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Percutaneous absorption of piroxicam from ointment bases in rabbits

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Summary

In order to investigate the process of percutaneous absorption from various ointment bases, the blood levels of piroxicam were determined at optimal intervals after the ointment application in rabbits.

After the oral and intravenous administrations, the plasma levels of piroxicam were described by the two-compartment model. A pharmacokinetic model similar to the percutaneous absorption of indomethacin was developed to test the concepts regarding the percutaneous absorption of piroxicam from topical ointment bases.

A reasonably good fit between experimental and calculated values was obtained by taking into account identical absorption rate constant (K_a) and the changes in drug release constant (K_r) and the fraction of drug absorbed (F).

We found that piroxicam in the o/w ointment base (UCH ointment containing 12% propylene glycol) had a better percutaneous absorption effect than the other three different kinds of ointment bases which were a simple ointment, PEG ointment and petrolatum rosewater ointment.

The pH value of the water phase in UCH ointment containing 12% propylene glycol was adjusted to pH 9.2 by the sodium bicarbonate-buffered solution, then the percutaneous absorption of piroxicam could be increased. The effect of the amount of piroxicam on the percutaneous absorption was also investigated.

The optimal effect with the additives in the ointment was finally attained with an addition of 5% urea.

Introduction

Piroxicam is a non-steroid anti-inflammatory, antipyretic and analgesic agent (Schiantarelli and Cadel, 1981). Oral administration of piroxicam has been the

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principle route for the treatment of rheumatoid arthritis (Hobbs and Twomey, 1979). Oral therapy is very effective, but has an irritation side-effect concerning gastrointestinal mucosa (Schiantarelli and Cadel, 1981). Recently administration of topical nitroglycerin as an ointment was shown to be clinically effective for angina pectoris (Reichek et al., 1974; Karsh et al., 1978). We therefore attempted to design a piroxicam ointment to overcome the side-effect and to obtain a therapeutic plasma concentration (i.e. a sustained plasma concentration during dosing without a high initial peak concentration).

The topical anti-inflammatory effects of percutaneous piroxicam from ointment have been studied by some researchers (Schiantarelli et al., 1982; Larson et al., 1980), but the pharmacokinetic properties and the factor that influenced the percutaneous absorption effect of piroxicam from the ointment bases have not yet been studied.

The primary aim of the present study was to examine the influence of the types of ointment bases, pH values, amount of piroxicam and the various additives regarding the percutaneous absorption of piroxicam, employing rabbits as the test animals. The objective of the present work was also to develop a pharmacokinetic model for elucidating the percutaneous absorption of piroxicam.

Materials and Methods

Materials

The following reagents were used: piroxicam [1], acetonitrile [2], acetic acid, diethyl ether, indomethacin [3], propylene glycol, taurine, urea, N-methylpyrrolidone, sodium bicarbonate, CMC, simple ointment (U.S.P.), PEG ointment (U.S.P.), petrolatum rosewater ointment (U.S.P.), UCH [4] ointment (pharmaceutical science). All other chemicals were of analytical reagent grade.

Piroxicam suspension for oral administration

The piroxicam suspension was prepared by suspending 200 mg of piroxicam powder in 100 ml of a 1% CMC solution.

Piroxicam solution for i.v. administration

The piroxicam solution for i.v. injection was prepared by dissolving 200 mg of piroxicam in 100 ml of a sodium bicarbonate-buffered solution (pH 9.2).

Piroxicam ointment

Piroxicam, previously reduced to fine powder in a mortar and sifted through a 100-mesh filter, was made into an ointment base representing each of the four physical types. The bases selected were: simple ointment (U.S.P.), an oleageneous

[1] Pfizer, U.S.A.
[2] E. Merck, U.S.A.
[3] Sumitomo Chemicals, Osaka, Japan.
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base; PEG ointment (U.S.P.), a water-soluble base; petrolatum rosewater ointment (U.S.P.), a water-in-oil emulsion base; UCH ointment (pharmaceutical science), an oil-in-water emulsion base. The piroxicam ointment was prepared so as to contain 3.3% of the active ingredient. An additive if necessary was incorporated into the water phase of these ointments. The compositions of the various piroxicam ointments are summarized in Table 1.

Test animals

White male rabbits weighing 1.8–2.2 kg that were fasted for 24 h, and were then anesthetized by inhalation of diethyl ether, and finally sections were fixed on a plate.

TABLE 1

COMPOSITION OF PIROXICAM OINTMENTS

Serial no.	Ointment base	mg of piroxicam ointment in 6 g of ointment	Additive	pH of added water
1	simple ointment	200	none	7.2
2	PEG ointment	200	none	7.2
3	petrolatum rosewater ointment	200	none	7.2
4	UCH ointment	200	none	7.2
5	UCH ointment containing 12% propylene glycol	200	none	7.2
6	UCH ointment containing 12% propylene glycol	200	70% PEG400 aq. solution	7.2
7	UCH ointment containing 12% propylene glycol	200	none	9.2 *
8	UCH ointment containing 12% propylene glycol	200	1% urea	7.2
9	UCH ointment containing 12% propylene glycol	200	2.5% urea	7.2
10	UCH ointment containing 12% propylene glycol	200	5% urea	7.2
11	UCH ointment containing 12% propylene glycol	200	1%N-methyl-pyrrolidone	7.2
12	UCH ointment containing 12% propylene glycol	200	5% N-methyl-pyrrolidone	7.2
13	UCH ointment containing 12% propylene glycol	200	1% taurine	7.2
14	UCH ointment containing 12% propylene glycol	200	5% taurine	7.2
15	UCH ointment containing 12% propylene glycol	100	none	9.2
16	UCH ointment containing 12% propylene glycol	50	none	9.2
17	UCH ointment containing 12% propylene glycol	20	none	9.2

* containing sodium bicarbonate buffered solution

Route of administration

Oral administration. A dose of 10 mg/kg of piroxicam suspension was administered orally into the stomach of the rabbits with a Nelaton Catheter tube No. 10. The inside of the tube was then rinsed 5 times with 5 ml of water.

