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Short communication

The influence of the physicochemical characteristics and pharmacokinetic properties of selected NSAID's on their transdermal absorption

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Abstract

The purpose of this study was to determine the plasma concentrations of selected NSAIDs after topical gel administration and to determine the influence of the physicochemical characteristics of these drugs on transdermal absorption. Plasma concentrations of the drugs were determined using high performance liquid chromatography. The log *P* values obtained from literature for piroxicam, ketoprofen, naproxen, ibuprofen and indomethacin, (1.8, 0.97, 3.22, 3.6 and 3.8, respectively) correlated with the area under the plasma–time curve (AUC) values. The AUC values determined were 527.00 (piroxicam) 269.45 (ketoprofen) 258.65 (naproxen) 243.22 (indomethacin) and 88.09 (ibuprofen) μg/ml per h. It was concluded that the most reliable parameter for transdermal absorption was the lipophilic character of a drug (log *P* value). The molecular mass, solubility constraint and percentage unionized moiety can only be used in combination with other properties in the prediction of possible transdermal drug delivery. © 2000 Published by Elsevier Science B.V. All rights reserved.

Keywords: Transdermal; Indomethacin; Ketoprofen; Piroxicam; Naproxen; Ibuprofen; Physicochemical; Pharmacokinetic

The NSAIDs has prominent anti-inflammatory, analgesic and antipyretic properties. Oral therapy of NSAIDs is very effective, but the clinical use is often limited because of their potential to cause adverse effects such as irritation and ulceration of the gastro-intestinal (GI) mucosa. Administration of these agents via the dermal route can bypass these disadvantages of the oral route and may maintain relatively consistent plasma levels for long term therapy from a single dose (Berba et al., 1991). Several studies on different aspects of the transdermal delivery of the selected NSAIDs have been published, however, none of these have investigated the correlation of the transdermal ab-

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sorption and the physicochemical and pharmacokinetic parameters.

The physicochemical properties investigated during this study include the molecular mass, ionization of the drug at physiological pH, the lipid/water partition coefficient and the solubility constraint (and melting point) in the stratum corneum (SC). The aim of this study was to determine whether a correlation exists between the absorption of selected NSAIDs and their physicochemical and pharmakokinetic properties.

Naproxen (Aldrich Chemical Co. Inc., Milwaukee), ibuprofen (Boots Pharmaceuticals, Nottingham, UK), mefenamic acid (internal standard; Yung ZIP manufacturers, China), indomethacin (Adcock Ingram Pharmaceuticals Johannesburg, South Africa), ketoprofen (Sigma, St. Louis, MO), piroxicam (Secifarma, Milan, Italy), acetonitrile (BDH, Poole, UK), acetic acid, perchoric acid and phosphoric acid (Saarchem, Johannesburg, South Africa), dibuthylamine (E. Merck, Darmstadt, F.R., Germany), HPLC grade deionized water (Milli-Q 50 purification system, Millipore, Milford). Eutha-naze® solution (sodium pentobarbitone; Premier Pharmaceutical Company Ltd., Bryanston, RSA) and Halothane (Zeneca, Woodmead, South Africa). Methods used were described previously (Goosen et al., 1998).

Table 1 provides a summary of the physicochemical properties of interest as well as relevant pharmacokinetic parameters. Significant differences ($P < 0.05$) were indicated for the area under the plasma–time curve (AUC) parameter between all of the drugs. Piroxicam showed the highest bioavailability followed by ketoprofen, naproxen, indomethacin and ibuprofen. Smaller molecules permeate the skin more rapidly than larger molecules, but within a narrow range of molecular mass (200–500), there is little correlation between size and penetration rate (Liron and Cohen, 1984; Guy and Hadgraft, 1985). The molecular masses of the NSAIDs investigated ranged between 206.30 and 357.80. Due to this slight variation in molecular mass, one could assume that no major differences in the transdermal absorption would be observed. As expected no correlation could be found when this parameter was correlated with the AUC values.

Drugs would preferably have a balanced lipophilic/hydrophilic character and a drug with a log P value of ≤ 2 is considered to be a potential candidate for transdermal delivery (Guy and Hadgraft, 1989). From the log P values in Table 1 (piroxicam 1.8, ketoprofen 0.97, naproxen 3.22, indomethacin 3.80 and ibuprofen 3.60), it is evident that the transdermal absorption of these drugs should be piroxicam > ketoprofen > naproxen > ibuprofen > indomethacin. The order of the AUC values were piroxicam > ketoprofen > naproxen > indomethacin > ibuprofen. The only difference being the order of penetration for indomethacin and ibuprofen. Since the log P values of these two NSAIDs are very similar, the difference in skin penetration could be explained by their half-lives. Both drugs are lipophilic and would therefore form reservoirs in the stratum corneum and be exposed to enzymatic breakdown in the dermis (Täubner, 1982). Becuase ibuprofen has a half-life of 2.2 h compared with the 6.1 h of indomethacin (Ritschel, 1988), the effect of enzymatic degradation would be more marked in ibuprofen, thus lowering the plasma levels and total bioavailability of the drug.

