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PERCUTANEOUS ABSORPTION OF INDOMETHACIN FROM OINTMENT BASES IN RABBITS

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SUMMARY

A pharmacokinetic model was developed to test certain concepts regarding the percutaneous absorption of indomethacin from topical ointment bases. Both the drug release from the ointment bases and absorption from the skin followed first-order kinetics, with the exception of the initial period (lag time). The ointment bases selected for study were solution-type and suspension-type ointment bases. Indomethacin was most effectively absorbed from absorption ointment bases. The effect of additives on the percutaneous absorption was also investigated using absorption ointment bases. The optimal effect with additives in the ointment bases was finally attained with the addition of 0.5% urea.

INTRODUCTION

Indomethacin is a non-steroid anti-inflammatory, antipyretic and analgesic agent (Winter et al., 1963). Oral administration of indomethacin has been the principal route for the treatment of rheumatoid arthritis (Wanka et al., 1964). Oral therapy is very effective, but the clinical efficacy is not long-lasting (Alvan et al., 1975) and side-effects such as irritation of the gastrointestinal mucosa, production of erosion, and light-headache are easily provoked (Japan Pharmacopoeia, 1976). The side-effect of headache appears to be due to a high initial plasma concentration of the drug and can be overcome by using the indomethacin in suppository form (Alvan et al., 1975). Recently, nitroglycerin administered topically as an ointment was shown to be clinically effective for angina pectoris (Reichek et al., 1974; Karsh et al., 1978), and the slower absorption rate after topical administration results in a longer duration of action than after sublingual administration. We therefore attempted to design an indomethacin ointment and to obtain a therapeutic plasma concentration (i.e. a sustained plasma concentration during dosing without high initial peak concentrations).

Studies on percutaneous absorption have been carried out by many workers on certain

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drugs such as steroids (Mckenzie, 1962; Scheuplein et al., 1969), nicotinic acid derivatives (Albery and Hadgraft, 1979), nitroglycerin (Horhota and Fung, 1979) and salicylic acid (Stolar et al., 1960; Arita et al., 1970). Percutaneous absorption involves two consecutive steps: release of the drug from the vehicle and its subsequent penetration through the skin barrier. Experimental evidence indicates that the characteristics of an ointment base influence the rate of drug release from the base (Higuchi, 1961; Higuchi, 1962; Poulsen et al., 1968; Ayres and Laskar, 1974; Chowhan and Pritchard, 1975) and the rate and quantity of percutaneous penetration and absorption (Stolar et al., 1960; Coldman et al., 1969; Marcus et al., 1970; Ostrenga et al., 1971; Feldmann and Maibach, 1974; Washitake et al., 1975). Knowledge of the specific influence of each of these factors can assist the formulation and choice of ointment bases designed to elicit a specified rate and magnitude of percutaneous drug absorption for a particular drug administered topically. However, the skin constitution is complex and many problems remain to be solved. The primary aim of the present study was to examine the influence of the type of ointment base and various additives on the percutaneous absorption of indomethacin, employing rabbits as test animals.

An experimental model for use in the thermodynamic consideration of the relation between the vehicle and percutaneous absorption has been presented (Wagner, 1961), but many problems still remain. The percutaneous absorption of salicylic acid and carbinoxamine from oily vehicles was estimated to follow first-order kinetics (Washitake et al., 1975). Relatively little quantitative information has appeared in the literature correlating drug release and absorption data with variations in plasma concentration produced by compositional changes in the formulation of the ointment base. The present work also aimed to develop a pharmacokinetic model for elucidating the percutaneous absorption of indomethacin.

MATERIALS AND METHODS

Materials

The following reagents were used: indomethacin [1], acetonitrile, acetic acid, ethyl ether, citric acid, sodium phosphate dibasic 12 hydrate, *p*-hydroxybenzoic acid, sodium bicarbonate, propylene glycol, taurine, urea, Brij-35, salicylic acid, cetyl alcohol, stearyl alcohol, sodium lauryl sulfate, lecithin, gall powder [2], simple ointment (JP), macrogol ointment (JP), hydrophilic ointment (JP), hydophilic vaselin (JP), white vaselin (JP) [3] and sorbitan sesquioleate [4].

Indomethacin solution for oral administration

The indomethacin solution was prepared by dissolving 50 mg of the dry powder in 1 ml of distilled water containing 30 mg of sodium bicarbonate by heating at about 60°C and stirring for 3 h.

