Skin Penetration of Nonsteroidal Antiinflammatory Drugs out of a Lipophilic Vehicle: Influence of the Viable Epidermis

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Abstract □ The skin penetration of 10 nonsteroidal antiinflammatory drugs (NSAIDs) was investigated after application in the lipophilic vehicle light mineral oil. The skin permeabilities and maximum fluxes, which were calculated from the concentration decreases of the applied solutions in the steady state phases, were correlated with physicochemical parameters, mainly the vehicle solubilities and the partition coefficients of the model drugs according to the Fickian diffusion laws. The objective of the study was to characterize the barrier function of the stratum corneum and the viable epidermis and to predict their influences on the skin permeabilities and the maximum fluxes of the NSAIDs by model equations. The permeability of the human skin for NSAIDs applied in a lipophilic vehicle is a function of their hydrophilicity, while the maximum flux is primarily dependent on their vehicle solubilities. The viable epidermis was found to represent the decisive resistance to the drug transport.

Introduction

The percutaneous treatment of rheumatic diseases with nonsteroidal antiinflammatory drugs (NSAIDs) causes less side effects than the peroral application. It has been controversially discussed whether NSAIDs applied to the skin will directly penetrate into tissues and joints deeper than 1 cm.[1−4] Based on this background, the question shall be investigated of whether skin penetration of the NSAIDs as model drugs out of the lipophilic vehicle light mineral oil can be described by the same physicochemical parameters according to the Fickian diffusion laws as out of a hydrophilic vehicle. The stratum corneum is considered as the main barrier for the percutaneous drug transport.[5−7] Thus, for the prediction of skin permeability, the partition coefficient between the stratum corneum and the vehicle $PC_{SC/V}$ is of particular importance. It is often related to the in vitro partition coefficient between octanol and the vehicle $PC_{Oct/V}$.[8−10] Consequently, drugs of similar size and high lipophilicity show high permeabilities out of aqueous solutions, as it has been repeatedly shown in the literature.[8−12] In contrast, the permeabilities of lipophilic drugs out of lipophilic vehicles should be low,[11,12] which was demonstrated for the first time by Blank.[13] The additional resistance of the viable epidermis has not yet been investigated. In this case, it must be considered that the permeant has to partition not only out of the vehicle into the stratum corneum but subsequently from the stratum corneum into the barrier of the viable epidermis, not behaving like a sink. Accordingly, the partition coefficient between the stratum corneum and the viable epidermis $PC_{SC/E}$ or the partition coefficient between the viable epidermis and the vehicle $PC_{E/V}$ must be taken into account.[14]

For the prediction of the maximum flux of a drug, its solubility in the rate-limiting barrier(s) is decisive, being independent of the applied vehicle.[6,15] Because the solubility in the barrier(s) is unknown, the maximum flux of the drug is expressed as the product of its barrier permeability and its vehicle solubility and thus can be correlated with physicochemical parameters.[6,11,12,14,15]

Theory

Permeability—The permeability of a membrane for a diffusing substance is defined by its resistance. To characterize the influences of the resistances of the stratum corneum SC and the viable epidermis E, respectively, on the drug transport out of a lipophilic vehicle V in the steady state or the pseudo-steady-state,[15] respectively, three model equations can be derived.[14,16]

Model 1—The stratum corneum alone is decisive

$$R_{skin} = \frac{1}{P_{skin}} = \frac{d_{SC}}{D_{SC} PC_{SC/V}} \leftrightarrow P_{skin} = \frac{D_{SC} PC_{SC/V}}{d_{SC}} \leftrightarrow \lg P_{skin} = \lg\left(\frac{D_{SC}}{d_{SC}}\right) + \lg PC_{SC/V} \quad (1)$$

where R_{skin} is the skin resistance, P_{skin} is the skin permeability, d_{SC} is the thickness of the stratum corneum, D_{SC} is the diffusion coefficient in the stratum corneum, and $PC_{SC/V}$ is the partition coefficient between the stratum corneum and the vehicle.

Model 2—The viable epidermis alone is decisive

$$R_{skin} = \frac{1}{P_{skin}} = \frac{d_E}{D_E PC_{E/V}} \leftrightarrow P_{skin} = \frac{D_E PC_{E/V}}{d_E} \leftrightarrow \lg P_{skin} = \lg\left(\frac{D_E}{d_E}\right) + \lg PC_{E/V} \quad (2)$$

where d_E is the thickness of the rate-limiting layer in the viable epidermis, D_E is the diffusion coefficient in the viable epidermis, and $PC_{E/V}$ is the partition coefficient between the viable epidermis and the vehicle.

