[Chem. Pharm. Bull. 35(7)3054—3057(1987)]

Effect of Solvents on the Permeation of Nicardipine Hydrochloride through the Hairless Rat Skin[1)]

TOSHINOBU SEKI, KENJI SUGIBAYASHI and YASUNORI MORIMOTO*

Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-02, Japan

(Received January 21, 1987)

The effect of several pure or mixed solvent systems on the skin permeation of nicardipine hydrochloride (NC), a potential calcium antagonist, was examined. The effect was evaluated by measuring the steady-state permeation rate through the excised hairless rat skin mounted in a 2-chamber diffusion cell and by measuring the solubilities of NC in these solvents at 37 °C. Although the solubility of NC in propylene glycol (PG) was higher than those in water, ethanol (EtOH) and methylethylketone (MEK), the skin permeation rate of NC from PG suspension was as low as that from aqueous suspension and lower than those from EtOH and MEK suspensions. The solubilities of NC in a binary EtOH–water solvent system at various ratios were higher than those in the pure solvents. Such cosolvency was also observed in the ternary EtOH–MEK–water solvent system. The relationship between the logarithm of the calculated maximum flux of NC from the binary and ternary solvent systems and solvent composition was similar to that between the solubility of NC and the solvent composition. The highest permeability was observed from the solvent system which gave the highest solubility. These results suggest that the use of mixed solvents is effective as a vehicle for enhancing the skin permeation of NC.

Keywords——skin permeation; nicardipine hydrochloride; calcium antagonist; cosolvency; hairless rat skin

Nicardipine hydrochloride (NC), a calcium antagonist in the 1,4-dihydropyridine class, is useful for the therapy of hypertension.[2)] Although NC is rapidly absorbed following oral administration, its bioavailability is relatively low due to the first-pass metabolism in the liver, and its biological half-life is very short.[3)] The skin is useful as an administration site to avoid such first-pass metabolism in the liver. In addition, the use of the skin as an administration site can help to maintain the plasma concentration of drugs and also to improve patient compliance.[4)] Thus, it might be worthwhile to develop a transdermal therapeutic system (TTS) as a possible replacement for conventional dosage forms of NC such as oral tablet.

In the present study, we examined the effect of several pure or mixed solvent systems on the skin permeation of NC as the first step to develop a TTS. The effects were evaluated by measuring the steady-state permeation rate of NC through the excised hairless rate skin and by measuring the solubilities of NC in these solvents.

Experimental

Materials——NC was kindly supplied by Nissan Chemical Industries (Tokyo, Japan). Distilled water and reagent-grade ethanol (EtOH, Wako Pure Chemical Ind., Osaka, Japan), propylene glycol (PG, Wako Pure Chemical Ind.) and methylethylketone (MEK, Wako Pure Chemical Ind.) were used as solvents.

Preparation of Mixed (Binary or Ternary) Solvents——EtOH and 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 ternary solvent system (after mixing 25 ml of EtOH, 50 ml of MEK and an appropriate volume of water).

Solubility Measurements——Excess NC was added to pure or mixed solvents. Each suspension was incubated in a water bath at 37 °C for 24 h. The concentration of NC in the supernatant was determined by using a high

performance liquid chromatography (HPLC) system (LC-6A, Shimadzu Seisakusho, Kyoto, Japan). The conditions were as follows: 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.

***In Vitro* Skin Permeation Experiments**——The abdominal skin of WBN/kob hairless rat (180—200 g, Saitama Laboratory Animals, Sugito, Saitama, Japan) was excised and mounted in a 2-chamber diffusion cell.[5] NC was suspended in various pure solvents or dissolved (10 mg/ml) in various mixed solvents. The resulting suspension or solution was added to the donor-side half-cell. The same solvent (NC-free) 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 *vice versa* on the NC permeation through the skin. The cumulative amount of NC that permeated through the skin per unit area, Q, was determined by HPLC (conditions: same as above).

