with an adhesive tape.[7] In addition, the steady-state permeation rate observed in this experiment was compared with those through the skin alone and EVAl membrane alone.

Results and Discussion

Effect of Membrane Composition on the Permeation of NC through EVAc or EVAl Membrane

The steady-state permeation rate of drug per unit area, F, which is the differential of Q with respect to time, is generally expressed by[8]:

$$F=\frac{dQ}{dt}=\frac{a_d}{r_m}\frac{D}{L} \quad (1)$$

where a_d and r_m are the thermodynamic activity of the donor compartment and the activity coefficient of the drug in the membrane, respectively, and D and L are the diffusion coefficient of the drug in the membrane and the thickness of the membrane, respectively. Since the thickness of EVAc or EVAl membranes used in the present experiment varied, $F\times L$ value was used as an index of the membrane permeability.

Figure 2a and b shows the time course of Q from EtOH : MEK : H_2O = 1 : 2 : 1 mixed solvent through the EVAc (a) or EVAl (b) membrane. The F and $F\times L$ values are shown in Table I. In the case of NC permeation through the EVAc membrane, a greater vinyl acetate content resulted in a higher membrane permeation. On the other hand, in the case of the EVAl membrane increase in the vinyl alcohol content resulted in a slight decrease in the permeability of NC. Such a difference in the $F\times L$ values should have resulted from the difference in D and/or r_m values. Previous reports have shown that the EVAc and EVAl membrane permeabilities to various types of drugs increased with decrease in ethylene content.[5,6] The results of the NC permeation experiments through EVAc membrane are in agreement with these reports. However, the relationship between membrane composition and permeability of

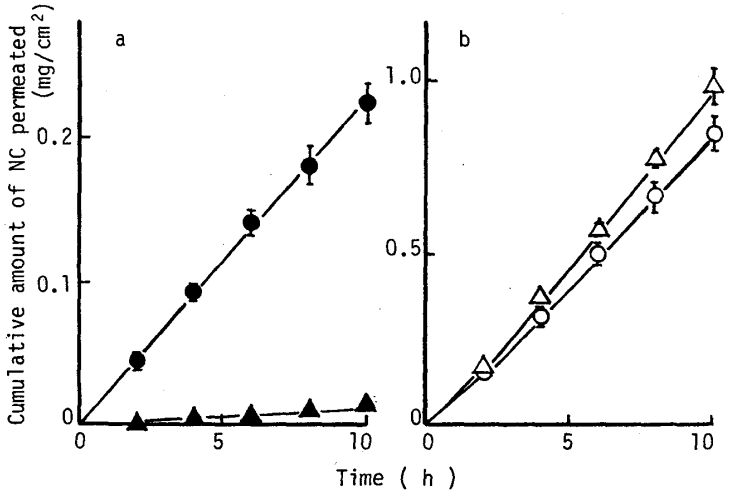

Fig. 2. Time Course of the Cumulative Amount of NC Permeated through EVAc or EVAl Membrane

a: EVAc membrane. Vinyl acetate content: ●, 18 mol%; ▲, 11 mol%. b: EVAl membrane. Vinyl alcohol content: ○, 68 mol%; △, 56 mol%. The data are means of three experiments and vertical bars show standard deviation.