I.v. administration. A dose of 10 mg/kg of the piroxicam solution was administered i.v. into the auricular vein of the rabbits over a period of 15 s.

Topical administration

The hair was removed with electric hair-clippers from the skin of the abdominal region 24 h prior to application of the ointment. An accurately weighted 6 g of the sample ointment was spread uniformly over a sheet of cloth, 6×10 cm^2. This was then applied to the shaved surface of the rabbits. To employ occlusive dressing techniques (ODT) and ensure adequate contact between the ointment and the skin, the cloth was covered with a thin plastic film and fastened with the aid of adhesive tape around the edges.

In vitro piroxicam release test

The apparatus for studying drug release from an ointment has been described previously (Shiozaki et al., 1982). The Visking seamless cellulose tubing (Visking, size C-110) was used as the membrane. The test ointment sample was poured into the left container of the cell and 12 ml of the pH 7.4 phosphate buffers were poured into the right container of the cell. The cell was immersed and shaken in a water bath at 37°C. One millimeter of sample solution was taken up through a sampling tube at an appropriate time and assayed with the spectrophotometer at 365 nm. The volume of the receptor phase was kept constant throughout the release run by replacing the removed sample with an equal volume of the pH 7.4 phosphate buffers.

Determination of the solubility of piroxicam in a buffered solution and PEG 400 aqueous solution

The excessive piroxicam was shaken with 6 ml of various buffers (pH 2–10) or various concentrations of the PEG aqueous solution (10–100% v/v) in a 15-ml glass-stoppered centrifuge tube for 48 h at 32°C. The concentration of piroxicam in the buffers and PEG aqueous solution was determined spectrophotometrically at 365 nm and by the HPLC method, respectively.

Measurement of the partition coefficient of piroxicam between ether and the PEG 400 aqueous solution

A 15-ml glass-stoppered centrifuge tube, containing 3 ml of ether (having been saturated with PEG 400) and 3 ml of the 10–100% v/v PEG 400 aqueous solution (having been saturated with ether) which contained 0.05% piroxicam. The mixture was gently shaken in a water bath at 32°C for 30 min. The concentration of piroxicam in the ether phase was determined by the HPLC method and the partition coefficient between ether and the PEG 400 aqueous solution was calculated.

Measurement of the partition coefficient of piroxicam between the octanol and buffers

A-15 ml glass-stoppered centrifuge tube, containing a 2-ml octanol solution of piroxicam (0.02% w/v) and 5 ml of the various buffers (pH 2–10). The mixture was gently shaken in a water bath at 32°C for 48 h. The concentration of piroxicam in the aqueous layer was determined spectrophotometrically and the partition coefficient between the octanol and buffers was calculated.

Analytical method

The method for analyzing piroxicam and 5-hydroxypiroxicam was that described previously (Tsai et al., 1984).

Cutaneous reserve of piroxicam

Employing experimental conditions similar to those in the percutaneous absorption mentioned above, a male rabbit was killed 28 h after the application of the test ointment, the test ointment was peeled off, and the abdominal skin of the applied area was first wiped clean 200 times with cotton to remove the residual ointment. The skin of the applied region was isolated to the corium, and the isolated skin, 3 cm^2, was then cut into strips with scissors.

For the determination of the drug content of the skin, the analytical method for piroxicam described previously was modified as regards the extraction process of piroxicam from the skin. A mixture of isolated skin in strips and 2 ml of distilled water in a glass homogenizing-tube was homogenized for 15 min. The homogenate was then mixed with 1 ml of Sørensen citrate buffer (pH = 3.0) mixed for 10 s and extracted with 5 ml of diethyl ether by mechanical shaking for 15 min. After centrifuging for 5 min at 3000 rpm, a 2-ml of aliquot of the ether phase was transferred to another tube and evaporated to dryness in a water bath at 50°C. The residue was redissolved in 1 ml of the mobile phase and 50 μl of the indomethacin methanol solution was added (internal standard) at a concentration of 1 mg/ml and mixed for 15 s by a vortex mixer. After the above process, 20 μl of this solution was injected into the column for HPLC through a stop-flow injection port (aufs 0.05).

Result and Discussion

For the purpose of studying the biopharmaceutical aspects of percutaneous absorption of piroxicam, one prerequisite was that the pharmacokinetic parameter of the i.v. administration should be known to correlate with the percutaneous absorption of piroxicam. After the i.v. administration of 10 mg/kg of piroxicam, the plasma concentration–time curve for piroxicam and 5′-hydroxypiroxicam was shown in Fig. 1 and the parameters of the piroxicam pharmacokinetic model were shown in Table 2. The data obtained indicated that the disposition of piroxicam in the plasma followed the first-order process. For comparison of the bioavailability, an oral administration of piroxicam (10 mg/kg) was carried out and it indicated that piroxicam was absorbed in the rabbit with the mean maximum peak concentration in the plasma being reached within 5 h as shown in Fig. 2. The equation expressing the amount of the oral absorption could be derived from the model shown in

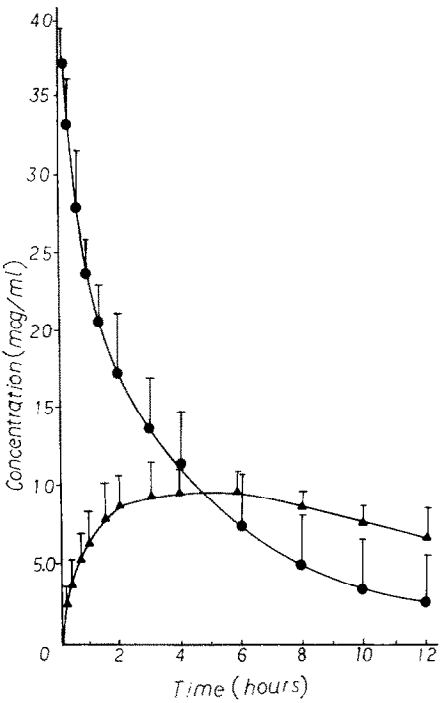


Fig. 1. Plasma concentration–time curve for piroxicam (●) and 5′-hydroxypiroxicam (▲) in the rabbit plasma after the i.v. administration of 10 mg/kg of piroxicam. Each point represents the mean of 4 determinations. Solid line for piroxicam calculated from the equation $C = 26.03 \cdot e^{-0.555t} + 14.39 \cdot e^{-0.0876t}$, where C is the piroxicam concentration in plasma. The figure is taken from a previous paper (Tsai et al., 1984).

