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Skin Permeability and Local Tissue Concentrations of Nonsteroidal Anti-Inflammatory Drugs after Topical Application[1]

P. SINGH[2] and M. S. ROBERTS

Departments of Pharmacy (P.S.) and Medicine (M.S.R.), The University of Queensland, Queensland, Australia

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are being administered increasingly by transdermal drug delivery for the treatment of local muscle inflammation. The human epidermal permeabilities of different NSAIDs (salicylic acid, diethylamine salicylate, indomethacin, naproxen, diclofenac and piroxicam) from aqueous solutions is dependent on the drug's lipophilicity. A parabolic relationship was observed when the logarithms of NSAID permeability coefficients were plotted against the logarithms of NSAID octanol-water partition coefficients (log P), the optimum log P being around 3. The local tissue concentrations of these drugs after dermal application in aqueous solutions were then determined in a rat model. The extent of local, as distinct from systemic delivery, for each NSAID was assessed by comparing the tissue concentrations obtained below a treated site to those in contralateral tissues. Local direct penetration was evident for all NSAIDs up to a depth of about 3 to 4 mm below the applied site, with distribution to deeper tissues being mainly through the systemic blood supply. A comparison of the predicted tissue concentrations of each NSAID after its application to human epidermis was then made by a convolution of the epidermal and underlying tissue concentration-time profiles. The estimated tissue concentrations after epidermal application of NSAIDs could be related to their maximal fluxes across epidermis from an applied vehicle.

NSAIDs are used for a variety of inflammatory conditions and their oral administration is associated with a variety of gastrointestinal side effects (Szabo *et al.*, 1989; Hawkey, 1990). Attempts have been made to deliver them in alternate oral dosage forms with mixed success. The possibility of delivering NSAIDs through the skin for either local or systemic effects is being investigated increasingly (Marty *et al.*, 1989; Hadgraft, 1989; McNeill *et al.*, 1992). There are conflicting reports in the literature concerning the actual depth and quantity of these drugs delivered to the local subcutaneous structures after topical application. Local direct deep tissue penetration of salicylate (Rabinowitz *et al.*, 1982; Baldwin *et al.*, 1984), ibuprofen (Giese, 1990) and diclofenac (Riess *et al.*, 1986) was demonstrated in dogs (Rabinowitz *et al.*, 1982) and pigs (Baldwin *et al.*, 1984), guinea pigs (Giese, 1990) and humans (Riess *et al.*, 1986), respectively. However, synovial tissue levels of topically applied diclofenac (Radermacher *et al.*, 1991) and biphenylacetic acid (Dawson *et al.*, 1988) were attributed to the systemic blood supply. It has also been shown recently that the direct penetration of salicylic acid after topical application is predominantly evident in the first 2 hr of application and up to a depth of about 3 to 4 mm below the applied site (Singh and Roberts, in press, 1993c).

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[2] Present address: Department of Dermatology, University of California-San Francisco, San Francisco, CA 94143-0989.

In our experience, animal epidermis is an inappropriate substitute for human epidermis. We therefore quantify the human epidermal penetration of any substance of interest and combine this with results from a dermal transport model (Roberts *et al.*, 1991; Roberts 1991). Accordingly, the major aims of this study were to use these approaches to evaluate the permeability of NSAIDs across isolated human epidermis and to quantify the depth of penetration of such drugs after topical application.

Theory

Combination of human epidermis and dermal absorption studies. Consider a solute of concentration (C_v) applied to the epidermis and removal of that solute from the epidermis by a dermal clearance (CL_D). The rate of change of concentration in epidermis (dC_e/dt) can then be expressed as

$$V_e\frac{dC_e}{dt} = k_pA(C_v - C_{ss}) - CL_DC_{ss} \quad (1)$$

where V_e is the volume of epidermal compartment, k_p is the epidermal (stratum corneum) permeability coefficient, C_{ss} is the steady-state concentration in the epidermis and A is the area of application. Equation 1 strictly applies only after the lag time for permeation from the stratum corneum. When the uptake process approaches a steady state, $dC_e/dt \rightarrow 0$ and equation 1 reduces to

$$\frac{C_{ss}}{C_v} = \frac{k_p A}{k_p A + CL_D} \quad (2)$$

Equation 2 is the expression used by Roberts (1991) to compare the likely epidermal concentration (C_{ss}) to the vehicle concentration (C_v) ratio for phenols and steroids and their octanol-water partition coefficients.