Theoretical

The steady-state permeation rate per unit area, F, which is the same as the differential of Q against time, t, is expressed by[6]:

$$F=\frac{dQ}{dt}=\frac{a_d}{\gamma_m}\frac{D}{L} \tag{1}$$

where a_d and γ_m are the thermodynamic activity of the drug in the donor compartment and the activity coefficient of the drug in the skin barrier, respectively, and D and L are the diffusion coefficient of the drug in the skin barrier and the thickness of the skin barrier, respectively. The activity, a_d, can be expressed by:

$$a_d=C_d\times\gamma_d \tag{2}$$

where C_d and γ_d are the concentration and activity coefficient of the drug in the donor compartment, respectively. When the drug is suspended in the donor compartment, Eqs. 1 and 2 can be expressed as follows:

$$F_{max}=\frac{a_{max}}{\gamma_m}\frac{D}{L} \tag{3}$$

$$a_{max}=C_s\times\gamma_{d,max} \tag{4}$$

where a_{max} and $\gamma_{d,max}$ are the activity and activity coefficient of the drug in the saturated solution, respectively, and C_s is the solubility of the drug. Assuming that $\gamma_d=\gamma_{d,max}$, the calculated maximum flux, F_{max}, is expressed by[7]:

$$F_{max}=F\times\frac{C_s}{C_d} \tag{5}$$

The effect of solvents on the skin permeation of NC from the binary and ternary solvent systems was evaluated in terms of the F_{max} value. In the case of permeation experiments using pure solvents on the donor side, the F value can be assumed to be F_{max}. On the other hand, with mixed solvents, F_{max} was calculated by using Eq. 5 from the observed F value. Comparison in terms of F_{max} was done to ensure equal thermodynamic activity of NC in different solvents.

Results and Discussion

Table I shows the solubilities of NC in pure solvents at 37 °C. The solubility of NC in PG was higher than those in water, EtOH and MEK.

Figure 1 shows the solubilities of NC in binary EtOH–water and ternary EtOH–MEK–water solvent systems. The solubilities of NC in several binary EtOH–water solvents were higher than those in both pure solvents; this effect is called cosolvency. The highest solubility

TABLE I. Solubility of NC at 37 °C

	Solubility at 37 °C (mg/ml)
Water[a)]	8.71
EtOH	19.1
PG	48.5
MEK	2.75

a) The pH of NC suspension in water was 4.0.

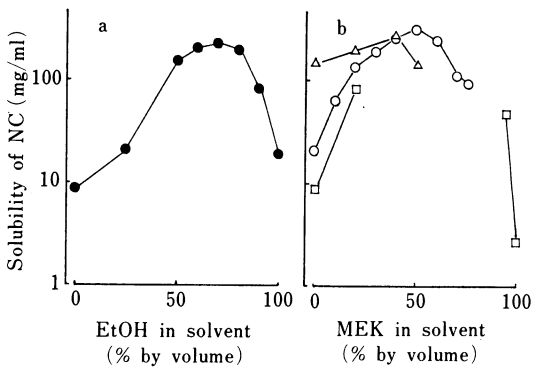

Fig. 1. Solubility of NC in Mixed Solvent Systems at 37 °C

a: EtOH–water binary system. b: EtOH–MEK–water ternary system. (○), EtOH 25% (v/v); (△), EtOH 50% (v/v); (□), without EtOH. The data are means of three experiments.

(228 mg/ml) in the binary EtOH–water solvent system was observed in EtOH : H_2O = 7 : 3 (70% (v/v) EtOH); it amounted to about 20 and 10 times those in water and EtOH, respectively. Cosolvency was also observed in the ternary EtOH–MEK–water solvent system. The highest solubility (316 mg/ml) was observed in the ternary EtOH : MEK : H_2O = 1 : 2 : 1 solvent system; it was about 1.5 times higher than the highest value for the binary EtOH–water system (EtOH : H_2O = 7 : 3).

Figure 2 shows the skin permeation profiles from NC suspensions in pure water, EtOH, PG and MEK. Although the solubility of NC in PG was higher than those in the other pure solvents, the skin permeation rate of NC from PG suspension was as low as that from aqueous suspension. Skin permeation rates of NC from EtOH and MEK suspensions were higher than those from aqueous and PG suspensions.