TABLE 2

VALUES FOR THE PARAMETERS OF A PHARMACOKINETIC MODEL DESCRIBING THE METABOLISM AND EXCRETION OF PIROXICAM IN RABBIT FOLLOWING i.v. ADMINISTRATION OF 10 mg/kg (n = 4)

Parameter	Value
$\alpha(h^{-1})$	0.555
$\beta(h^{-1})$	0.0876
$t_{1/2}\beta(h^{-1})$	7.911
$K_{el}(h^{-1})$	0.191
$k_{12}(h^{-1})$	0.198
$k_{21}(h^{-1})$	0.254
$V_c(ml\ kg^{-1})$	247.4
$V_T(ml\ kg^{-1})$	192.8

α and β are hybrid first-order rate constant and $t_{1/2}\beta$ is the half-life associated with the terminal exponential process; k_{el} = elimination rate constant from the central compartment; k_{12} = rate constant from the central to tissue compartment; k_{21} = rate constant from the tissue to central compartment; V_c = distribution volume of the central compartment; and V_T = distribution volume of the tissue compartment. These data are taken from a previous report (Tsai et al., 1984).

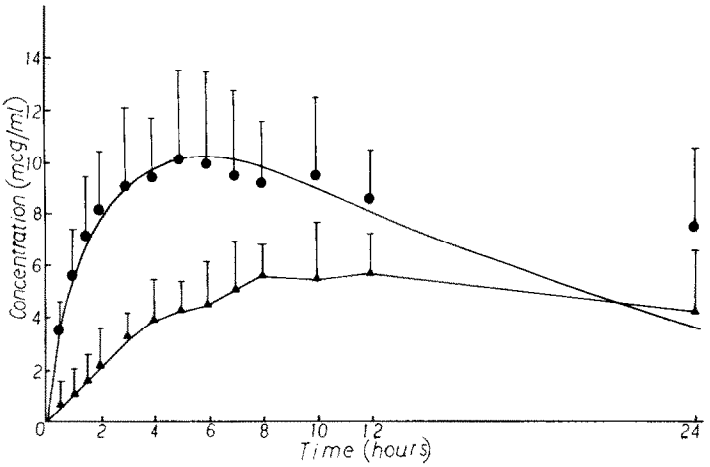


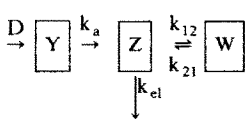
Fig. 2. Plasma concentration–time curve for piroxicam (●) and 5′-hydroxypiroxicam (▲) in rabbit plasma after p.o. administration of 10 mg/kg of piroxicam. Curve for piroxicam calculated from the equation $C = -10.618 \cdot e^{-0.555t} + 31.007 \cdot e^{-0.087t} - 20.389 \cdot e^{-0.162t}$. Vertical bars are standard deviations (n = 4).

Scheme 1 Model A in relation to the plasma–time data for the unchanged piroxicam. The best-fit curves obtained for the calculated lines compared with the experimental data suggest that the two-compartment model is sufficient to describe the disposition and elimination of piroxicam in rabbits.

Scheme 1.

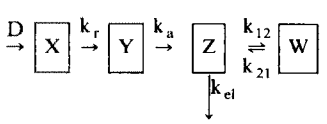
Pharmacokinetic compartment model used for piroxicam.
Model A — two-compartment model with first-order absorption

$$C = P e^{-\alpha t} + Q e^{-\beta t} + R e^{-k_a t}$$



Model B — two-compartment model with two consecutive first-order input steps

$$C = P e^{-\alpha t} + Q e^{-\beta t} + R e^{-k_a t} + S e^{-k_r t}$$



where D = dose administered; X = amount of drug in ointment base; Y = amount of drug in absorption site; Z, W = amount of drug in central and tissue compartment; k_r = drug release rate constant; k_a = absorption rate constant; k_{12}, k_{21}, α, β = distribution rate constant; k_{el} = elimination rate constant.

In order to explain the plasma concentration–time data for the unchanged piroxicam after the topical administration, it is a prerequisite that a theoretical model should be developed. Scheme 1 Model B (Naito and Tsai, 1981) gives a pharmacokinetic model which can account for the percutaneous absorption of the drug after the topical administration. All the curves for percutaneous absorption were calculated from the equation in Scheme 1 Model B. The calculated lines were fitted to the experimental data by the non-linear least regression method (Gauss-Newton method), and the results suggested that both the release and absorption were first-order processes at the dosage levels studied.

Fig. 3 shows the four types of ointment bases selected to investigate the variations in the percutaneous absorption of piroxicam. The UCH ointment containing 12% propylene glycol was found to yield the highest plasma peak concentration and the highest $AUC_{0\text{-}28h}$ value of piroxicam than the other three ointment bases which were the simple ointment, PEG ointment and petrolatum rosewater ointment. The $AUC_{0\text{-}28h}$ values of these four ointments (shown in Table 3) was significantly different (ANOVA test, $P < 0.05$). Omitting the propylene glycol and using the UCH ointment only the percutaneous effect was able to be decreased as shown in Fig. 3A and the $AUC_{0\text{-}28h}$ values of these two ointments described in Table 3 were significantly different (t-test, $P < 0.05$). From the solubility test, the solubility of piroxicam for 100 ml of propylene glycol and water were 150 mg and 48.9 mg of piroxicam, respectively. Thus, the propylene glycol enhanced the percutaneous absorption of piroxicam from the UCH ointment may be due to its higher solubility to piroxicam. Propylene glycol might have the same effect on the percutaneous