Model 3—Both the stratum corneum and the viable epidermis contribute to the skin resistance

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$$R_{skin} = \frac{1}{P_{skin}} = \frac{d_{SC}}{D_{SC} PC_{SC/V}} + \frac{d_E}{D_E PC_{E/V}} \leftrightarrow$$

$$P_{skin} = \frac{D_{SC} D_E PC_{SC/V}}{d_{SC} D_E + d_E D_{SC} PC_{SC/E}} \quad (3)$$

$$\leftrightarrow \lg P_{skin} = \lg(D_{SC} D_E) + \lg PC_{SC/V} - \lg(d_{SC} D_E + d_E D_{SC} PC_{SC/E}) \quad (4)$$

where $PC_{SC/E}$ is the partition coefficient between the stratum corneum and the viable epidermis, equal to $PC_{SC/V}/PC_{E/V}$.

The in vivo partition coefficients $PC_{SC/V}$, $PC_{E/V}$, and $PC_{SC/E}$ can be approached in vitro by partition coefficients with octanol (for the stratum corneum) and phosphate buffer (pH 7.4) (for the viable epidermis), respectively, in a linear regression equation according to Collander[17] (eqs 5−7)

$$\lg PC_{SC/V} = a \lg PC_{Oct/MO} + b \quad (5)$$

$$\lg PC_{E/V} = a' \lg PC_{PBS/MO} + b' \quad (6)$$

$$\lg PC_{SC/E} = a'' \lg PC_{Oct/PBS} + b'' \quad (7)$$

where $PC_{Oct/MO}$ is the partition coefficient between octanol and the vehicle light mineral oil, (for its determination see the Experimental Section), $PC_{PBS/MO}$ is the partition coefficient between phosphate buffer (pH 7.4) and light mineral oil, $PC_{Oct/PBS}$ is the partition coefficient between octanol and phosphate buffer (pH 7.4), a, a', a'' are regression coefficients according to Collander, and b, b', b'' are intercepts according to Collander.

From the substitution of the in vivo partition coefficients in the model eqs 1, 2, and 4 by the Collander terms in eqs 5−7, eqs 8−10 result.

$$\text{model 1: } \lg P_{skin} = \lg\left(\frac{D_{SC}}{d_{SC}}\right) + a \lg PC_{Oct/MO} + b \quad (8)$$

$$\text{model 2: } \lg P_{skin} = \lg\left(\frac{D_E}{d_E}\right) + a' \lg PC_{PBS/MO} + b' \quad (9)$$

$$\text{model 3: } \lg P_{skin} = \lg(D_{SC} D_E) + a \lg PC_{OCT/MO} + b - \lg(d_{SC} D_E + d_E D_{SC} PC_{Oct/PBS}{}^{a''} 10^{b''}) \quad (10)$$

Correlations of the experimentally determined skin permeabilities with the partition coefficients of eqs 8−10 give information about the importance of the resistances of the stratum corneum and the viable epidermis, respectively, for the transport of the NSAIDs through the skin. The diffusion coefficients of the NSAIDs in eqs 8−10, which are mainly dependent on the molecular size, represented by the molecular volume, are assumed to be equal. On the basis of the theory of the required volume for free diffusion, Cohen and Turnbull[18] derived an exponential relationship between the diffusion coefficient D and the molecular volume MV (eq 11)

$$D = D^0 e^{-\beta MV} \quad (11)$$

where D is the diffusion coefficient, D^0 is the diffusion coefficient of a hypothetical molecule with a molecular volume 0, β is the regression coefficient of the molecular volume, and MV is the molecular volume.

With the help of eq 11 the model equations for the models 1 and 2 (eqs 8 and 9) can be rewritten as eqs 12 and 13

$$\text{model 1: } \lg P_{skin} = \lg\left(\frac{D^0_{SC}}{d_{SC}}\right) - \frac{\beta_{SC}}{2.303} MV + a \lg PC_{Oct/MO} + b \quad (12)$$

$$\text{model 2: } \lg P_{skin} = \lg\left(\frac{D^0_E}{d_E}\right) - \frac{\beta_E}{2.303} MV + a' \lg PC_{PBS/MO} + b' \quad (13)$$

where β_{SC} and β_E are regression coefficients of the molecular volumes concerning the stratum corneum and the viable epidermis, respectively.