Penetration into deeper tissues. Expressions analogous to equation 2 can be written for other tissues. Hence the expression for the dermis after the application of an aqueous solution under pseudosteady-state conditions is

$$\frac{C_{d_{ss}}}{C_s} = \frac{k_a V_s}{k_a V_s + CL_{sc}} \quad (3)$$

where k_a is the disappearance rate constant from the dermis, C_s is the concentration of solution applied to dermis, $C_{d_{ss}}$ is the concentration in the dermis at steady state, V_s is the volume of solution applied to dermis and CL_{sc} is the clearance into subcutaneous tissue.

Mathematical expressions for concentrations in deeper tissues are defined by a convolution of the tissues in series. These expressions require estimates of the proportion of the fraction of clearance that results from penetration into deeper tissues. Singh and Roberts used such an approach in describing the dermal pharmacokinetics of polar nonelectrolytes (1993b) and salicylic acid (in press, 1993c). A solution of drug was applied directly to the dermis (*i.e.*, to skin stripped of its epidermis) and concentrations in the dermis and underlying tissues were monitored with time. In this approach, the solute is transported to the ith tissue compartment from the tissue compartment overlying it ($i + 1$) and into the tissue compartment underlying it ($i - 1$) (fig. 1). The differential mass balance equations for the applied solution and underlying dermis and tissue compartments were derived and can be written as (Singh and Roberts, 1993b; in press, 1993c) the following

For the cell solution:

$$V_s \frac{dC_s}{dt} = CL_{s\leftrightarrow d} C_0 \exp(-k_{s\leftrightarrow d} t) \quad (4)$$

For the dermis:

$$V_{ud} \frac{dC_{ud}}{dt} = V_d \frac{dC_d}{dt} = CL_{s\leftrightarrow d}\, C_0 \exp(-k_{s\leftrightarrow d} t) + Q_d f_{ub}\, C_b - Q_d f_{ud} C_d + CL_{d\leftrightarrow sc}\,(f_{usc} C_{sc} - f_{ud} C_d) \quad (5)$$

where C_0 and C_s are the concentrations in the cell solution at zero time and at time t; V_{ud} and V_d are the apparent volumes of distribution of unbound solute in the dermis and of the total solute in the dermis ($V_{ud} f_{ud}$), respectively; $k_{s\leftrightarrow d}$ is the transfer rate constant between the cell solution and dermis; f_{ud}, f_{ub} and f_{usc} are the fractions unbound in dermis, blood and subcutaneous tissue, respectively; C_b and C_d are the concentrations of solute in the blood and dermis, respectively; Q_d is the blood flow to the dermis, $CL_{s\leftrightarrow d}$ is the clearance between cell solution and dermis; and $CL_{d\leftrightarrow sc}$ is the clearance between the dermis and subcutaneous tissue.