TABLE I. Steady-State Permeation Rate of NC through EVAc or EVAl Membrane

Type	Composition of membrane	Solvent (EtOH : MEK : H_2O)	Thickness[a] L (cm)	F[a] ($\mu g/cm^2/s$)	$F \times L$ ($\mu g/cm/s$)
EVAc 40	Vinyl acetate 18 mol%	1 : 0 : 3	0.0279 $\pm$0.0004	2.5×10^{-4} $\pm 0.6 \times 10^{-4}$	7.0×10^{-6}
		1 : 1 : 2	0.0249 $\pm$0.0010	3.7×10^{-3} $\pm 0.7 \times 10^{-3}$	9.2×10^{-5}
		1 : 2 : 1	0.0287 $\pm$0.0015	6.2×10^{-3} $\pm 0.4 \times 10^{-3}$	1.8×10^{-4}
EVAc 260	Vinyl acetate 11 mol	1 : 0 : 3	0.0360 $\pm$0.0021	2.3×10^{-6} $\pm 1.0 \times 10^{-6}$	8.2×10^{-8}
		1 : 1 : 2	0.0380 $\pm$0.0019	2.0×10^{-4} $\pm 0.3 \times 10^{-4}$	7.6×10^{-6}
		1 : 2 : 1	0.0373 $\pm$0.0021	4.4×10^{-4} $\pm 0.2 \times 10^{-4}$	1.6×10^{-5}
		1 : 3 : 0	0.0470 $\pm$0.0004	2.0×10^{-2} $\pm 0.1 \times 10^{-2}$	9.4×10^{-4}
EVAl EF-F	Vinyl alcohol 68 mol%	1 : 0 : 3	0.0014 $\pm$0.0001	8.1×10^{-3} $\pm 0.2 \times 10^{-3}$	1.1×10^{-5}
		1 : 1 : 2	0.0015 $\pm$0.0001	4.6×10^{-2} $\pm 0.3 \times 10^{-2}$	6.9×10^{-5}
		1 : 2 : 1	0.0015 $\pm$0.0001	2.4×10^{-2} $\pm 0.1 \times 10^{-2}$	3.6×10^{-5}
		1 : 3 : 0	0.0016 $\pm$0.0001	2.7×10^{-5} $\pm 0.7 \times 10^{-5}$	4.3×10^{-8}
EVAl EF-E	Vinyl alcohol 56 mol%	1 : 0 : 3	0.0020 $\pm$0.0001	1.1×10^{-3} $\pm 0.1 \times 10^{-3}$	2.2×10^{-6}
		1 : 1 : 2	0.0020 $\pm$0.0001	2.6×10^{-2} $\pm 0.2 \times 10^{-2}$	5.2×10^{-5}
		1 : 2 : 1	0.0021 $\pm$0.0001	2.8×10^{-2} $\pm 0.1 \times 10^{-2}$	5.9×10^{-5}
		1 : 3 : 0	0.0022 $\pm$0.0001	4.8×10^{-5} $\pm 0.4 \times 10^{-5}$	1.1×10^{-7}

a) Mean $\pm$ S.D. ($n=3$).

the membrane needs further investigation.

Effect of Solvent Composition on the Permeation of NC through the EVAc or EVAl Membrane

In a previous paper,[4a] we reported that the permeability of NC through excised skin was affected by the composition of EtOH–MEK–water mixed solvent system. In the present study, the solvent effect on the permeability of NC through the EVAc or EVAl membrane was examined.

The F and $F \times L$ values from various NC suspensions are shown in Table I and the relationship between the $F \times L$ value and solvent composition is shown in Fig. 3a and b. The NC permeation through the EVAc membrane increased when the content of MEK was increased (Fig. 3a). On the other hand, the NC permeability through the EVAl membrane showed maximum values (Fig. 3b). The profile observed in the EVAl membrane is similar to that observed in the excised skin in our previous study.[4a]

On the assumption that activity in a saturated solution in each of the solvents is the same as that in the solid, a_d, the activity of NC in solution, may be considered to be constant in all permeation experiments, since NC suspension was used as the donor solution. Therefore, the difference in the permeation rates of NC may be due to differences in D and/or r_m values. It is