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[1] Sumitomo Chemicals LTD., Osaka, Japan.
[2] Nakarai Chemicals LTD., Kyoto, Japan.
[3] Maruishi Pharmaceutical Co., LTD., Osaka, Japan.
[4] Tokyo Chemicals LTD., Tokyo, Japan.

Suspension-type ointment

Indomethacin, previously reduced to fine powder in a mortar and sifted through a 100-mesh sieve, was incorporated into an ointment base representing each of 4 physical types. The bases selected were: simple ointment (JP), an oleaginous base; hydrophilic vaselin (JP), a water-in-oil emulsion base; hydrophilic ointment (JP), an oil-in-water base; and macrogol ointment (JP), a water-soluble base. The indomethacin ointment was prepared so as to contain 2.86% of the active ingredient.

Solution-type ointment

The water phase of the absorption ointment base was prepared by dissolving 200 mg of indomethacin in 4 ml of distilled water containing 120 mg of sodium bicarbonate, and an additive if necessary was then incorporated into it. The oil phase contained 26.7% white vaselin, 12% cetyl alcohol, 4% sorbitan sesquioleate and 0.4% Brij-35. The aqueous and oil phases were heated separately to about 75°C in a water bath, and the aqueous phase was added to the oil phase with appropriate stirring. After formation of an emulsion, the stirring was continued until the temperature of the cream reached 30°C. Materials such as urea, taurine, salicylic acid, lecithin and gall powder were used as additives.

The preparation of the indomethacin hydrophilic ointment solution-type followed the same method as that of the absorption ointment described above except for the oil phase. This contained 17% white vaselin, 15% stearyl alcohol, 8.2% propylene glycol and 1% sodium lauryl sulfate.

Test animals

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

Route of administration

Oral administration

A dose of 20 mg/kg of indomethacin solution was administered orally into the stomach of rabbits with a Nelaton Catheter No. 10 tube. The inside of the tube was then rinsed 5 times with 5 ml of water.

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 weighed 7 g sample of ointment was spread uniformly over a sheet of cloth, 6×10 cm^2. This was then applied to the shaved surface of the rabbit. 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. However, in the case of 'without ODT', the cloth was fastened only with the aid of adhesive tape around the edges.

Analytical method

The method for the analysis of indomethacin was that described previously (Tsai and Naito, 1980).

Cutaneous reserve of indomethacin

Employing experimental conditions similar to those in the percutaneous absorption mentioned above, a male rabbit was killed 5 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, 2×3 cm^2, was then sliced with scissors.

For the determination of the drug contents of the skin, the analytical method for indomethacin described previously was modified as regards the extraction process of indomethacin from the skin. A mixture of isolated skin in slices and 5 ml of distilled water in a glass homogenizing tube was homogenized for 15 min. The homogenate was then mixed with 5 ml of Sørensen's citrate buffer (pH = 5.0), mixed for 10 sec and extracted with 7 ml of ethylene dichloride by mechanical shaking for 15 min. After centrifugation for 10 min at 3000 rpm, a 4-ml aliquot of the ethylene dichloride phase was transferred to another tube to which 1 ml of *p*-hydroxybenzoic acid solution (internal standard) had been added at a concentration of 2.5 μg/ml and evaporated to dryness on a water bath at 30°C in vacuo. The residue was redissolved in 200 μl of the mobile phase and 10 μl of the solution was injected into the column. The chromatographic conditions were the same as those described previously (Tsai and Naito, 1980).

RESULTS AND DISCUSSION

For the purposes of studying the biopharmaceutical aspects of percutaneous absorption of indomethacin, one prerequisite is that the pharmacokinetic parameter of intravenous administration should be known to correlate with the percutaneous absorption of indomethacin. In a previous report (Tsai and Naito, 1980), the data obtained indicated that the disposition of indomethacin in the plasma followed a first-order process with an initial rapid phase lasting for up to 4 h after dosing. For comparison of the bioavailability, oral administration of indomethacin was carried out to determine whether indomethacin was well absorbed in rabbits, with the mean maximum peak concentration in the plasma being reached within 40 min. The equation expressing the amount of oral absorption could be derived from the model shown in Scheme I in relation to the plasma–time data