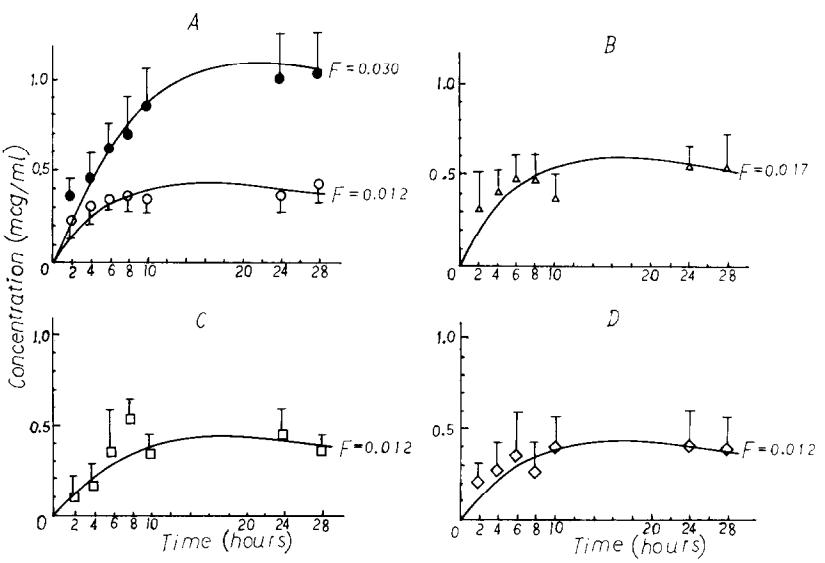


Fig. 3. Effect of type of ointment base on the percutaneous absorption of piroxicam. Key: ●, UCH ointment containing 12% propylene glycol; ○, UCH ointment; △, PEG ointment; □, simple ointment; ◇, rosewater ointment. F = fraction of drug absorbed to the total drug in the ointment base. Solid lines for piroxicam were calculated from Equation of Scheme 1. Vertical bars are standard errors (n = 4).

TABLE 3

PHARMACOKINETIC PARAMETER ON PERCUTANEOUS ABSORPTION FROM PIROXICAM OINTMENT

Serial no.	F	K_a	K_r	Piroxicam AUC $*_{0\text{-}28h}$ ($\mu g \cdot h/ml$)
1	0.012	0.028	1.0	10.03 ± 1.54
2	0.017	0.028	2.0	12.30 ± 4.23
3	0.012	0.028	1.0	10.16 ± 1.83
4	0.012	0.028	2.0	9.84 ± 3.10
5	0.030	0.028	0.3	16.9 ± 3.80
6	0.012	0.028	2.0	9.89 ± 3.10
7	0.099	0.028	0.42	62.7 ±15.5
8	0.014	0.028	0.35	10.24 + 2.08
9	0.030	0.028	0.10	13.9 ± 2.5
10	0.099	0.028	0.07	46.7 ± 7.9
11	0.012	0.003	2.0	9.8 ± 1.96
12	0.085	0.1	4.0	40.4 ± 5.2
13	0.014	0.003	2.0	10.724± 1.074
14	0.052	0.1	3.5	17.71 ± 5.04
15	0.069	0.028	0.4	53.8 ±10.04
16	0.064	0.028	0.4	48.31 ± 4.8
17	0.030	0.028	0.175	20 ± 4.5

* Obtained by trapezoidal rule technique.

F = fraction of drug absorbed to the total drug in the ointment base. K_a = absorption rate constant. K_r = drug release rate constant.

absorption of estradiol and betamethasone (Møllgaard and Hoelgaard, 1983; Busse et al., 1969).

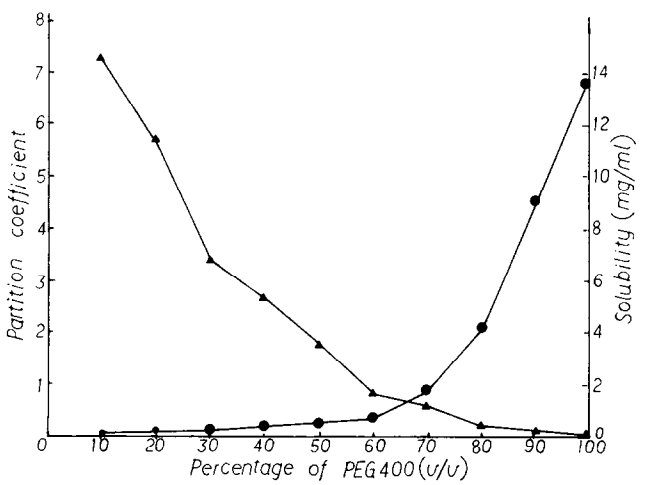


Fig. 4. Relationship between partition coefficient (▲) and solubility (●) of piroxicam in PEG 400 aqueous solutions.

Fig. 4 shows the relationship between partition coefficient (ether/PEG 400 aqueous solution) and solubility of piroxicam for various concentrations of the PEG 400 aqueous solution. The most proper value of partition coefficient and solubility of piroxicam was found to be the 70% PEG 400 aqueous solution as shown in Fig. 4. When the water in the UCH ointment containing 12% propylene glycol was replaced by the 70% PEG 400 aqueous solution, the percutaneous absorption of piroxicam was reduced as shown in Fig. 5. The $AUC_{0\text{-}28h}$ values of these two ointments described in Table 3 were significantly different (t-test, $P < 0.05$). Although the higher solubility, 185 mg of piroxicam is soluble in 100 ml of the 70% PEG 400 aqueous solution, the lower partition coefficient of piroxicam at the 70% PEG 400 aqueous solution and the stronger binding force between piroxicam and PEG in the ointment would reduce the drug release from the ointment base to the skin. PEG might have the same effect on the percutaneous absorption of methyl nicotinate from the ointment (Sarkany et al., 1965).