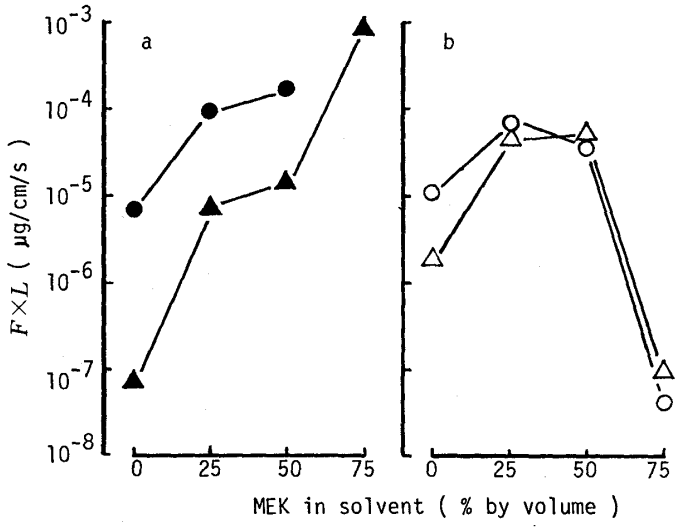

Fig. 3. Relationship between the Product of Steady-State Flux and Membrane Thickness and Solvent Composition

a: EVAc membrane. Vinyl acetate content: ●, 18 mol%; ▲, 11 mol%. b: EVAl membrane. Vinyl alcohol content: ○, 68 mol%; △, 56 mol%. The data are means of three experiments.

clear from the results that the membrane permeation of NC was affected greatly by the solvent composition as well as the membrane composition.

Swelling of EVAc or EVAl Beads by Mixed Solvents

The swelling of EVAc or EVAl beads by solvent penetration was determined by measuring the weight change of the beads (weight at time t, W_t, divided by initial weight, W_0). Figures 4 and 5 show the time course of the weight change of these beads. The swelling of EVAc beads reached the maximum level 10 h after the beginning of the experiment (Fig. 4a and b), whereas the swelling of EVAl beads proceeded for about 10 d (Fig. 5a and b). Figure 6 shows the relationship between the composition of solvents and degree of swelling at 24 h for EVAc beads and at 14 d for EVAl beads. The profile in Fig. 6 is similar to the relationship between the solvent composition and logarithm of $F \times L$ value, as shown in Fig. 3.

These results suggest that the difference in $F \times L$ values of various solvents was induced by the solvent penetration into the membrane. The degree of swelling of a polymer is used occasionally as an index for determination of the solubility parameter of the polymer.[9] The swelling of EVAc and EVAl beads should be affected by the difference in the solubility parameter between the solvent and the polymer. The solvent penetration should affect both the diffusivity and solubility of NC in the membranes. Similarity of physicochemical properties, such as lipophilicity, of the membrane and NC may be important for membrane permeation. In this case, however, similarity of physicochemical properties of the membrane and solvent would be more important, since the membrane permeation of NC would be greatly affected by the solvent penetration into the membrane.

The presoaking time for the membrane in the membrane permeation experiments was determined by comparing NC permeation through a 14 h-presoaked EVAl membrane (vinyl alcohol content 68 mol%) with a 38 h-presoaked one. The NC permeability through the 14 h-presoaked membrane was the same as that after 38 h, which suggests that the presoaking time of 14 h would be long enough for complete swelling. The difference in swelling rate between the beads and the membrane should be caused by the difference in specific surface area.

Effect of Solvent Composition on the Permeation of NC through Excised Rat Skin

In the previous study,[4a] the maximum flux from NC suspension was calculated by multiplying the solubility of NC in various EtOH–MEK–H_2O mixed solvents and the permeability of NC through the excised skin from NC solution (10 mg/ml) in the corresponding solvent. The highest value of the calculated maximum flux was observed in EtOH : MEK : H_2O = 1 : 2 : 1 mixed solvent which also had the highest solubility. The