Scheme I. Mathematical model for oral absorption.

$$\text{(X)} \xrightarrow{k_a} \text{(Y)} \xrightarrow{K}$$

Drug in the G-I tract — Drug in the plasma

$$\frac{dX}{dt} = -k_a X$$

$$\frac{dY}{dt} = k_a X - KY$$

When integrated,

$$X = De^{-k_a X}$$

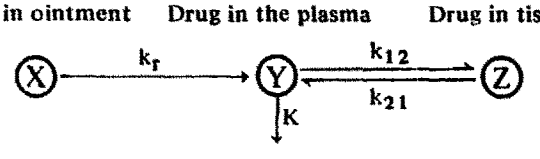
$$Y = \frac{k_a D}{V(K - k_a)} (e^{-k_a t} - e^{-Kt})$$

where D, oral dose; k_a, absorption rate constant; K, elimination rate constant from the central compartment; V, distribution volume.

for unchanged indomethacin. The good fits obtained for the calculated lines against the experimental data suggest that a two-compartment model is sufficient to describe the disposition and elimination of indomethacin in rabbits (Fig. 1) and the values of the AUC measurements may be compared to topical administration as regards bioavailability (Table 1).

In order to explain the plasma–time data for unchanged indomethacin after topical administration, it is a prerequisite that a theoretical model should be developed. Scheme II gives a pharmacokinetic model which can account for the percutaneous absorption of

Scheme II. Pharmacokinetic model for percutaneous absorption.



where k_r, drug release rate constant; k_{12}, rate constant from the central to tissue compartment; k_{21}, rate constant from the tissue to central compartment; K, elimination rate constant from the central compartment.

drug after topical administration. Since percutaneous absorption of indomethacin was obtained after a long lag time of about 2 h, the model cannot explain the percutaneous absorption of indomethacin. A new pharmacokinetic model for determining the plasma

TABLE 1

RELATIVE RATIOS OF THE GRAPHIC PAPER WEIGHT OF THE AREA UNDER THE PLASMA CONCENTRATION VS THE TIME CURVE AFTER ORAL AND TOPICAL ADMINISTRATION OF INDOMETHACIN

	Mean t_{max} (h) in the plasma	Ratio of AUC
40 mg, oral	0.67	1 (AUC_{0-8h})
200 mg, topical *	8	1.18 (AUC_{0-10h})

* Absorption ointment base was used.

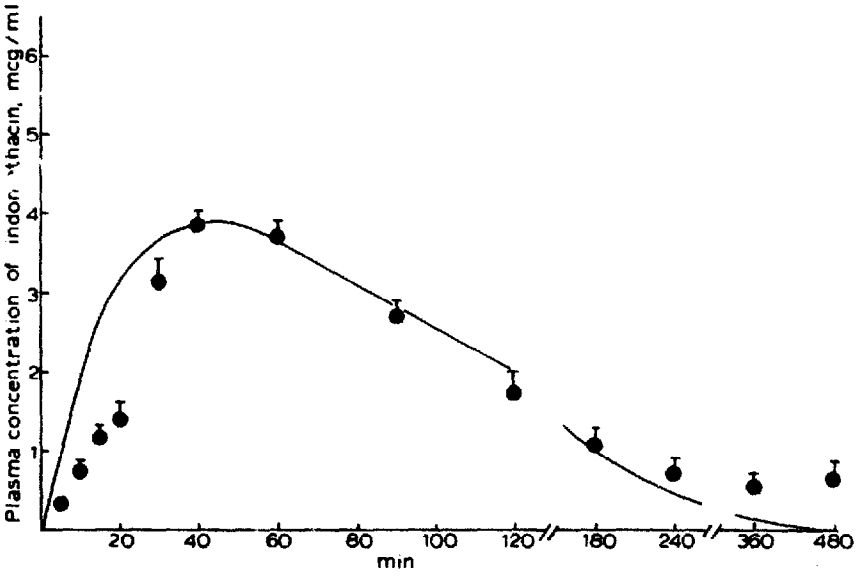
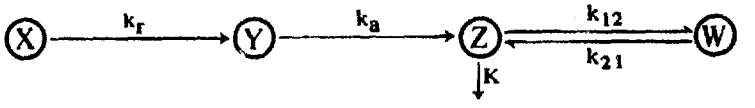


Fig. 1. Plasma concentration time course of indomethacin solution after oral administration (20 mg/kg). Solid line shows calculated curve obtained from the equation in Scheme I. Each point represents the mean of 5 rabbits with the standard error.

concentration of indomethacin after topical administration was therefore developed and is shown in Scheme III. Except for indomethacin absorption ointment containing 1% urea

Scheme III. Mathematical model for percutaneous absorption of indomethacin.