The contributions of the molecular volumes in eqs 12 and 13 can be determined by a multiple linear regression analysis.

Maximum Flux—The maximum flux J_{max} results from the multiplication of the skin permeability with the vehicle solubility (eq 14)

$$J_{max} = P_{skin} c_{sMO} \quad (14)$$

where J_{max} is the maximum flux, and c_{sMO} is the solubility in the vehicle light mineral oil.

After finding the logarithms for eq 14, $\lg J_{max}$ is the sum of the skin permeability term and the vehicle solubility term, which can again be evaluated by a multiple linear regression analysis with $\lg P_{skin}$ being expressed by the model eqs 8−10.

$$\lg J_{max} = \lg P_{skin} + \lg c_{sMO} \quad (15)$$

Experimental Section

Materials—The following NSAIDs were used: aspirin (Merck, Darmstadt, Germany), diclofenac free acid (Novartis, Basel, Switzerland), diflunisal (MSD, Rahway, NJ), flufenamic acid, ibuprofen (Sankyo, Pfaffenhofen, Germany), ketoprofen (Bayer, Leverkusen and Rhône Poulenc Rorer, Cologne, Germany), naproxen (PharmActiv, Feldkirchen-Westerham, Germany), nabumeton (SmithKline Beecham, Worthing, Great Britain), piroxicam (Pfizer, Karlsruhe, Germany), tenoxicam (Hoffmann-La Roche, Basel, Switzerland). Light mineral oil was a gift of Parafluid Mineralölgesellschaft, Hamburg, Germany.

Solubilities—For the determination of the solubilities of the NSAIDs in the vehicle light mineral oil an excess amount of substance was suspended in 25 mL of light mineral oil, and the suspension was moved in a water bath of 32 °C in rotating bottles (30 min^{-1}) for 24 h. The suspension was filtered through warmed cellulose acetate filters with 0.45 μm pore diameter (Sartorius, Göttingen, Germany) in a warmed flask. After the appropriate dilution, the concentrations of the saturated solutions were measured spectrophotometrically (DMR 10, Carl Zeiss, Oberkochen, Germany). The solubilities were calculated as the mean of three determinations with a standard deviation less than 10%.

Partition Coefficients—The partition coefficients between octanol (Oct) and the aqueous phase (W*) $PC_{Oct/W*}$, between light mineral oil (*MO*) and the aqueous phase W* $PC_{MO/W*}$, and between octanol and phosphate buffer (pH 7.4) $PC_{Oct/PBS}$ were determined after shaking at 32 °C and spectrophotometric measurement of the separated, clearly centrifuged phases (Varifuge, Heraeus, Osterode, Germany). W* stands for the aqueous phase containing the NSAIDs in the undissociated form, i.e., 0.1 M hydrochloric acid and citrate buffer (pH 3.6 for piroxicam and 3.2 for tenoxicam), ionic strength 0.1, containing citric acid and sodium hydroxide, respectively. *PBS* stands for phosphate buffer (pH 7.4), ionic strength 0.17, containing monobasic potassium phosphate and dibasic sodium phosphate. The experiments were performed as triplicate, and the standard deviations were generally less than 10%. The partition coefficients between octanol and the vehicle light mineral oil $PC_{Oct/MO}$ were calculated by dividing $PC_{Oct/W*}$ by $PC_{MO/W*}$.[19] The partition coefficients between phosphate buffer (pH 7.4) and light mineral oil $PC_{PBS/MO}$ were obtained from the quotients of $PC_{Oct/MO}$ and $PC_{Oct/PBS}$. The $PC_{Oct/W*}$ could be confirmed by R_{MW}-values obtained with TLC[4,20,21] and by calculation with

Table 1.—Molecular Volumes MV, Vehicle Solubilities c_{sMO}, Skin Permeabilities P_{skin} with Geometrical Standard Deviations s_g, and Maximum Fluxes J_{max} with s_g of the Investigated NSAIDs