The pK_a values of all the drugs investigated ranged from 4.2 to 5.3. Since the buffer capacity of the gel formulae was negligible, the acid mantle of the skin (pH 4.8) was used to calculate the nonionised moiety of each drug. The percentages of nonionised forms calculated for the three drugs are shown in Table 1 (piroxicam = 75.97, ketoprofen = 30.88, naproxen = 20.08, indomethacin = 33.39 and ibuprofen = 75.97). Because it can be expected that the nonionised moiety of a drug will penetrate the skin best, one can assume that piroxicam and ibuprofen would be the better candidates, followed by indomethacin, ketoprofen and lastly naproxen. The AUC values did not follow this pattern, however, the AUC of piroxicam showed that the large fraction of unionized drug benefited the bioavailability of the drug. The same benefit for ibuprofen (75.97%) could not be shown. The high log P value of 3.6 might be the reason for the poor absorption of ibuprofen in spite of the high percentage of unionized drug.

By making use of the melting point of the drugs, as based on the efforts by Hadgraft and

Table 1
The physicochemical and pharmacokinetic properties of piroxicam, ketoprofen, naproxen, indomethacin and ibuprofen after transdermal application in vivo in rats

Properties	Piroxicam[1]	Ketoprofen[2]	Naproxen[3]	Indomethacin[4]	Ibuprofen[5]	References
Physicochemical						
Formula	$C_{15}H_{13}N_3O_4S$	$C_{16}H_{14}O_3$	$C_{14}H_{14}O_3$	$C_{19}H_{16}ClNO_4$	$C_{13}H_{18}O_2$	(Lund, 1994)
Molecular mass	331.40	254.29	230.30	357.80	206.30	(Lund, 1994)
Log *P*	1.8	0.97	3.22	3.8	3.60	[1](Mihalic et al., 1986; [2]Liversidge, 1981; [3]Lund, 1994; [4]Hansch and Leo, 1997; [5]Chiarini et al., 1984)
PK_a	5.3	4.45	4.2	4.5	5.3	(Lund, 1994)
% Unionised at acid mantle of skin pH 4.8	75.97	30.88	20.08	33.39	75.97	(Ritschel, 1988)
Solubility constraint	12.38	175.38	31.52	28.67	319.15	Eq. 1
Melting point	199°C	94.5°C	156°C	160°C	76.5°C	(Lund, 1994)
Pharmacokinetic						
AUC (μg/ml per h) [a]	527.00	269.45	258.65	243.22	88.09	
$t_{1/2}$ (h)	40.80	1.80	17.10	6.10	2.2	(Ritschel, 1992)
C_{max} (μg/ml)	16.23	7.1	10.25	11.95	4.43	
T_{max} (h)	30	24	2	24	2	

[a] In order of decreasing bioavailability.

Wolff (1993) the solubility constraint of piroxicam, ketoprofen, naproxen, indomethacin and ibuprofen was calculated and is shown in Table 1. According to the values obtained, ketoprofen and ibuprofen will be retained in the stratum corneum to a greater extent than indomethacin, naproxen and piroxicam. One could therefore expect that the amount of drug that is finally bioavailable would decrease in the following order, namely piroxicam > indomethacin > naproxen > ketoprofen > ibuprofen. When the latter was compared with the AUC values of the different NSAIDs, a correlation only existed for ibuprofen and piroxicam.

Piroxicam showed the best bioavailability with an AUC value of 527.0 μg/ml per h because all the properties considered were favorable for transdermal absorption. The percentage unionized moiety is high, the log P value is close to the optimum value of about 2.5 indicated for NSAIDs and the solubility constraint in the stratum corneum is low. Because piroxicam has a half-life of 40.8 h, it is slowly eliminated resulting in higher blood plasma levels.

Ibuprofen showed the poorest bioavailability of all (AUC = 88.09 μg/ml per h). It is a more lipophilic drug than piroxicam (log $P = 3.6$) which have a depot effect in the stratum corneum (solubility constraint 319.15). With this unfavorable characteristics together with a half-life of only 2.2 h, the systemic absorption and bioavailability of ibuprofen would be expected to be low, especially when compared with piroxicam.

The bioavailibility of ketoprofen, naproxen and indomethacin as indicated by their AUC values (Table 1) fell within a narrow range (269.45–243.22 μg/ml per h). The percentage-unionized moiety of these three drugs did not differ much, while the lipid/water partition coefficient for ketoprofen is more favorable for absorption than that of naproxen and indomethacin. The solubility constraint of ketoprofen will result in a stronger depot effect in the stratum corneum than naproxen and indomethacin while it also has the shortest half-life. One would thus expect that naproxen and indomethacin should have better bioavailability than ketoprofen (which is not the case). When one considers the log P values, keto-profen tends to be the closest to the optimum value indicated for NSAIDs. One can thus conclude that in this case the log P value is a more important parameter to consider than solubility constraint and half-life to predict bioavailability.

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