Drug in ointment Drug on the skin Drug in the plasma Drug in tissue



$$\frac{dX}{dt} = -k_r X$$

$$\frac{dY}{dt} = k_r X \quad k_a Y$$

$$\frac{dZ}{dt} = k_a Y + k_{21} W - k_{12} Z - KZ$$

$$\frac{dW}{dt} = k_{12} - k_{21} W$$

When these equations are integrated, then

$$X = De^{-k_r t} \tag{1}$$

$$Y = \frac{k_r D}{k_a - k_r}(e^{-k_r t} - e^{-k_a t}) \tag{2}$$

$$Z = k_r k_a D\left[\frac{(\alpha + k_{21})\,e^{\alpha t}}{(\alpha - \beta)(\alpha + k_a)(\alpha + k_r)} + \frac{(\beta + k_{21})\,e^{\beta t}}{(\beta - \alpha)(\beta + k_a)(\beta + k_r)}\right.$$
$$\left. + \frac{(k_{21} - k_a)\,e^{-k_a t}}{(k_a + \alpha)(k_a + \beta)(k_r - k_a)} + \frac{(k_r - k_{21})\,e^{-k_r t}}{(k_r + \alpha)(k_r + \beta)(k_r - k_a)}\right] \tag{3}$$

$$W = k_r k_a k_{12} D\left[\frac{e^{\alpha t}}{(\alpha - \beta)(\alpha + k_a)(\alpha + k_r)} + \frac{e^{\beta t}}{(\beta - \alpha)(\beta + k_a)(\beta + k_r)}\right.$$
$$\left. + \frac{e^{-k_a t}}{(k_a + \alpha)(k_a + \beta)(k_r - k_a)} + \frac{e^{-k_r t}}{(k_r + \alpha)(k_r + \beta)(k_a - k_r)}\right] \tag{4}$$

where

$$\alpha = \frac{-(k_{21} + k_{12} + K) + \sqrt{(k_{21} + k_{12} + K)^2 - 4k_{21}K}}{2}$$

$$\beta = \frac{-(k_{21} + k_{12} + K) - \sqrt{(k_{21} + k_{12} + K)^2 - 4k_{21}K}}{2}$$

D, drug concentration in the ointment base; k_r, drug release rate constant; k_a, absorption rate constant; k_{12} *, rate constant from the central to tissue compartment, equal to 1.40 h^{-1}; k_{21} *, rate constant from the tissue to central compartment, equal to 0.43 h^{-1}; K *, elimination rate constant from the central compartment, equal to 2.46 h^{-1}; V_c *, distribution volume of the central compartment, equal to 462 ml; V_T *, distribution volume of the tissue compartment, equal to 1518 ml.

* Known pharmacokinetic parameters were obtained from the previous report (Tsai and Naito, 1981).

and 5% taurine, all the curves for percutaneous absorption were calculated from Eqn. 3 of Scheme III. The calculated lines were fitted to the experimental data by adjusting the values of Z (drug in plasma) to the observed values, and the results suggested that both the release and absorption were first-order processes at the dosage levels studied.

Fig. 2 shows the type of ointment bases selected to investigate the variations in percutaneous absorption of indomethacin. Solution type absorption ointment base was found