NSAIDs	MV ($cm^3 \cdot mol^{-1}$)	c_{sMO} (mg·100 mL^{-1})	P_{skin} ($cm \cdot h^{-1}$)	s_g	J_{max} ($\mu g \cdot cm^{-2} \cdot h^{-1}$)	s_g
diclofenac	210.5	2.83	0.0135	+0.0075 –0.0048	0.38	+0.27 –0.16
flufenamic acid	196.4	95.1	0.0041	+0.0028 –0.0017	3.94	+2.68 –1.59
ibuprofen	184.1	2522.6	0.0046	+0.0028 –0.0018	116.65	+80.54 –47.64
ketoprofen	203.1	12.8	0.0164	+0.0181 –0.0086	2.10	+2.40
naproxen	181.4	7.87	0.0297	+0.0297 –0.0146	2.34	+2.64 –1.24
nabumeton	189.5	351.2	0.0051	+0.0020 –0.0014	17.81	+8.35 –5.68
piroxicam	243.9	5.98	0.0221	+0.0088 –0.0063	1.32	+0.55 –0.39
tenoxicam	236.3	0.60	0.0720	+0.0343 –0.0232	0.43	+0.24
aspirin	117.5	3.12	0.1093	+0.0640 –0.0404	3.41	+2.13 –1.31
diflunisal	174.2	1.69	0.0532	+0.0361 –0.0213	0.88	+0.66 –0.38

the fragmental constant system according to Rekker and Mannhold.[4,22,23] All partition coefficients mentioned above could be described by the corresponding solubility ratios[24,25] with a good correlation.[4]

Molecular Volumes—The molecular volumes of the NSAIDs were calculated from the incremental van der Waals volumes according to Bondi.[26,27]

In Vivo Studies—Twenty-four healthy volunteers, their ages ranging from 20 to 40, took part in the study, which was approved by the ethics committee of the University of Düsseldorf. Every volunteer gave written consent after detailed information. The skin penetration of the NSAIDs was investigated according to the statistical plan of a 4 × 4 × 2 Latin rectangle in three series with eight volunteers and diclofenac as reference drug in every series. Every volunteer could take four substances on his upper arms whose positions were varied systematically. Special glass chambers for the reception of the test solutions were fixed on every volunteer's upper arms with wire frames and elastic bandages, preventing leakage.[9,28] After conditioning with the vehicle light mineral oil for 2 h (renewed hourly) to elute most of the extractable material, the drug solutions with concentrations[4] between 0.45 and 126 mg·100 mL^{-1} were filled in the glass chambers over a time period of 7 or 8 h and exchanged by the original solutions every 1 to 2 h, respectively. The concentration depletion in the glass chambers varies between 2 and 33% per hour in the steady state, depending on the respective drug.[4] The solutions of the NSAIDs taken out of the glass chambers were diluted and their concentration decreases measured spectrophotometrically. The skin permeabilities were calculated as geometrical means from the last three or four data points of the steady-state phases,[9,28] which became apparent after 3 or 4 h, respectively (Figure 1).[4] Changes of the chamber volumes and UV-active material extracted from the skin were taken into account by correction factors.[4,28] The maximum fluxes were calculated from eq 14.

Statistical Calculations—A linear regression analysis was performed for the models 1 and 2 using Excel 8.0 (Microsoft Corporation, Redmond, WA) and PlotIt 3.0 (Scientific Programming Enterprises, Haslet, MI). The nonlinear regression analysis for model 3 and the multiple linear regression analyses of eqs 12, 13, and 15 were calculated with the statistical program SPSS 6.1.3 (SPSS, Inc., Chicago, IL).

Results

The molecular volumes MV, vehicle solubilities c_{sMO}, skin permeabilities P_{skin}, and maximum fluxes J_{max} of the investigated NSAIDs are shown in Table 1. The geometrical standard deviations s_g are also listed for the skin penetration data. Most of them amount up to ±60%, as already documented by Southwell et al.,[29] and partially exceed this range (ketoprofen, naproxen). The skin permeabilities were found to be log-normally distributed.[4,30–32] The logarithms of the skin permeabilities, maximum fluxes, $PC_{Oct/MO}$, $PC_{PBS/MO}$, $PC_{Oct/W*}$, and $PC_{Oct/PBS}$, all necessary for the correlations according to eqs 8–10, are arranged in Table 2.