When the water (pH = 7.2) in the UCH ointment containing 12% propylene glycol was replaced by the pH 9.2 sodium bicarbonate-buffered solution, the percutaneous absorption of piroxicam was increased as shown in Fig. 6. The $AUC_{0\text{-}28h}$ values of these two ointments described in Table 3 were significantly different (t-test, $P < 0.001$). Fig. 7 shows the apparent partition coefficient (octanol/buffers) and solubility of piroxicam for the various pH values of the buffered solution. According to the Eqn. 1 and the values of the solubility of piroxicam, the value of pK_a calculated was 5.5 as shown in Fig. 8.

$$\log \frac{S - S_0}{S_0} = pH - pK_a \qquad (1)$$

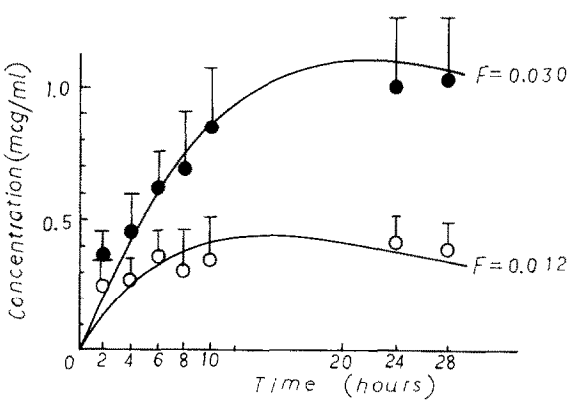


Fig. 5. Effect of the 70% PEG 400 aqueous solution replacing the water in UCH ointment containing 12% propylene glycol on the percutaneous absorption of piroxicam. Key: ●, UCH ointment containing 12% propylene glycol; ○, the 70% PEG 400 aqueous solution replacing the water in the UCH ointment containing 12% propylene glycol. F = fraction of drug absorbed to the total drug in the ointment base. Solid lines for piroxicam were calculated from equation of Scheme 1. Vertical bars are standard errors (n = 4).

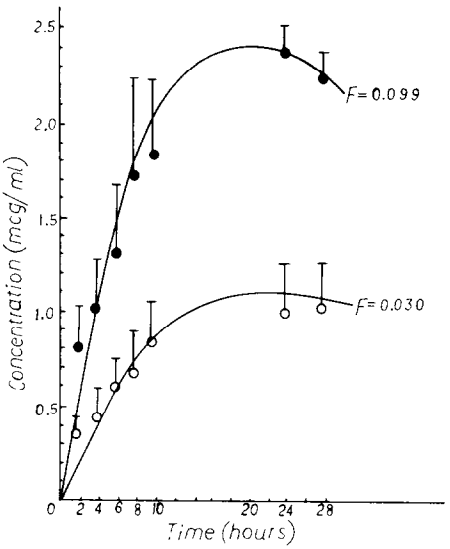


Fig. 6. Effect of the pH 9.2 phosphate buffer solution replacing the water in the UCH ointment containing 12% propylene glycol on the percutaneous absorption of piroxicam. Key: ●, the pH 9.2 buffer solution replacing the water in the UCH ointment containing 12% propylene glycol; ○, UCH ointment containing 12% propylene glycol. F = fraction of drug absorbed to the total drug in the ointment base. Solid lines for piroxicam were calculated from equation of Scheme 1. Vertical bars are standard errors (n = 4).

In Eqn. 1, S_0 is the solubility of the neutral form of piroxicam (solubility below pH 4), S is the apparent solubility of piroxicam at the various pH values, and K_a is the acid dissociation constant.

$$\log P' = \log P_{AH} - \log\left(1 + \frac{K_a}{H^+}\right) \tag{2}$$

In Eqn. 2 (Inagi et al., 1981), P′ is the apparent partition coefficient (octanol/buffers) as shown in Fig. 7, P_{AH} is the partition coefficient of the unionized piroxicam. The log P_{AH}, calculated according to Eqn. 2 based on P′ at a given pH, was always greater than 1.433 (dotted line in Fig. 9), and the difference between P_{AH} determined from P′ at acidic pH and that from P′ at higher than pH 5 became greater with an increase in the pH (shown as ○ in Fig. 9). Thus, the partition process of piroxicam does not involve only the unionized species being transferred from the aqueous phase to the organic phase. Thus, when the water in the UCH ointment containing 12% propylene glycol was replaced by the pH 9.2 sodium bicarbonate-buffered solution, piroxicam was more soluble in the ointment (562.5 mg of piroxicam dissolved in 100 ml of pH 9.2 buffers) and the piroxicam anion may be readily transferred to the hydrophobic skin region by forming ion-pair complexes with cations in the aqueous phase. The enhancement of the percutaneous absorption of the alkali ointment also may be due to the irreversible destructive effect on the keratin caused by the strongly alkali of the ointment and renders the skin more

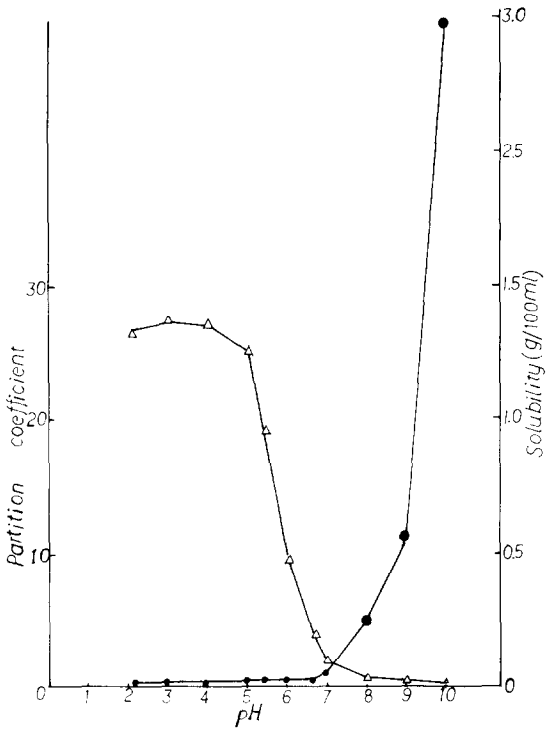


Fig. 7. Relationship between partition coefficient (△) and solubility (●) of piroxicam in various pH-buffered solutions.