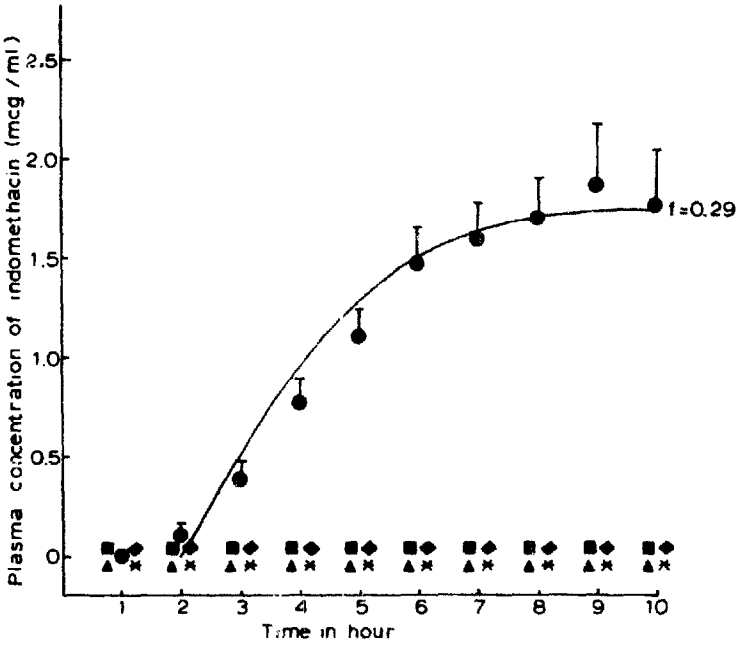


Fig. 2. Effect of type of ointment base on the percutaneous absorption of indomethacin. Key: solution-type ointment; ●, absorption ointment. Suspension-type ointments; ■, simple ointment; ◆, hydrophilic vaselin; ▲, macrogol ointment; ★, hydrophilic ointment. Solid line shows calculated curve for indomethacin from Eqn. 3 of Scheme III. f = fraction of drug absorbed to the total drug in the ointment base. Each point represents the mean of 4 rabbits with the standard error.

to yield the highest plasma concentration of indomethacin compared to other suspension-type ointment bases. This phenomenon indicates that the ionized form of indomethacin can penetrate the skin and appears similar to the intestinal absorption (Fuwa et al., 1971). According to the Higuchi equation (Higuchi, 1961), the solubility of the drug in the vehicle affects the amount and rate of release of the drug suspended in the ointment base. The solubility of indomethacin in a simple ointment, hydrophilic ointment and hydrophilic vaselin was so low that HPLC analysis could not determine it in the plasma after topical administration. However, indomethacin can readily dissolve in macrogol ointment. The affinity between indomethacin and macrogol ointment base was found to be so strong that drug release was difficult through the vehicle to the skin (Washitake et al., 1975; Stolar et al., 1960).

The effects of solution-type ointment base, absorption ointment and hydrophilic ointment, on the percutaneous absorption of indomethacin are shown in Fig. 3. The data indicate that indomethacin was absorbed to a greater extent from the absorption ointment base (w/o) than from the hydrophilic ointment base (o/w).

Fig. 4 shows the effects of various additives on the percutaneous absorption of indomethacin from absorption ointment base. In this series of experiments on the enhancement of percutaneous absorption of indomethacin by additives, the changes in the plasma concentration were influenced by all the additives tested. Urea was found to be a very strong accelerant among the additives. The surface activity of urea has been determined by Sears (1968) and was found to be dependent on the nature of the interface. Feldmann