For the underlying (ith) tissue:

$$Vu_{T.i} \frac{dC_{uT.i}}{dt} = V_{T.i} \frac{dC_{T.i}}{dt} = CL_{T.i+1\leftrightarrow i}(f_{uT.i+1} C_{T.i+1} - f_{uT.i} C_{T.i}) + Q_{T.i}\,(C_b\, RM_{T.i} - f_{uT.i} C_{T.i}) + CL_{T.i\leftrightarrow i-1}\,(f_{uT.i-1}\, C_{T.i-1} - f_{uT.i} C_{T.i}) \quad (6)$$

where $V_{uT.i}$ and V_T are apparent volumes of distribution of unbound and total solute ($V_{uT} f_{uT}$) in tissue; $CL_{T.i+1\leftrightarrow i}$ is the clearance between the $i + 1$ tissue and ith tissue; $CL_{T.i\leftrightarrow i-1}$ is the clearance between ith tissue and the $i - 1$ tissue; $C_{T.i}$, $C_{T.i+1}$, $C_{T.i-1}$ are the concentrations in the ith tissue, $i + 1$ tissue and $i - 1$ tissue, respectively; $f_{uT.i}$, $f_{uT.i+1}$ $f_{uT.i-1}$ are the fractions unbound in the ith tissue, $i + 1$ tissue and $i - 1$ tissue, respectively; $Q_{T.i}$ is the blood flow to the ith tissue; and $RM_{T.i}$ is the ith tissue-plasma partition coefficient.

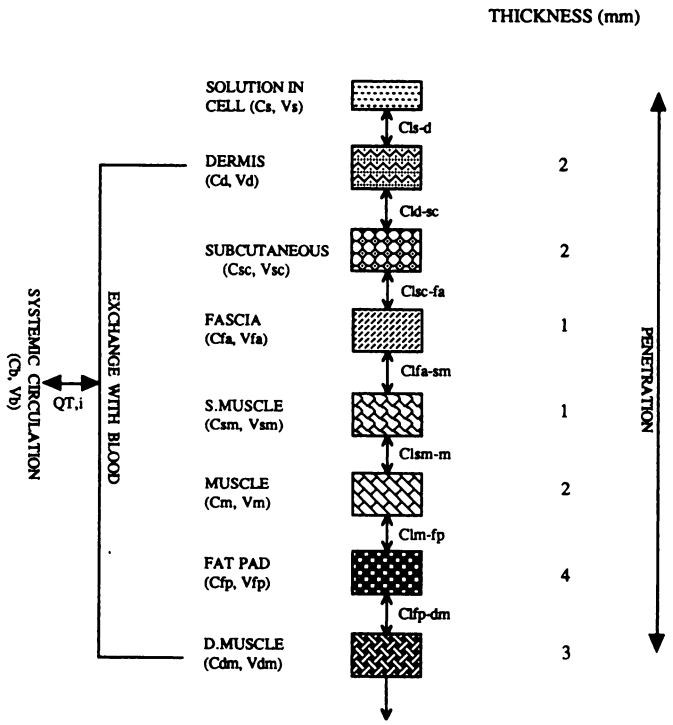

Fig. 1. A physiological pharmacokinetic model for local tissue penetration of compounds after dermal application. C, concentration of the drug in the particular compartment; V, volume of the compartment; s.muscle, superficial muscle; d.muscle, deep muscle; Cl, clearance; and Q, blood

Materials and Methods

The ^{14}C-salicylic acid and diethylamine salicylate, ^{14}C-diclofenac sodium and unlabeled diclofenac, ^{3}H-naproxen and unlabeled naproxen, ^{14}C-indomethacin and unlabeled indomethacin and ^{3}H-piroxicam and unlabeled piroxicam were gifts from Hamilton Laboratories (Adelaide, Australia); Ciba-Geigy, Sydney, Australia; Syntex, Sydney, Australia; Merck Sharp & Dohme, Sydney, Australia; and Pfizer (Sydney, Australia), respectively. Tritiated water and ^{14}C-phenol were purchased from New England Nuclear via DuPont (Australia), Sydney, Australia. The salicylic acid was obtained from Sigma (St. Louis, MO). Zimmer's electrodermatome (model 901, Warsaw, Indiana) was used for removing the rat's epidermis. Tissue solubilizer, NCS, and the liquid scintillation cocktails OCS (organic counting scintillant) and BCS (biodegradable counting scintillant) for tissue and aqueous samples, respectively, were purchased from Amersham International, England. All other reagents used were of analytical grade. A liquid scintillation counter (model MINIAX Tri-carb 4000 series, United Technologies Packard) was used to determine the radioactivity in the samples.