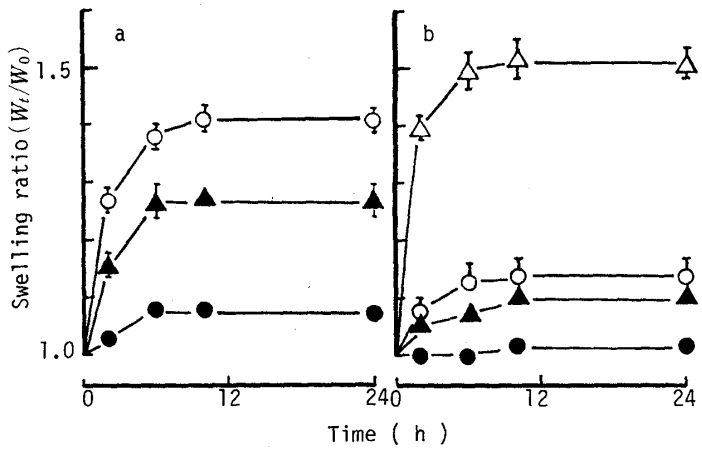

Fig. 4. Time Course of Swelling of EVAc Beads in Several Solvent Systems

a: Vinyl acetate content, 18 mol%. EtOH : MEK : H_2O = ●, 1 : 0 : 3; ▲, 1 : 1 : 2; ○, 1 : 2 : 1. b: Vinyl acetate content, 11 mol%. EtOH : MEK : H_2O = ●, 1 : 0 : 3; ▲, 1 : 1 : 2; ○, 1 : 2 : 1; △, 1 : 3 : 0. The data are means of three experiments and vertical bars show standard deviation.

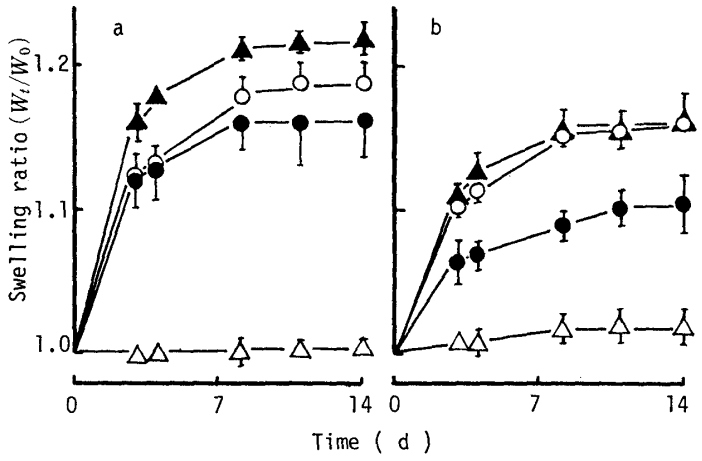

Fig. 5. Time Course of Swelling of EVAl Beads in Several Solvent Systems

a: Vinyl alcohol content, 68 mol%. EtOH : MEK : H_2O = ●, 1 : 0 : 3; ▲, 1 : 1 : 2; ○, 1 : 2 : 1; △, 1 : 3 : 0. b: Vinyl alcohol content, 56 mol%. EtOH : MEK : H_2O = ●, 1 : 0 : 3; ▲, 1 : 1 : 2; ○, 1 : 2 : 1; △, 1 : 3 : 0. The data are means of three experiments and vertical bars show standard deviation.

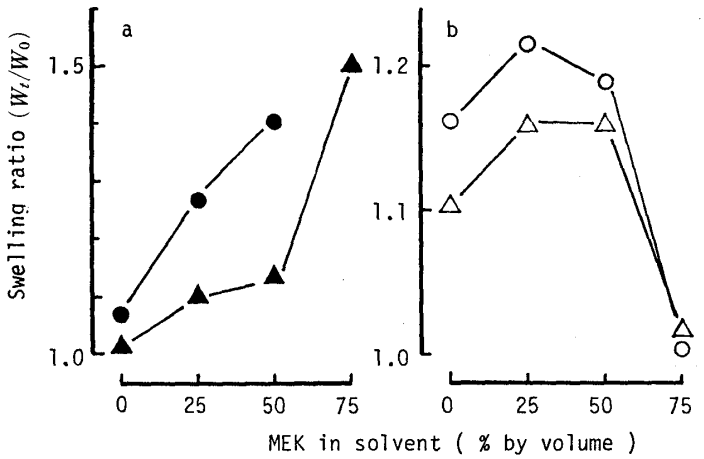

Fig. 6. Effect of Solvent Composition on the Swelling of EVAc and EVAl beads

a: EVAc beads. Vinyl acetate content: ●, 18 mol%; ▲, 11 mol%. b: EVAl beads. Vinyl alcohol content: ○, 68 mol%; △, 56 mol%. The data are means of three experiments.