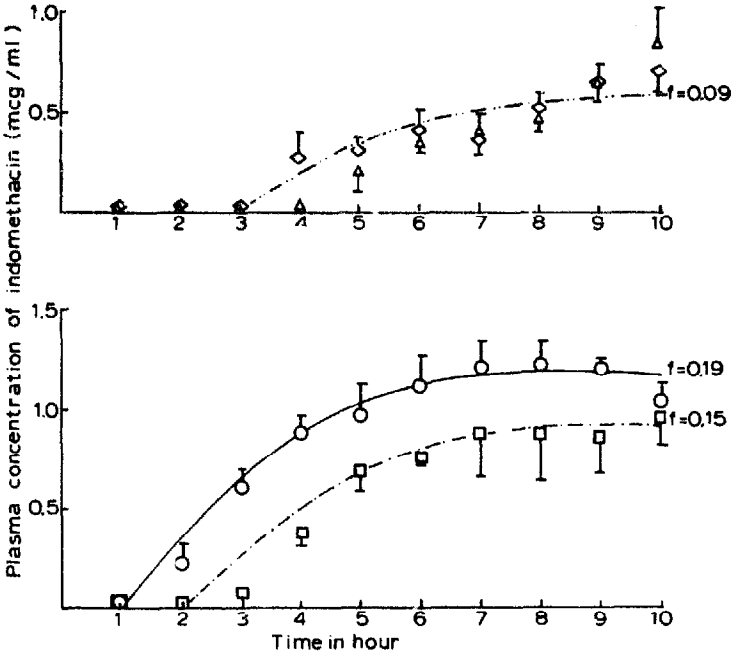


Fig. 3. Effect of solution-type ointment base on the percutaneous absorption of indomethacin. Key: o———o, absorption ointment base containing 5% urea; △, absorption ointment base containing 5% taurine; □· – · – ·□, hydrophilic ointment base containing 5% urea; ◇– · · –◇, hydrophilic ointment base containing 5% taurine. All curves (solid and broken lines) for indomethacin were calculated from Eqn. 3 of Scheme III. f = fraction of drug absorbed to the total drug in the ointment base. Each point represents the mean of 4 rabbits with the standard error.

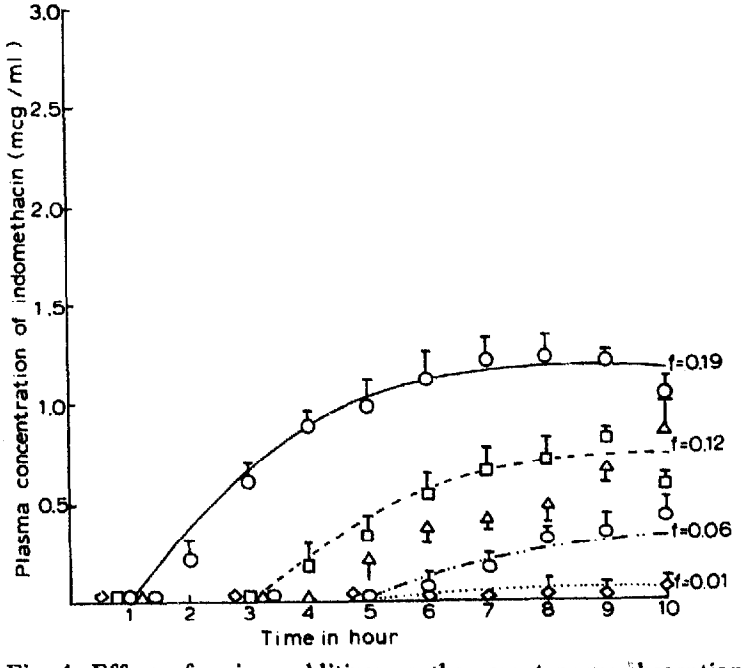


Fig. 4. Effect of various additives on the percutaneous absorption of indomethacin from absorption ointment base. Key: o———o, 5% urea; □- - - - -□, 50 mg salicylic acid; △, 5% taurine; o– · · –o, 2% lecithin; ◇· · · · ·◇, 50 mg gall powder. All curves (solid and broken lines) for indomethacin were calculated from Eqn. 3 of Scheme III. f = fraction of drug absorbed to the total drug in the ointment base. Each point represents the mean of 4 rabbits with the standard error.

et al. (1974) studied the percutaneous penetration of hydrocortisone with urea and found that the addition of urea to the cream increased the penetration approximately two-fold. These data substantiate the findings of the present study.

Fig. 5 shows the effects of various urea concentrations on the percutaneous absorption of indomethacin from absorption ointment. The results obtained indicate that the presence of urea in the absorption ointment base may increase, decrease or exert no effect on the extent of absorption of indomethacin. A marked increase in drug absorption occurred at a concentration of 0.5% urea. However, a decrease in drug absorption was observed after the addition of increasing concentrations of urea up to 2.5% or 5%. Table 2 shows that the pH values of the aqueous phase of the absorption ointment base increase with