Animals. Male Wistar rats (weight range, 300–350 g) were used in the studies. The animals were housed under standard laboratory conditions at 20.0 ± 0.5°C with a relative humidity of 55% to 75% and

had previously been approved by the Animal Experimentation Committees of the University of Queensland and the Princess Alexandra Hospital.

Isolated human epidermis penetration studies. Human skin was obtained from the midabdominal region of cadavers and the epidermis was separated from the dermis by a heat method (Kligman and Christophers, 1963). On receipt, the subcutaneous fat was carefully trimmed and the full-thickness skin was immersed in deionized water at 60°C for 90 sec. The epidermis was then gently peeled off the dermis with blunt forceps. The isolated epidermis was dried between folds of filter paper and refrigerated until further use. It was rehydrated by immersing it in deionized water for 1 hr before use. Isolated human epidermis was mounted in side-by-side glass diffusion cells and submerged in a water bath at 37°C. After equilibration with the buffer of interest, normal saline was added to the receptor compartment and the drug solution was introduced into the donor compartment. The surface area of the epidermis exposed to the drug solution was 0.785 cm^2. Samples were removed from the receptor side at predetermined times and analyzed for the solute concentration. The donor solution was tested both at the beginning and at the end of a given study.

***In vivo* dermal penetration and local tissue uptake studies (anesthetized animals).** The rats were lightly anesthetized with pentobarbital (35 mg/kg) and their body temperatures were maintained at 37°C by placing them on a heating pad. The hair from a 4-cm^2 dorsum area was removed by electric clippers and the epidermis was removed by means of an electrodermatome set at a thickness of 80 μm (Singh and Roberts, 1993a). A glass cell (internal diameter, 1.8 cm) was then adhered to the exposed dermis and warmed to 37°C by means of an external heating device (Singh and Roberts, 1993a; Siddiqui *et al.*, 1985). A solution of solute previously warmed to 37°C was introduced into the dermal glass cell and the solution was stirred with a glass stirrer driven by an external motor.

Samples were removed from the dermal cell at various times and analyzed for the concentration of the solute. The glass cell that contained the drug solution was removed from the rat dermis at predetermined times and a blood sample was taken from the tail vein. The animals were then sacrificed with an overdose of anesthetic ether and the tissues below the treated site (*i.e.*, dermis, subcutaneous tissue, fascia, muscle lining or superficial muscle, muscle, fat pad and deep muscle) were dissected and placed in preweighed scintillation vials (Singh and Roberts, 1993a). Similar tissues from the contralateral side were also removed. The tissue and plasma samples were stored at −20°C before analysis.

***In vivo* dermal penetration and local tissue uptake studies (sacrificed animals).** The rats were initially anesthetized by i.p. injection of pentobarbital (35 mg/kg) and, after removing the epidermis as described earlier, they were sacrificed by an overdose of anesthetic ether. Dermal perfusion studies were then conducted in postmortem rats.

Sample treatment. Aqueous samples removed from the glass cells in *in vivo* dermal studies and *in vitro* epidermal studies were mixed with 5 ml of the liquid scintillation cocktail BCS and the radioactivity was counted using a liquid scintillation counter. The tissue samples were solubilized with 50 μl of water and 1 ml of the tissue solubilizer NCS at 50°C for 6 to 8 hr. After cooling the digested samples to room temperature, 0.03% glacial acetic acid was added to each tissue sample followed by 10 ml of the organic scintillant OCS. The plasma samples were solubilized with tissue solubilizer (five parts for one part of plasma) at room temperature and treated with glacial acetic acid before adding OCS. Each sample was then counted on the liquid scintillation counter for 10 min (Singh and Roberts, 1993a).