Table 2.—Logarithms of the Partition Coefficients between Octanol and the Vehicle Light Mineral Oil $PC_{Oct/MO}$, between Phosphate Buffer (pH 7.4) and Light Mineral Oil $PC_{PBS/MO}$, between Octanol and Phosphate Buffer (pH 7.4) $PC_{Oct/PBS}$ and between Octanol and Water with the Drug in Its Undissociated Form $PC_{Oct/W*}$, Skin Permeabilities P_{skin} (in $cm \cdot h^{-1}$), and Maximum Fluxes J_{max} (in $\mu g \cdot cm^{-2} \cdot h^{-1}$) of the Investigated NSAIDs

NSAID	lg $PC_{Oct/MO}$	lg $PC_{PBS/MO}$	lg $PC_{Oct/PBS}$	lg $PC_{Oct/W*}$	lg P_{skin}	lg J_{max}
diclofenac	2.91	0.93	1.98	4.32	–1.87	–0.42
flufenamic acid	1.93	–0.22	2.15	4.67	–2.38	0.60
ibuprofen	1.15	–0.07	1.22	4.21	–2.34	2.07
ketoprofen	3.54	3.57	–0.03	3.35	–1.79	0.32
naproxen	2.84	2.49	0.35	3.22	–1.53	0.37
nabumeton	0.57	–2.31	2.88	3.29	–2.30	1.25
piroxicam	1.49	1.69	–0.20	1.69	–1.66	0.12
tenoxicam	1.67	2.51	–0.84	0.78	–1.14	–0.36
aspirin	3.96	5.94	–2.04	1.26	–0.96	0.53
diflunisal	3.36	2.78	0.58	4.24	–1.28	–0.05

Permeabilities—The results of the correlations according to the models 1–3 (eqs 8–10) are presented in eqs 16–18 and graphically shown in Figures 2–4:

model 1 (Figure 2, eq 8):

$$\lg P_{skin} = 0.28 \lg PC_{Oct/MO} - 2.37 \quad (16)$$
$$r = 0.615,\ s = 0.42,\ p_{slope} = 0.058,\ n = 10$$

model 2 (Figure 3, eq 9):

$$\lg P_{skin} = 0.19 \lg PC_{PBS/MO} - 2.05 \quad (17)$$
$$r = 0.856,\ s = 0.28,\ p_{slope} = 0.0016,\ n = 10$$

model 3 (Figure 4, eq 10):

$$\lg P_{skin} = 4.50 + 0.10 \lg PC_{Oct/MO} - \lg(5.40 \times 10^{-7} + 2.03 \times 10^{-3}(PC_{Oct/PBS})^{0.25}) \quad (18)$$
$$r = 0.876,\ s = 0.26,\ n = 10$$

(assumptions:

$$D_{SC} = 10^{-10}\ cm^2 \cdot s^{-1} \text{ and } D_E = 10^{-7}\ cm^2 \cdot s^{-1})^{4,9}$$

The insignificant influence of the molecular volumes on the diffusion coefficients is described by the results of the multiple linear regression analyses according to eqs 12 and 13, which are presented in eqs 19 and 20.

model 1 (eq 12):

$$\lg P_{skin} = -2.72 - 0.00154MV + 0.30 \lg PC_{Oct/MO} \quad (19)$$
$$r = 0.622,\ s = 0.45,\ n = 10$$

model 2 (eq 13):

$$\lg P_{skin} = -2.41 - 0.00177MV + 0.20 \lg PC_{PBS/MO} \quad (20)$$
$$r = 0.863,\ s = 0.29,\ n = 10$$

The contributions of the different molecular volumes (Table 1) to the skin permeabilities and the improvement of the correlation coefficients compared with eqs 16 and 17 are not statistically significant ($F = 0.0989$ and $F =$

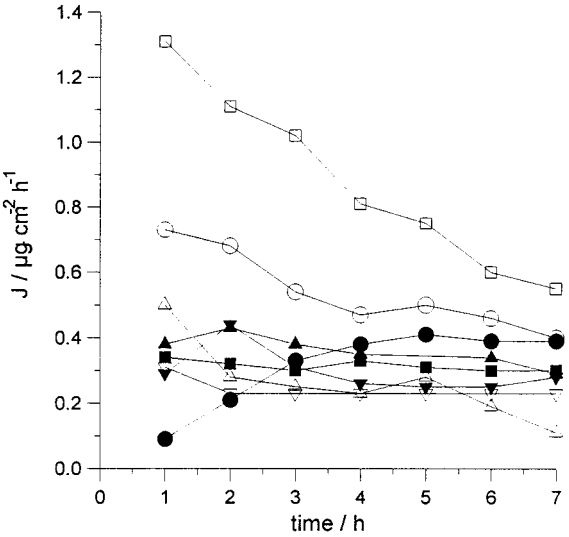

Figure 1—Penetration profiles of tenoxicam, vehicle light mineral oil, c = 0.45 mg·100 mL^{-1}, n = 8 volunteers.