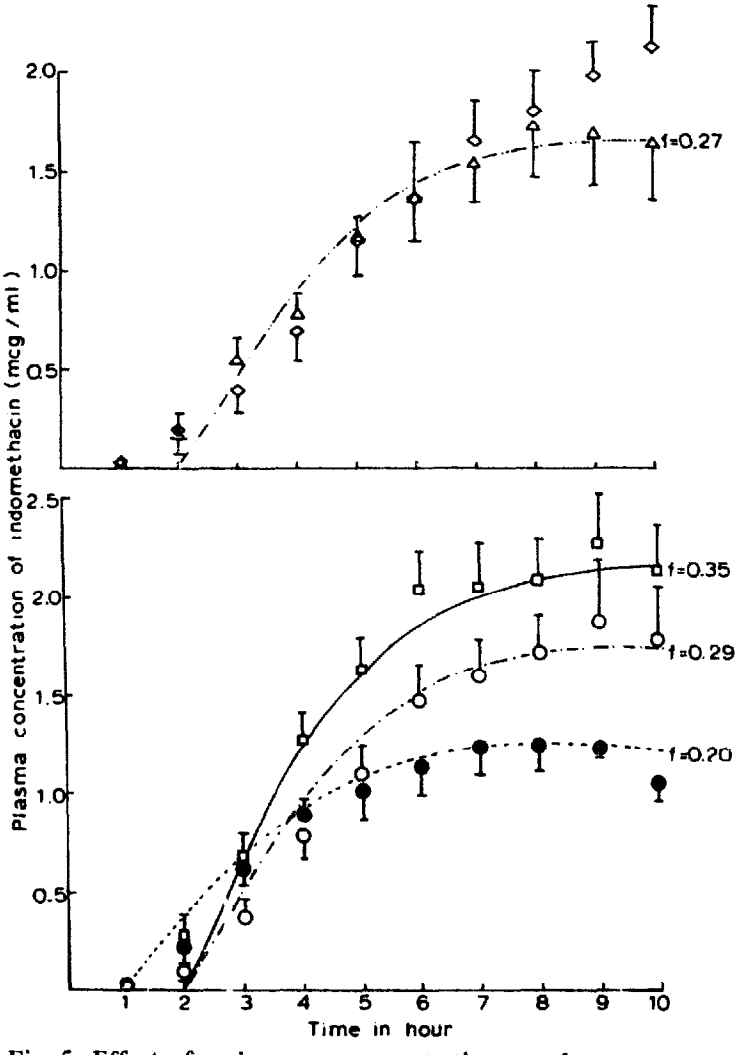


Fig. 5. Effect of various urea concentrations on the percutaneous absorption of indomethacin from absorption ointment base. Key: o- - - -o, 0%, □———□, 0.5%; ◇, 1%; △— · · —△, 2.5%; ●- - - - -●, 5%. All curves (solid and broken lines) for indomethacin were calculated from equation (3) of Scheme III. f = fraction of drug absorbed to the total drug in the ointment base. Each point represents the mean of 4 rabbits with the standard error.

TABLE 2

COMPARATIVE pH VALUES AT VARIOUS PERCENTAGES OF UREA IN THE AQUEOUS PHASE OF THE ABSORPTION OINTMENT

Per cent of urea	pH of the aqueous phase of the absorption ointment
0	7.73
0.5	7.75
1.0	7.85
2.5	8.03
5.0	8.22

increase in the concentration of urea. The penetration of fatty acid soap varies inversely with pH from 6 to 10.8 (Blank and Gould, 1961; Sprott, 1965; Blank and Gould, 1959). At higher pH values the action of the anionic surfactant upon the skin appears to be attenuated or overshadowed by the influence of the more alkaline pH itself. These data substantiate the results of the present work.

All the calculated curves have identical pharmacokinetic parameters, such as $k_a = 0.51$ (absorption rate constant) and $k_r = 0.05$ (drug release rate constant), and changes among the curves were followed by a variational fraction (f) of indomethacin absorbed to the total indomethacin in the ointment bases. In the present investigation, the indomethacin