Data analysis. In isolated epidermal penetration studies, the cumulative amount of solute appearing in the receptor compartment was plotted against time. The slope of the linear portion of the plot is the steady-state flux and the flux divided by the initial concentration yields the permeability coefficient (Roberts *et al.*, 1977). The maximal flux for a given compound was estimated from the product of its permeability coefficient and its aqueous solubility (Roberts 1991). The permeonly the un-ionized form of a compound penetrates the human epidermis. Zero-time samples from the cell in dermal absorption studies were used to represent the concentration of the initial solution and the ^{14}C or ^{3}H activity in the tissues and plasma was converted to a fraction of the initial concentration in the solution (*i.e.*, concentration fraction; Singh and Roberts, 1993a). Clearance into the dermis was estimated from the plot of the percent of solute remaining in the dermal perfusion cell with time using the following equation:

$$CL = kV \quad (7)$$

where k is the disappearance rate constant and V is the volume of solution applied to the dermis (Singh and Roberts, 1993a; Siddiqui *et al.*, 1985).

The tissue-to-plasma partition coefficients ($RM_{T,i}$) were calculated using pseudosteady-state plasma (C_p) and the contralateral tissue concentrations ($C_{T,i}$) of NSAIDs at 2-hr postdermal perfusion according to the following equation:

$$RM_{T,i} = C_{T,i}/C_p \quad (8)$$

The Minim computer program (Purves, 1992) was used for nonlinear regression and numerical integration of equations 4, 5 and 6 by assuming experimentally determined blood flows (Singh and Roberts, 1993b) and estimated tissue-tissue clearances for salicylic acid (Singh and Roberts, in press, 1993c) as constants for all NSAIDs. The predicted concentrations were compared with those obtained experimentally after the application of NSAIDs to the exposed rat dermis.

Results

Isolated human epidermal penetration studies. The penetration of salicylic acid, diethylamine salicylate, naproxen, indomethacin, diclofenac and piroxicam across isolated human epidermis was investigated at two pH levels: first, when the drugs were fully ionized (pH 7.4) and, second, at 50% ionization (pH = pK_a of the compound). The percentage loss from the donor half cell for each drug was less than 10% and the integrity of epidermal membranes was checked by quantifying the flux of tritiated water after each epidermal diffusion study. The results from experiments were discarded if the permeability coefficient of water exceeded 0.0025 cm/hr. Table 1 lists the permeability coefficients for the drugs at the two pH levels. The permeability coefficients for all compounds were found to increase with an increase in the un-ionized fraction, consistent with the premise of better penetration of un-ionized forms of compounds through the skin compared with ionized forms (Swarbrick *et al.*, 1984). Figure 2 shows a plot of logarithmic permeability coefficients (log k_p, which correspond to the 100% un-ionized fraction by assuming that only the un-ionized form of a compound penetrates human epidermis) *versus* the logarithmic octanol-water partition coefficients (log P) for various NSAIDs. Phenol (an acid) is not a NSAID but is often used as a local anesthetic in products like calamine lotion (Roberts, 1991). It was used in epidermal studies to increase the range of compounds with varying lipophilicities. The observed permeability coefficients for salicylic acid and diethylamine salicylate were similar because diethylamine salicylate is ionized under the conditions used and is therefore equivalent to salicylic acid. Figure 2 shows that a parabolic relationship exists between log k_p and log P, the optimal log P being around 3.