The reason why the permeation rate of NC from PG suspension is similar to that from aqueous suspension might be that the thermodynamic activity of NC in PG suspension is the same as that in the aqueous suspension for the donor compartment. The partition of drugs from the donor compartment containing highly drug-solubilizing solvents to the skin barrier phase is usually low.[8)] If drugs were suspended in solvents and the solvents did not affect the skin barrier, the skin permeation rate of drugs should be constant independently of the kind of solvent. This conclusion is easily derived from Higuchi's theory[6)] (Eq. 1).

On the other hand, the skin permeation rates of NC from EtOH and MEK suspensions were much higher than those in aqueous and PG suspensions. The rapid skin permeations from EtOH and MEK suspensions might be related to the changes of D and/or γ_m which are induced by the penetration of such solvents, since the thermodynamic activities of NC in these suspensions are the same. Although PG and water also affect such parameters, the changes of these parameters should be very low compared to those by EtOH and MEK in this experimental system.

Figure 3a and b shows the F_{max} values calculated from the observed F values in the experiments using NC solutions prepared from binary EtOH–water and ternary EtOH–MEK–water solvent systems, respectively. The relationship between the logarithm of the calculated maximum flux of NC from the binary and ternary solvent systems and the composition of the solvent was similar to that between the solubility of NC and the composition of the solvent. Within the F_{max} values calculated by using Eq. 5 from comparable F values, the highest value (4.6×10^{-1} $\mu g/cm^2/s$) was observed in the ternary

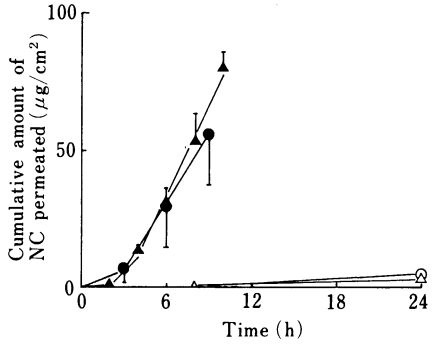

Fig. 2. Effect of Solvents on NC Permeation through the Hairless Rat Skin

(○), water; (●), EtOH; (△), PG; (▲), MEK. The data are means of three experiments and vertical bars show standard errors.

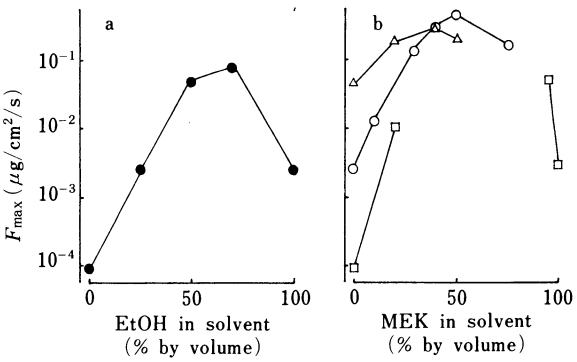

Fig. 3. Relationship between F_{max} Values and Compositions of Mixed Solvent Systems

a: EtOH–water binary system. b: EtOH–MEK–water ternary system. (○), EtOH 25% (v/v); (△), EtOH 50% (v/v); (□), without EtOH. The data are means of three experiments.

system of EtOH : MEK : H_2O = 1 : 2 : 1, which also gives the highest solubility. The F_{max} value was about 5000 times higher than that from pure water.

The marked difference of F_{max} values would result from changes of D and/or γ_m values. The changes of these parameters might be caused by solvent penetration into the skin barrier (stratum corneum). The penetration rates of EtOH, MEK and other solvents containing either one into the skin barrier might be very fast, so that these solvent systems would give high skin permeation of NC regardless of the thermodynamic activity of NC on the donor side.

These results suggest that mixed solvents containing EtOH and MEK might be effective as vehicles for topical application to enhance the skin permeation of NC. Transdermal absorption of drugs, therefore, might be enhanced by using various solvents which could not only freely solubilize the drugs but also change the values of D and γ_m in the skin barrier. Further experiments are under way in our laboratory using indomethacin,[9] an anti-inflammatory drug, and nicorandil,[10] a potent coronary vasodilator.

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