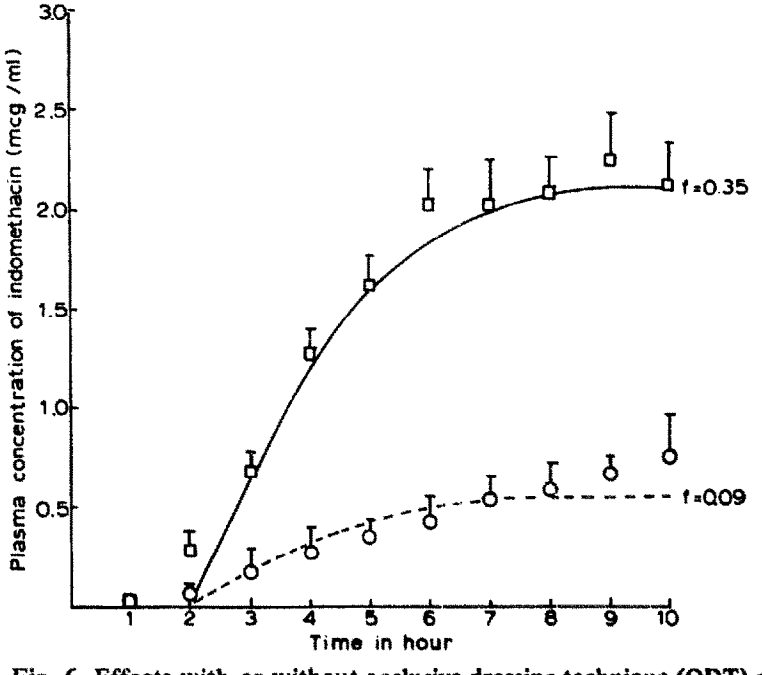


Fig. 6. Effects with or without occlusive dressing technique (ODT) on the percutaneous absorption of indomethacin from absorption ointment containing 0.5% urea. Key: □——□, with ODT; ○- - - - -○, without ODT. All curves (solid and broken lines) for indomethacin were calculated from Eqn. 3 of Scheme III. f = fraction of drug absorbed to the total drug in the ointment base. Each point represents the mean of 4 rabbits with the standard error.

absorbed depended upon the f-value except in the case of absorption ointment base containing 1% urea and 5% taurine. According to the significance of the f-value, it may be considered that indomethacin was observed from a very thin layer of ointment base facing the skin. In other words, the f-value reflects the thickness of ointment base which was utilized for absorption of the drug. In the present series of experiments, the differences in indomethacin concentration in the blood arose not from changes in k_r but from changes in f-value.

The technique of using a thin plastic film as an occlusive dressing for a topically applied drug has been exploited to promote percutaneous absorption of the drug (Idson, 1975). The effect with or without ODT on the percutaneous absorption of indomethacin is illustrated in Fig. 6. The results indicate that the percutaneous absorption was affected by ODT and was apparently 3.7-fold greater than that obtained without ODT.

Fig. 7 shows the effect of ointment bases on the amount of indomethacin retained in the skin after topical administration for 5 h. The amount of indomethacin retained from solution-type absorption ointment base was much larger than that from any of the other suspension-type ointment bases. These experimental results agreed approximately with the percutaneous absorption, and it was found that the types of ointment base together with the physicochemical properties of the drug exert a great effect on the cutaneous reservoir and the percutaneous absorption of the drug from the test ointment bases.

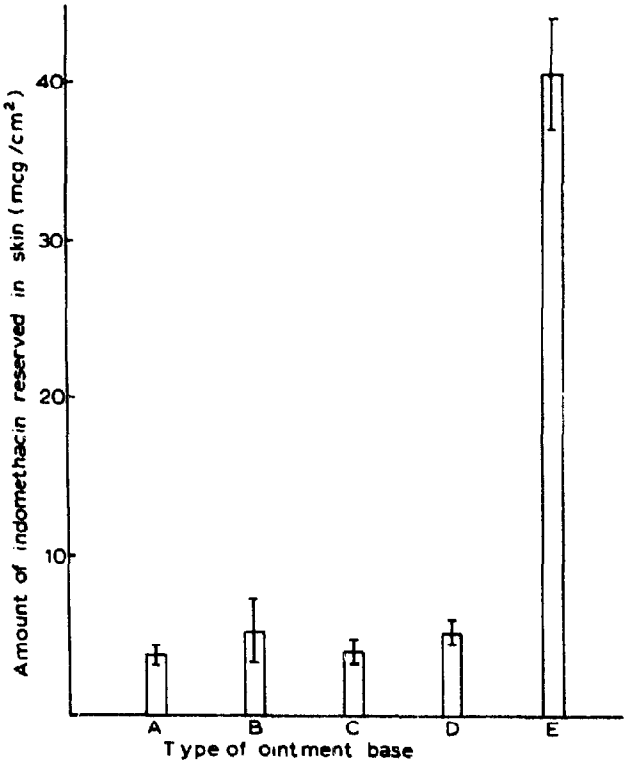


Fig. 7. Effect of ointment base on the amount of indomethacin retained in the skin after application of test ointment for 5 h. Key: A, simple ointment; B, hydrophilic vaselin; C, macrogol ointment; D, hydrophilic ointment; E, absorption ointment. Each column shows the mean of 5 rabbits with the standards error.

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