The maximal flux of a given solute from a particular vehicle can be estimated from the product of its permeability coefficient across the membrane and its solubility in the vehicle. The maximal fluxes estimated for different compounds from an aqueous vehicle (water) are given in table 1. The maximal

TABLE 1

Permeability coefficients (k_p) and maximal fluxes for various NSAIDs across human epidermis

Compound	k_p (~100% Ionization)	k_p (~50% Ionization)	k_p (~0% Ionization)	Solubility	Maximal flux	Log P^a	Molecular Weight
	$cm/hr \times 10^4$	$cm/hr \times 10^2$	$cm/hr \times 10^2$	$mol/l \times 10^{-4}$	$mmol/cm^2/hr \times 10^6$		
Salicylic acid	3.31 ± 0.55	1.52 ± 0.30	3.04 ± 0.60	110[b]	352	2.25	138
Indomethacin	2.15 ± 0.75	0.74 ± 0.21	1.48 ± 0.42	0.05[c]	0.07	4.42	357
Diclofenac	3.57 ± 0.31	0.91 ± 0.20	1.82 ± 0.40	0.08[d]	0.15	4.31	318
Naproxen	7.07 ± 2.02	1.91 ± 0.31	3.82 ± 0.62	0.69[d]	2.72	3.18	230
Piroxicam	1.54 ± 0.33	0.17 ± 0.04	3.40 ± 0.08	110[d]	18.76	0.05[e]	331
Diethylamine salicylate	6.30 ± 1.05	1.88 ± 0.42	3.76 ± 0.80	—	—	—	211
Phenol	—	—	1.95 ± 0.31	9120[b]	1.78	1.46[f]	94

[a] Yano *et al.* (1986).
[b] Yalkowsky *et al.* (1983).
[c] Itoh *et al.* (1990).
[d] Fini *et al.* (1985).
[e] Kasting *et al.* (1987).
[f] Roberts *et al.* (1977).

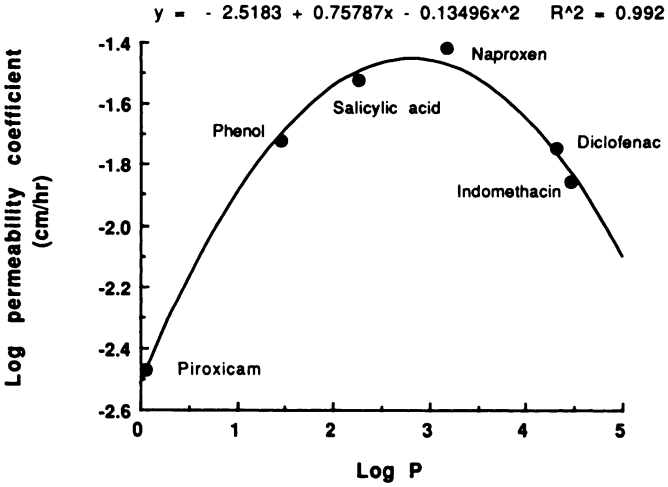

Fig. 2. Aqueous permeability coefficients (log k_p) *vs.* octanol-water partition coefficients (log P) for NSAIDs and phenol across isolated human epidermis.

consistent with similar declines observed for phenols and *n*-alkanols (Roberts, 1991). However, piroxicam was clearly an outlier. The logarithms of maximal fluxes were also found to decrease with increasing molecular weights with a reasonable correlation ($r^2 = .83$).

Disappearance of compounds into the dermis. It has been previously shown that rat and human dermis have similar permeability characteristics (Singh and Roberts, 1993a). To establish whether NSAIDs can bypass dermal microcirculation to reach underlying tissues, solutions of drugs were applied directly on the exposed rat dermis in the absence of the stratum corneum barrier *in vivo* (Singh and Roberts, 1993a, 1993b). Table 2 lists the dermal clearance values for anesthetized and sacrificed rat dermis *in vivo*. The importance of dermal blood flow in solute removal is readily apparent in table 2 in which the clearance in anesthetized rats was an order of magnitude higher than that in sacrificed rat.