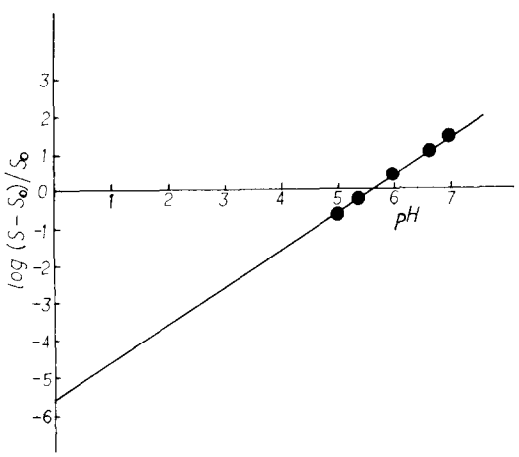


Fig. 8. Relationship between log $(S - S_0)/S_0$ and pH. S = apparent solubility of piroxicam; S_0 = solubility of the neutral form of piroxicam.

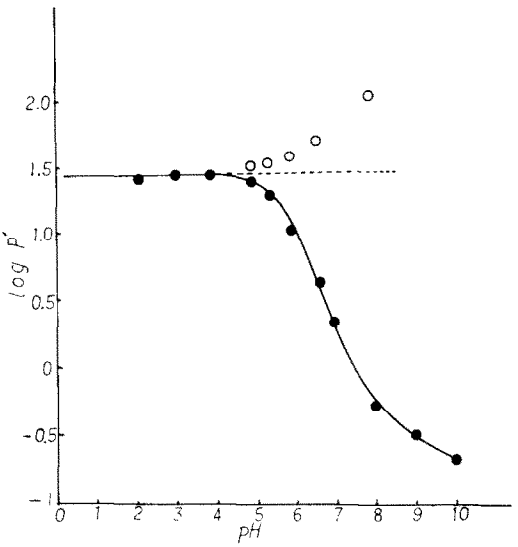


Fig. 9. pH dependence of log p′ of piroxicam. Key: ●, log p′ determined by partition experiments; ○, log p_{AH} determined from log p′ (●) according to the Eqn.: $\log p' = \log p_{AH} - \log(1 + K_a/H^+)$.

permeable (Grasso and Lansdown 1972). According to the in vitro release test of these two ointments, Fig. 10 and Table 4 show the alkali one has a higher release rate constant than the other. Thus, the in vitro release test has a good correlation with the percutaneous absorption of the piroxicam ointments.

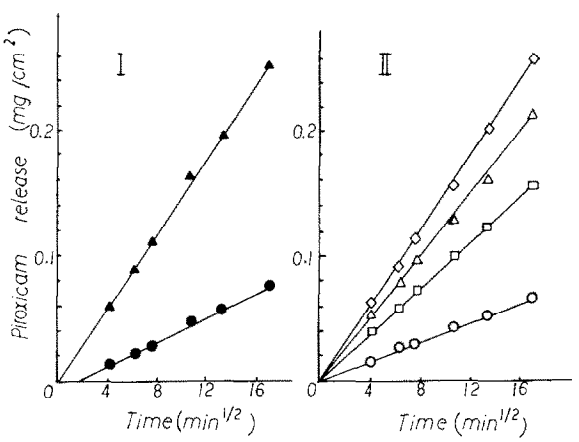


Fig. 10. Plots of the amount of piroxicam released from various UCH ointment containing 12% propylene glycol versus the square-root of time. I: pH 9.2 phosphate-buffered solution replacing water (pH = 7.2) in the ointment. Key: ▲, pH 9.2; ●, pH 7.2. II: Various amount of piroxicam in 6 g of UCH ointment containing 12% propylene glycol in which the pH of water was 9.2. Key: ◇, 200 mg; △, 100 mg; □, 50 mg; ○, 20 mg.

TABLE 4

APPARENT RELEASE RATE CONSTANT OF PIROXICAM FROM VARIOUS UCH OINTMENTS CONTAINING 12% PROPYLENE GLYCOL

Additives	mg of piroxicam in 6 g of ointment	pH of water in ointment	$K^* \times 10^3$
None	20	9.2	3
None	50	9.2	12
None	100	9.2	14
None	200	9.2	14.7
None	200	7.2	4.9
1% urea	200	7.2	5.2
2.5% urea	200	7.2	5.18
5% urea	200	7.2	5.16
5% taurine	200	7.2	5
5% N-methylpyrrolidone	200	7.2	9.65

* K = apparent release rate constant. $mg/cm^2/min^{0.5}$.

In order to study the effects of the various amounts of piroxicam on the percutaneous absorption of piroxicam, 20 mg, 50 mg, 100 mg and 200 mg of piroxicam were individually prepared in 6 g of the UCH ointment containing 12%

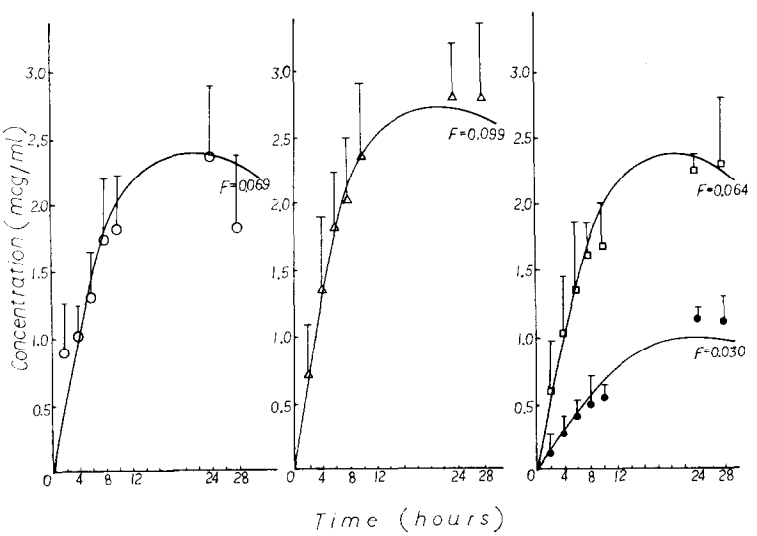


Fig. 11. Effect of various amount of piroxicam on the percutaneous absorption of piroxicam from UCH ointment containing 12% propylene glycol in which the pH of water was 9.2. Key: ○, 100 mg of piroxicam in 6 g of ointment; △, 200 mg of piroxicam in 6 g of ointment: □, 50 mg of piroxicam in 6 g of ointment; ●, 20 mg of piroxicam in 6 g of ointment. F = fraction of drug absorbed to the total drug in the ointment base. Solid lines for piroxicam were calculated from equation of Scheme 1. Vertical bars are standard errors (n = 4).