0.330).[33] Thus, the diffusion coefficients of the investigated NSAIDs can be considered as constant.

Maximum Fluxes—According to eqs 15 and 16−18, the regression eqs 21−23 result for the maximum fluxes J_{max} (Table 2). In the equations of model 1 and 2 (eqs 21 and 22) the logarithms of the skin permeabilities have been substituted by eqs 16 and 17, respectively.

model 1 (eq 16, eq 15):

$$\lg J_{max} = 0.08 \lg PC_{Oct/MO} + 0.67 \lg c_{sMO} - 1.18 \quad (21)$$
$$r = 0.939,\ s = 0.29,\ n = 10$$

model 2 (eq 17, eq 15):

$$\lg J_{max} = 0.11 \lg PC_{PBS/MO} + 0.78 \lg c_{sMO} - 1.44 \quad (22)$$
$$r = 0.970,\ s = 0.21,\ n = 10$$

model 3 (eq 18, eq 15):

$$\lg J_{max} = 0.64 \lg P_{skin\ calcd} + 0.78 \lg c_{sMO} - 0.15 \quad (23)$$
$$r = 0.978,\ s = 0.18,\ n = 10$$

The regression coefficients of the vehicle solubilities c_{sMO} in all three models contribute most significantly ($p \ll 0.001$) to the regressions, while the significance of the regression coefficients of the partition coefficients and the calculated skin permeabilities $P_{skin\ calcd}$, respectively, increases from an insignificant ($p = 0.4849$, model 1) to a significant ($p = 0.0270$, model 2) and finally to a highly significant level ($p = 0.0085$, model 3).

Discussion

Permeabilities—As expected, the experimentally determined permeabilities P_{skin} generally decrease with increasing lipophilicity of the NSAIDs expressed as $PC_{Oct/W*}$ (Table 2). For example, aspirin and tenoxicam, the two drugs with the highest permeabilities (Table 1), show the lowest $PC_{Oct/W*}$ (Table 2). Vice versa, flufenamic acid and ibuprofen, the two drugs with the lowest permeabilities (Table 1), exhibit rather high $PC_{Oct/W*}$ values. However, assuming the stratum corneum as the decisive barrier, the respective regression equation relating the permeabilities to $PC_{Oct/MO}$ according to model 1 (Figure 2, eq 16) leads to an unsatisfactory correlation ($r = 0.615$). In contrast, Hagedorn-Leweke and Lippold[9] found a good correlation ($r = 0.949$) for the skin permeabilities of sunscreens and

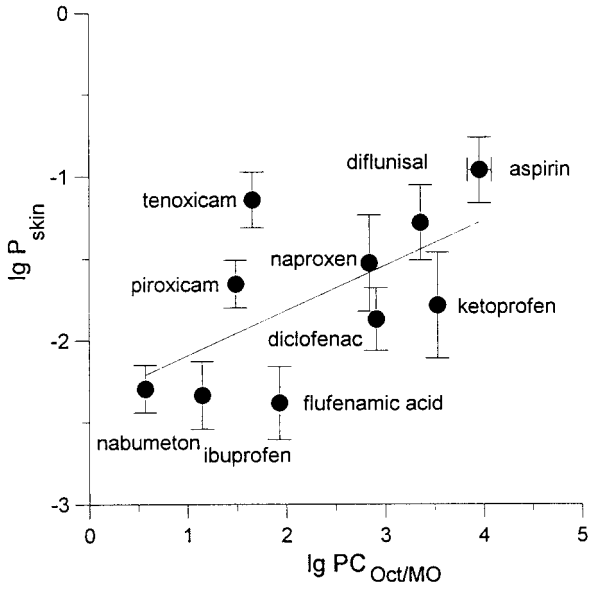

Figure 2—Correlation of the skin permeabilities P_{skin} (in cm·h^{-1}) with the partition coefficients between octanol and the vehicle light mineral oil $PC_{Oct/MO}$ according to model 1 (eq 16).