Tissue distribution of NSAIDs. Figure 3 shows tissue concentration (expressed as a fraction of the initial concentration) *versus* depth profiles of various nonsteroidal anti-inflammatory drugs after a 2-hr application to anesthetized and sacrificed rat dermis. As shown, the concentrations of all compounds were higher in underlying dermis and subcutaneous

TABLE 2

Clearance of NSAIDs applied to exposed rat dermis *in vivo*

Compound	Dermal Clearance		
	Anesthetized	Sacrificed	Blood Supply
		ml/hr	
Salicyclic acid	0.58 ± 0.08	0.10 ± 0.02	0.48
Diethylamine salicylate	0.62 ± 0.11	0.15 ± 0.04	0.37
Indomethacin	0.32 ± 0.08	0.13 ± 0.02	0.19
Naproxen	0.65 ± 0.09	0.20 ± 0.04	0.45
Piroxicam	0.48 ± 0.07	0.26 ± 0.04	0.22
Diclofenac sodium	0.66 ± 0.10	0.30 ± 0.04	0.36

trations in similar tissues on the contralateral side. The concentrations in underlying fascia were comparable to the plasma concentrations. At greater tissue depths, the concentrations in underlying tissues were always less than the plasma concentrations and higher, but comparable, to those in similar tissues from the contralateral site. These results imply that the direct deep tissue penetration of different NSAIDs after application to exposed rat dermis occurs to an almost equal extent and to a depth of about 3 to 4 mm below the applied site.

A physiologically based pharmacokinetic model earlier was suggested to describe local tissue concentrations of polar nonelectrolytes (Singh and Roberts, 1993b), and salicylic acid, after topical application (Singh and Roberts, in press, 1993c). The tissue concentrations of NSAIDs in underlying dermis, subcutaneous tissue and fascia were predicted from the model according to the equations 4, 5 and 6 and then compared with experimentally observed tissue concentrations after application to the exposed rat dermis (fig. 4). The apparent tissue-plasma partition coefficients were estimated from the plasma and contralateral tissue concentrations at 2 hr postdermal perfusion by assuming a pseudosteady-state equilibrium. The establishment of equilibrium between contralateral tissue and plasma concentrations at 2 hr earlier was shown for salicylic acid (Singh and Roberts, in press, 1993c) and piroxicam (McNeill *et al.*, 1992). The experimentally determined concentrations compared reasonably well with the concentrations predicted from the model (fig. 4).