propylene glycol and the water was adjusted to pH 9.2. Fig. 11 shows the one which contained 20 mg of piroxicam having a lower plasma concentration than the others. The ointment which contained 50 mg, 100 mg and 200 mg of piroxicam all had the same plasma concentration. The $AUC_{0\text{-}28h}$ of these four ointments described in Table 3 was significantly different (ANOVA test, $P < 0.05$). In the in vitro release test, the ointment which contained 20 mg of piroxicam in the 6 g ointment base also had a lower release rate constant than others as shown in Fig. 10 and Table 4. However, the $AUC_{0\text{-}28h}$ of these three ointments containing 50 mg, 100 mg and 200 mg of piroxicam, respectively, in 6 g of the UCH ointment was not significantly different (ANOVA test, $P > 0.05$). Therefore, the effective concentration of piroxicam for the percutaneous absorption may be appropriate at 50 mg of piroxicam in 6 g of the UCH ointment.

Comparison of the difference between the plasma concentration for the UCH ointment containing 12% propylene glycol with urea additives of 1%, 2.5% and 5%,

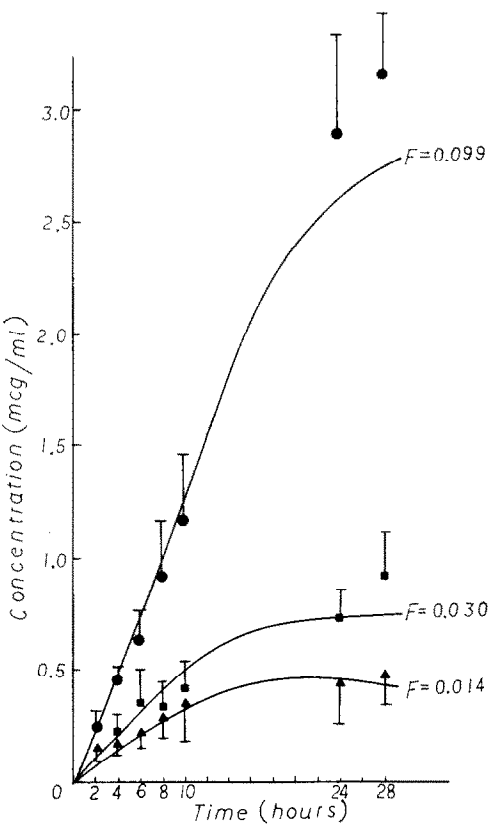


Fig. 12. Effect of various urea concentrations on the percutaneous absorption of piroxicam from UCH ointment containing 12% propylene glycol. Key: ▲, 1% urea; ■, 2.5% urea; ●, 5% urea. F = fraction of drug absorbed to the total drug in the ointment base. Solid lines for piroxicam were calculated from equation of Scheme 1. Vertical bars are ± standard errors (n = 4).

respectively are shown in Fig. 12. It was indicated that the one containing 5% urea had a better plasma concentration than the others. The $AUC_{0\text{-}28h}$ of these ointments described in Table 3 was significantly different (ANOVA test, $P < 0.05$). In the in vitro release test, there were no significantly different in the release rate constant (shown in Table 4) regarding ointments. Thus, the urea in the ointment will enhance the percutaneous absorption and the reason might be due to the increase in the percutaneous penetration of piroxicam. Urea has the same effect on the percutaneous penetration of hydrocortisone (Feldmann and Maibach, 1974).

The effects of additives, N-methylpyrrolidone and taurine at 1% and 5% concentrations on the percutaneous absorption of piroxicam from the UCH ointment containing 12% propylene glycol were compared. Fig. 13A shows that the ointment containing 5% taurine yielded a better plasma concentration than the ointment containing 1% taurine, but the $AUC_{0\text{-}28h}$ of these two ointments was not significantly different (*t*-test, $P > 0.05$). Fig. 13B shows that the ointment containing 5% N-methylpyrrolidone had a better plasma concentration than the ointment containing 1% N-methylpyrrolidone. The $AUC_{0\text{-}28h}$ of these two ointments was significantly different (*t*-test, $P < 0.001$). According to the solubility test, 14.5 g of piroxicam dissolved in 100 ml of N-methylpyrrolidone. According to the in vitro release test, the ointment containing 5% N-methylpyrrolidone had a higher release rate constant than the ointment containing 5% taurine and 5% urea as can be seen in Table 4. Thus, N-methylpyrrolidone enhanced the percutaneous absorption of piroxicam and its reason might be due to the higher solubility of piroxicam and its higher release rate constant.

Table 3 shows the comparisons of the $AUC_{0\text{-}28h}$ of piroxicam from the topical administration of 17 selected piroxicam ointments. The serial number and composition of the piroxicam ointments are shown in Table 1. It has been found that serial no. 7 (200 mg of piroxicam in UCH ointment which contained 12% propylene glycol

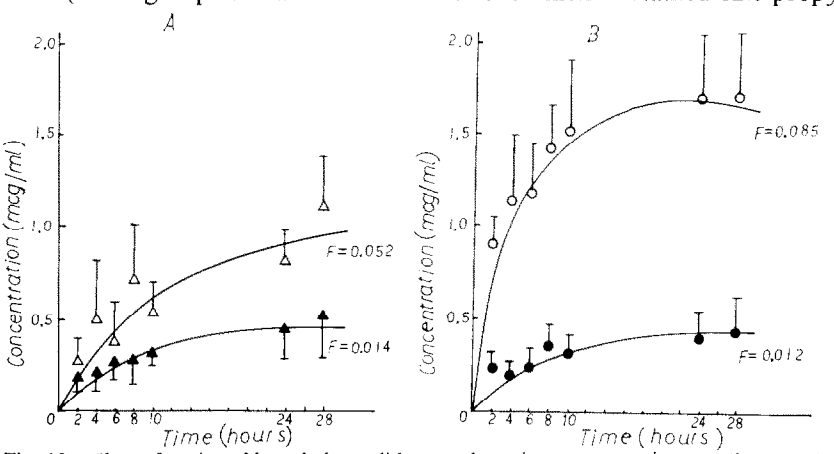


Fig. 13. Effect of various N-methylpyrrolidone and taurine concentrations on the percutaneous absorption of piroxicam from UCH ointment containing 12% propylene glycol. Key: ○, 5% N-methylpyrrolidone; ●, 1% N-methylpyrrolidone; △, 5% taurine; ▲, 1% taurine. Solid lines for piroxicam were calculated from equation of Scheme 1. F = fraction of drug absorbed to the total drug in the ointment base. Vertical bars are ± standard errors (n = 4).