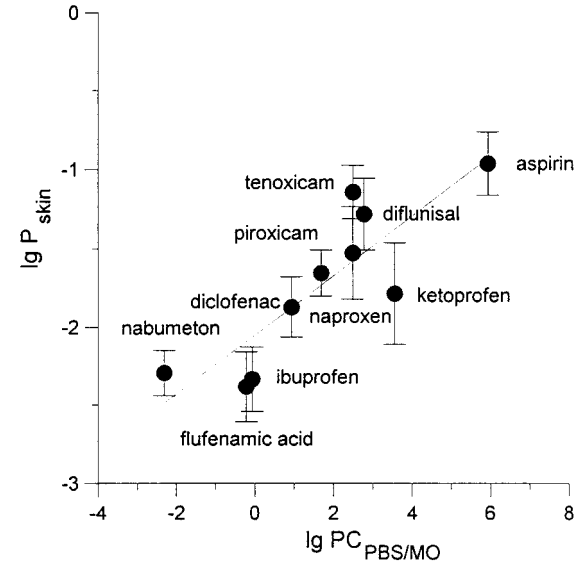

Figure 3—Correlation of the skin permeabilities P_{skin} (in cm·h^{-1}) with the partition coefficients between phosphate buffer (pH 7.4) and the vehicle light mineral oil $PC_{PBS/MO}$ according to model 2 (eq 17).

other compounds out of a propylene glycol−water mixture 30:70 (v/v) with the same study design using the partition coefficients between octanol and the hydrophilic vehicle $PC_{Oct/V}$ for the calculations in analogy to model 1 (eq 1). When using the lipophilic vehicle light mineral oil, the stratum corneum does not seem to represent the decisive resistance to the skin penetration of the NSAIDs. Considering the viable epidermis as the rate-limiting barrier to the drug transport (model 2), the correlation of the skin permeabilities with the respective partition coefficient between phosphate buffer (pH 7.4) and the vehicle light mineral oil $PC_{PBS/MO}$ clearly improves ($r = 0.856$, eq 17, Figure 3). A nonlinear regression analysis with $PC_{Oct/MO}$ and $PC_{Oct/PBS}$ (model 3) also leads to a very good correlation concerning the permeability data ($r = 0.876$, eq 18, Figure 4). The proportion between the resistances of the stratum corneum and the viable epidermis can be calculated from eqs 3 (overall resistance R_{skin} of stratum corneum and viable epidermis), 17 (estimate of the permeability of the

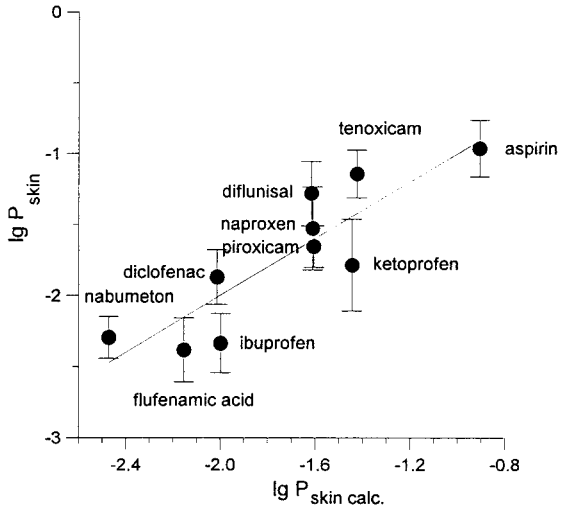

Figure 4—Correlation of the skin permeabilities P_{skin} (in cm·h^{-1}) with the skin permeabilities calculated from eq 18 $P_{skin\ calcd}$ (in cm·h^{-1}) according to model 3.

viable epidermis alone, equal to the reciprocal of its resistance), and 18 (overall permeability P_{skin} of stratum corneum and viable epidermis) and amounts to about 1:5. Thus, the viable epidermis seems to be the decisive barrier to the skin penetration of the NSAIDs out of the lipophilic vehicle light mineral oil.

Altogether, the skin permeabilities of the NSAIDs out of light mineral oil are determined by their hydrophilicity, which is under the assumption of the viable epidermis as the main barrier a function of the $PC_{PBS/MO}$. However, when using a hydrophilic vehicle, the permeabilities will primarily depend on the lipophilicity of the penetrating substances according to model 1.[8,9] This is in accordance with the observations documented by Blank[11−13] that the skin permeabilities of homologous alkanols decrease with their chain length out of lipophilic vehicles (isopropyl palmitate, mineral oil, olive oil) but increase out of hydrophilic vehicles (buffer solution, poly(ethylene glycol) 600).