Discussion

The penetration of any drug across the skin involves parti-

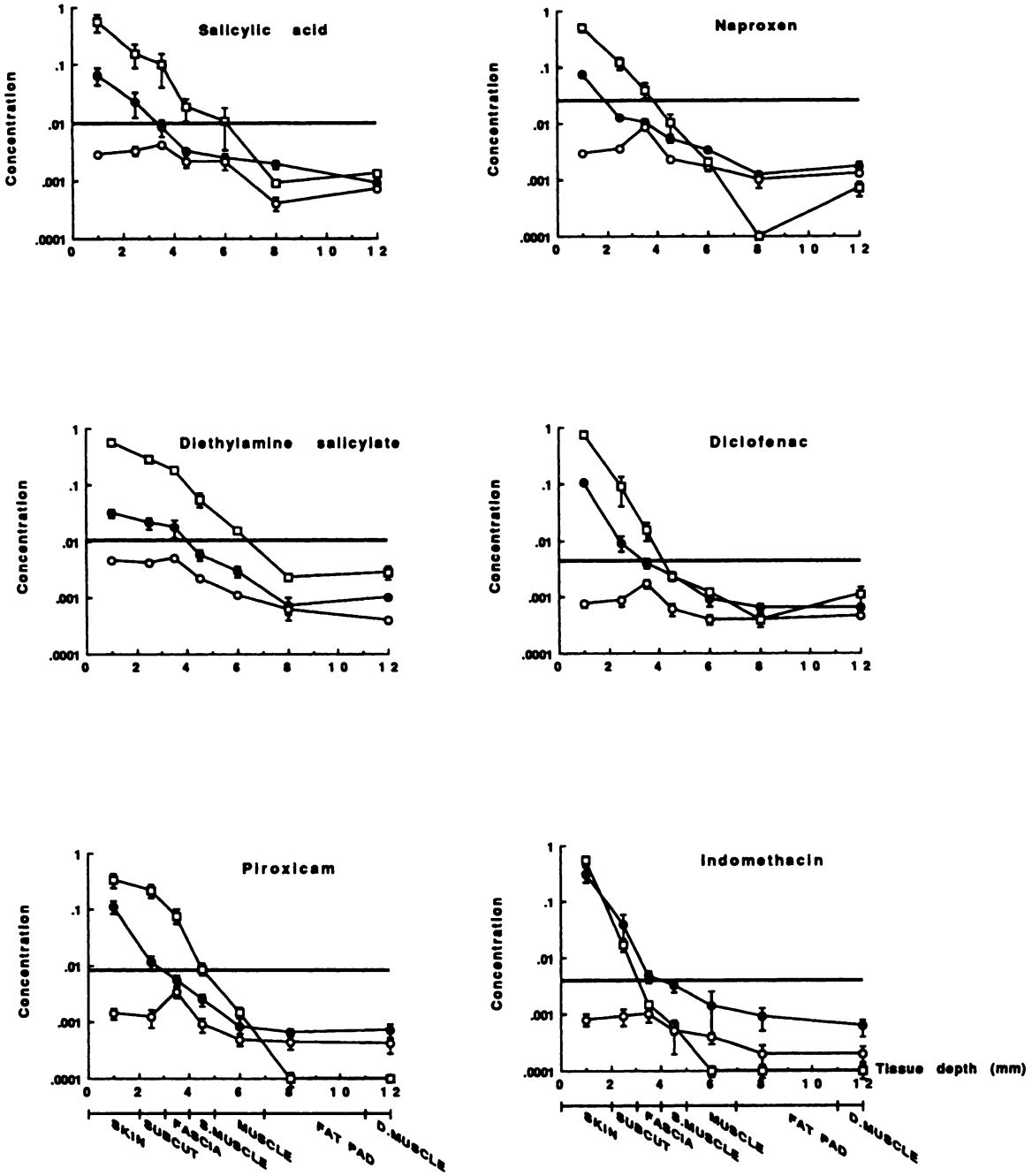

Fig. 3. The concentration (fraction of initial donor concentration) *vs.* tissue depth profile for NSAIDs applied to rat dermis *in vivo*. ●, underlying tissues after application to anesthetized rat dermis; ○, contralateral tissues after application to anesthetized rat dermis; □, underlying tissues after application to sacrificed rat dermis. The bold line represents plasma levels. SUBCUT, subcutaneous tissue; S.MUSCLE, superficial muscle; D. MUSCLE, deep muscle.

titioning into viable epidermis, diffusion in epidermis and subsequent uptake into the dermal microcirculation or further deep tissue penetration. The stratum corneum, which is the outermost layer of the skin, offers the principal resistance to any topically applied compound. Lipophilic un-ionized drugs are known to traverse this barrier better than do ionized compounds. The parabolic relationship between log k_p and log P for various NSAIDs (fig. 2) suggests that permeability coefficient values increase with log P over a range and then decline at higher values. An optimal hydrophilic-lipophilic balance is therefore essential for the cutaneous penetration of drugs (Hadgraft, 1989). A similar relationship previously was observed for skin *in vivo* (Yano *et al.*, 1986). Guy and Hadgraft (1989) reported that drug absorption was related to log P by the following relationship: log (percent of dose absorbed) = 0.42 + 1.14 log P − 0.23 (log P)^2. The corresponding relationship deduced from the present epidermal penetration study is given by: log P = −2.52 + 0.76 log P − 0.13 (log P)^2 (fig. 2). The two relationships appear to show a similar order of dependency of the penetration on the solute's lipophilicity, as defined by log P.

A number of authors invoked size as a determinant in percutaneous absorption, with the relationship between permeability coefficient and size being equivocal (Roberts, 1991). Potts

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