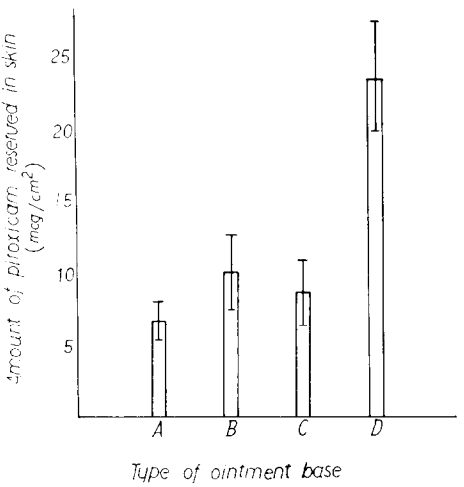


Fig. 14. Effect of ointment base on the amount of piroxicam reserved in the skin after application of test ointment for 28 h. Key: A, simple ointment; B, PEG ointment; C, petrolatum rosewater ointment; D, UCH ointment containing 12% propylene glycol. Each column shows the mean of 4 rabbits ± the standard error.

and water replacing a pH 9.2 buffer) had the best percutaneous absorption of piroxicam. The next best were the ointments of serial nos. 15, 16, 10, 12 and so on. The optimal effect with additives in the ointment was finally attained with an addition of 5% urea (serial no. 10).

The calculated lines of all the above experimental data were obtained from the formula of the pharmacokinetic Model B shown in Scheme 1. Almost all experimental data fit the calculated lines which have been drawn in the respective figures. Then, drug release rate constant (K_r), absorption rate constant (K_a), and the fraction of the drug absorbed to topical dose, (F), in 17 different kinds ointment bases could be calculated and are shown in Table 3. Except for four cases from Table 3, we found that all ointment bases had an identical K_a value, this being 0.028, and K_r from 0.07 to 4.0. These four exceptions were the ointments containing N-methylpyrrolidone and taurine. The greater difference between the K_r value and K_a value indicated that piroxicam was easily released from the ointment base. K_a value was considered to be the main rate-limiting factor in piroxicam percutaneous absorption process due to its small value. Fig. 14 shows the effect of the ointment bases regarding the amount of piroxicam retained in the skin after the topical administration for 28 h. The amount of piroxicam retained from the UCH ointment containing 12% propylene glycol was much larger than the other three types ointment bases which were simple ointment, PEG ointment and petrolatum rosewater ointment. The data in Table 3 showed the parallel results of reserve to AUC.

References

Busse, M.J., Hunt, P. Lees, K.A., Maggs, P.N.D. and McCarthy, T.M., Release of betamethasone derivatives from ointments — in vivo and in vitro studies. Br.J. Dermatol., 81 (1969) 103–112

Feldmann, R.J. and Maibach, H.I., Percutaneous penetration of hydrocortisone with urea. Arch. Dermatol., 109 (1974) 58–59

Grasso, P. and Lansdown, A.B.G., Methods of measuring, and factors affecting, percutaneous absorption. J. Soc. Cosmet. Chem., 23 (1972) 481–521

Hobbs, D.C. and Twomey, T.M., Piroxicam pharmacokinetics in man: aspirin and antacid interaction studies. J. Clin. Pharmacol., 19 (1979) 270–281

Inagi, T., Muramatsu, T., Nagai, H. and Terada, H., Mechanism of indomethacin partition between *n*-octanol and water. Chem. Pharm. Bull., 29 (1981) 2330–2337

Karsh, D.L., Umbach, R.E., Cohen, L.S. and Langou, R.A., Prolonged benefit of nitroglycerin ointment on exercise tolerance in patients with angina pectoris. Am. Heart J., 96 (1978) 587–595

Larson, D.L. and Lombardino, J.G., The topical anti-inflammatory effects of piroxicam in rodents. Agents and Actions, 10 (1980) 246–251

Møllgaard, B. and Hoelgaard, A., Permeation of estradiol through the skin — effect of vehicles. Int. J. Pharm., 15 (1983) 185–197

Naito, S.I. and Tsai, Y.H., Percutaneous absorption of indomethacin from ointment bases in rabbits. Int. J. Pharm., 8 (1981) 263–276

Reicheck, N., Goldstein, R.E., Redwood, D.R. and Epstein, S.E., Sustained effects of nitroglycerin ointment in patients with angina pectoris. Circulation, 50 (1974) 348–352

Sarkany, I., Hadgraft, J.W., Caron, G.A. and Barrett, C.W., The role of vehicles in the percutaneous absorption of corticosteroids. Br. J. Dermatol., 77 (1965) 569–575

Schiantarelli, P. and Cadel, S., Piroxicam pharmacologic activity and gastrointestinal damage by oral and rectal route. Arzneim-Forsch/Drug Res, 31 (1981) 87–92

Schiantarelli, P., Cadel, S., Acerbi, D. and Pavesi, L., Anti-inflammatory activity and bioavailability of percutaneous piroxicam. Arzneim-Forsch/Drug Res., 32 (1982) 230–235

Shiozaki, M., Nambu, N. and Nagai, T., Effect of additives on release of drugs from ointment bases. Yakuzaigaku, 42 (1982) 10–16

Tsai, Y.H., Hsu, L.R. and Naito, S.I., Simultaneous determination of piroxicam and its main metabolite in plasma and urine by high-performance liquid chromatography. Int. J. Pharm., in press.