Maximum Fluxes—The correlation coefficients of the maximum fluxes in eqs 21−23 are higher than those of the skin permeabilities in eqs 16−18, but they do not differentiate as clearly as those of the skin permeabilities between the three assumed models. Obviously, the maximum fluxes are more influenced by the vehicle solubilities c_{sMO}, which enclose about 4 orders of magnitude (Table 1), than by the partition coefficients. The regression coefficients of the vehicle solubilities in eqs 21−23 are highest significant, while the regression coefficients of the partition coefficients and the respective calculated skin permeabilities increase from insignificant to significant and finally to highly significant. Additionally, the latter are numerically lower than the regression coefficients of the vehicle solubilities. Thus, the maximum fluxes of the NSAIDs out of the lipophilic light mineral oil are primarily dependent on the vehicle solubilities. The increase of the significance levels of the regression coefficients of the skin permeabilities calculated from eqs 16−18 additionally confirms the importance of the viable epidermis as a barrier for the drug transport. Hagedorn-Leweke and Lippold[9] also found the decisive influence of the solubility of their investigated sunscreens in the hydrophilic vehicle on the measured maximum fluxes. Therefore, for the investigated cases, it can be concluded that the maximum flux is primarily dependent on the vehicle solubility and after that a function of the hydrophilicity or lipophilicity, expressed as octanol−vehicle partition coefficient, of the penetrating substances. For the development of cutaneous preparations, drugs with high vehicle solubilities can be recommended. In the case of a lipophilic vehicle, they should have a high partition coefficient between octanol and the vehicle and not a too high partition coefficient between octanol and phosphate buffer (pH 7.4) according to model 3.

The apparent diffusion distance of the NSAIDs out of the vehicle light mineral oil in the viable epidermis and dermis, that is, the thickness of the respective barrier d_E (eq 10) can be calculated from eq 18 (model 3) to about 2.6 mm. Obviously, real sink conditions in the skin can only be achieved beyond this distance. Singh and Roberts[1] found a direct penetration depth of about 3−4 mm from dermopharmacokinetic measurements with NSAIDs in vivo in rats. Therefore, a direct penetration of NSAIDs into deeper tissues and joints at high concentrations, as intended with the percutaneous treatment of relevant rheumatic diseases (see Introduction), does not seem to be realistic.

Conclusions

The viable epidermis, not the stratum corneum, is the rate-limiting barrier for the transport of NSAIDs out of a lipophilic vehicle. The skin permeability of NSAIDs is a function of the hydrophilicity of the drugs, i.e., of their partition coefficients between phosphate buffer (pH 7.4) and the lipophilic vehicle. However, the maximum flux of NSAIDs is primarily dependent on their vehicle solubility. For the development of cutaneous preparations, drugs with high vehicle solubilities and skin permeabilities as high as possible should be preferred.

Abbreviations

a, a', a''	regression coefficients according to Collander
b, b′, b″	intercepts according to Collander
β	regression coefficient of the molecular volume (eqs 11−13)
c_{sMO}	solubility in the vehicle light mineral oil
D	diffusion coefficient
d	thickness of the layer
E	living epidermis
F	statistical F-value
J_{max}	maximum flux
MO	light mineral oil
MV	molecular volume
n	number of experiments
NSAID	nonsteroidal antiinflammatory drug
Oct	octanol
p	statistical error probability
P_{skin}	skin permeability
$P_{skin\ calcd}$	skin permeability calculated from eq 18
PBS	phosphate buffer (pH 7.4)
$PC_{E/V}$	partition coefficient between the viable epidermis and the vehicle
$PC_{MO/W*}$	partition coefficient between the vehicle light mineral oil and the aqueous phase W*
$PC_{Oct/MO}$	partition coefficient between octanol and the vehicle light mineral oil
$PC_{Oct/PBS}$	partition coefficient between octanol and phosphate buffer (pH 7.4)
$PC_{Oct/V}$	partition coefficient between octanol and the vehicle
$PC_{Oct/W*}$	partition coefficient between octanol and the aqueous phase W*

$PC_{PBS/MO}$	partition coefficient between phosphate buffer (pH 7.4) and the vehicle light mineral oil
$PC_{SC/V}$	partition coefficient between the stratum corneum and the vehicle
r	correlation coefficient
R_{skin}	skin resistance
s	standard deviation
s_g	geometrical standard deviation
SC	stratum corneum
TLC	thin layer chromatography
V	vehicle
W*	aqueous phase containing the model drugs in the undissociated form

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