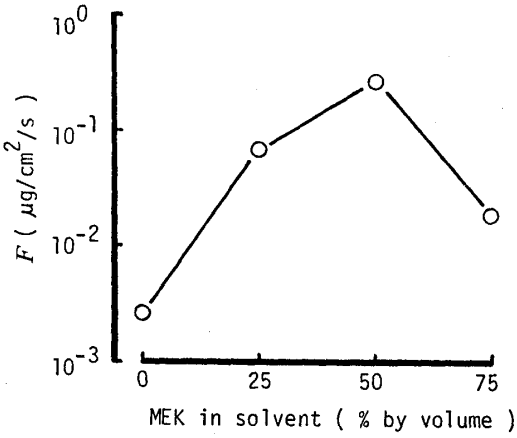

Fig. 7. Relationship between the Steady-State Flux from NC Suspension through the Excised Rat Skin and Solvent Composition

The data are means of three experiments.

maximum value was calculated under the hypothesis that the activity coefficient of NC in the donor solution is constant regardless of the concentration of NC. Therefore, the calculated values may not be equivalent to the real flux from NC suspension, since activity coefficient has concentration-dependency. In order to validate this prediction, the permeability from NC

suspension through hairless rat skin was measured in the present study.

Figure 7 shows the relationship between the solvent composition and logarithm of the observed flux of NC from various suspensions. The figure shows a parabolic relationship and the highest flux was observed in EtOH : MEK : H_2O = 1 : 2 : 1 mixed solvent. The observed flux in EtOH : MEK : H_2O = 1 : 2 : 1 mixed solvent was about half of the calculated maximum flux value. The overestimation of the calculated flux could be caused by the assumption that the activity coefficient is the same in NC solution and suspension.

Effect of EVAl Membrane on the Permeation of NC through Excised Rat Skin

The effect of the rate controlling membrane on the permeation of NC from suspension in EtOH : MEK : H_2O = 1 : 2 : 1 mixed solvent through intact (full thickness) or damaged (stripped) skin was measured. EVAl (vinyl alcohol 68 mol%) membrane was selected as a rate-controlling layer because of its relatively high permeability.

In the case of permeation of a drug through a piled layer of skin and membrane, the overall diffusional resistance of the permeation process, R_t, was expressed by[2c,10]:

$$R_t = R_v + R_m + R_a + R_s \tag{2}$$

where R_v, R_m, R_a and R_s are the diffusional resistances of vehicle, membrane, adhesive and skin, respectively. If R_v and R_a are assumed to be small in comparison to the other terms, Eq. 2 can be approximated as follows:

$$R_t = R_m + R_s \tag{3}$$

Since the diffusional resistance is equal to the reciprocal of the permeability coefficient, Eq. 3 can be rewritten as follows:

$$\frac{1}{P_t} = \frac{1}{P_m} + \frac{1}{P_s} \tag{4}$$

where P_t, P_m and P_s are the permeability coefficients of the drug overall, and through the membrane and skin layer, respectively. Since NC suspension was used as a drug donor in this experiment, Eq. 4 can be expressed in terms of flux as follows:

$$F_t = \frac{F_m \times F_s \times L}{F_s \times L' + F_m \times L} \tag{5}$$

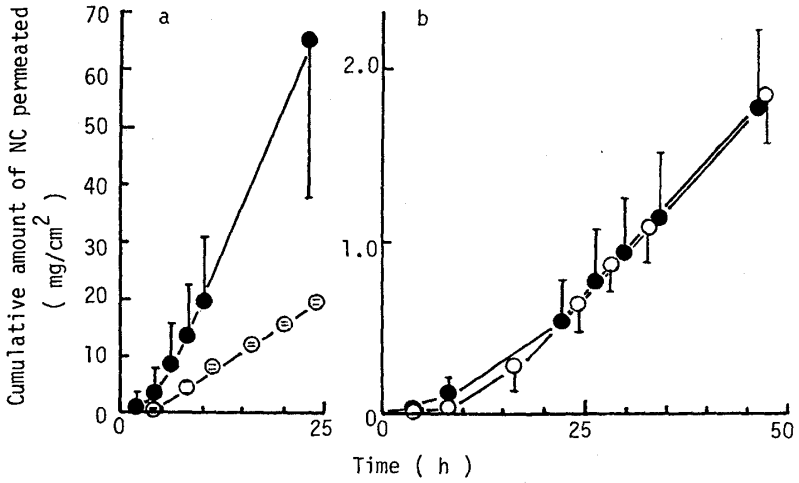

Fig. 8. Regulation of the *in Vitro* Skin Permeation of NC by EVAl Membrane

a: Skin alone. b: Piled layer of EVAl (vinyl alcohol 68 mol%) and skin. ○: Full-thickness skin. ●: Stripped skin. The data are means of three experiments and vertical bars show standard deviation.

TABLE II. Steady-State Permeation Rate of NC through Skin Alone or Piled Layer of Skin and EVAl Membrane

	Observed F_t values ($\mu g/cm^2/s$)	Calculated F_t values ($\mu g/cm^2/s$)
Intact skin	2.6×10^{-1}	—
Damaged skin	9.3×10^{-1}	—
Intact skin + membrane (0.0015 cm)	1.4×10^{-2}	2.2×10^{-2}
Damaged skin + membrane (0.0014 cm)	1.4×10^{-2}	2.5×10^{-2}

where F_t, F_m and F_s are the flux values of NC from suspension through a piled layer of skin and membrane, membrane alone and skin alone, and L and L' are the thicknesses of membrane used in the single membrane and piled permeation experiments, respectively. The F_t values can be calculated by means of Eq. 5 from F_m and F_s values.

Figure 8a shows the time course of Q through the intact or damaged skin without a rate-controlling membrane. The steady-state flux is shown in Table II. The NC permeation through the damaged skin was 3.6 times larger than that through the intact skin. Figure 8b shows the time course of Q through a piled layer of the EVAl membrane and intact or damaged skin. The observed flux is shown in Table II. The NC permeation through the damaged skin was similar to that through the intact skin. This result suggests that the skin permeation process is not rate-determining in the overall permeation process. Plasma concentration of drugs after application to the skin will be affected by the site and the condition of the skin, the pharmacokinetics of the drug in the body and other factors. If effective membrane permeation-controlled TTS are to be developed, the influences of these factors must be removed or decreased.

The calculated F_t values using Eq. 5 are shown in Table II. The calculated F_t values are higher than the observed F_t values. The difference between calculated and observed values may be due to the assumption that $R_a = 0$. An adhesive layer could play an important role in the overall permeation of drugs as well as the maintenance of an efficient permeation area.[11] Future studies should include determining the role of adhesives in skin permeation of NC and developing guidelines for adhesives to be used with membrane permeation-controlled TTS.

Conclusion

In the present study, the permeability of NC through EVAc or EVAl membrane was measured as one step in the development of a well designed membrane permeation-controlled TTS. The permeability of NC through EVAc or EVAl membrane was affected by the composition of the solvent as well as that of the membrane. The effect of solvent on the permeation of NC may be related to the swelling of the membrane. The results on permeation of NC through EVAc or EVAl membrane imply that similarity of physicochemical properties of the membrane and solvent is important rather than similarity of those of the membrane and NC.

In addition, the effect of a rate-controlling membrane, EVAl (vinyl alcohol 68 mol%), on the permeation of NC through intact or damaged skin was measured. The NC permeation through piled layers of EVAl membrane and intact skin was similar to that through piled layers of EVAl membrane and damaged skin. This result suggests that the permeation-control of drugs by such membranes will be useful in developing a well-designed TTS which shows little inter- and/or intra-subject variation in skin permeation of NC.

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