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Note

# Correlation between physicochemical characteristics, pharmacokinetic properties and transdermal absorption of NSAID's

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**Abstract**

The plasma concentrations of indomethacin, ketoprofen and piroxicam were determined as a function of time after topical gel administration, using male BD IX rats. Physicochemical characteristics such as the lipid/water partition coefficient (log *P* value), molecular mass of the respective drugs, percentage unionized moiety and the solubility constraint of the drug in the stratum corneum were investigated and correlated with the AUC values obtained after transdermal absorption of these drugs. One gram gel samples (equivalent to 5 mg drug) were applied to the dorsal areas of the rats ($n = 5$). The rats were sacrificed at 2, 4, 8, 24, 30, 48 and 96 h after gel administration. Plasma concentrations of indomethacin, ketoprofen and piroxicam were determined using a high performance liquid chromatography (HPLC) method. Sample preparation involved protein precipitation and centrifugation. The log *P* values obtained from literature for piroxicam, ketoprofen and indomethacin, (3.08, 0.97 and 1.8, respectively) correlated with the area under the plasma-time curve (AUC) values determined 527.00 (piroxicam) 269.45 (ketoprofen) and 243.22 (indomethacin) $\mu$g/ml/h, respectively. It was concluded that the most reliable parameter was the lipophilic character of a drug (log *P* value). The molecular mass, solubility constraint and percentage unionized moiety did not show any correlation concerning transdermal absorption and can therefore not be used on their own in the prediction thereof. However, all the parameters including the pharmacokinetic properties of drugs should be considered in combination in the prediction of possible transdermal drug delivery. 

*Keywords:* Transdermal; Absorption; Indomethacin; Ketoprofen; Piroxicam; Physicochemical; Pharmacokinetic

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## 1. Introduction

Indomethacin {1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid}, ketoprofen {3-Benzoyl-a-methylbenzeneacetic acid} and piroxicam{4 - Hydroxy - 2 - methyl - N - 2 - pyridinyl - 2H - 1,2-bensothiazine-3-carboxamide 1,1-dioxide} are non-steroidal anti-inflammatory drugs (NSAIDs), which possess analgesic and antipyretic properties (Merck Index, 1989; Babar et al., 1990). Each drug belongs to a different chemical group. Indomethacin is an arylacetic acid derivative, whereas ketoprofen belongs to the related aryl-propionic acids and piroxicam forms the oxicam group (Roth and Fenner, 1988).

The NSAIDs has prominent anti-inflammatory, analgesic and antipyretic properties. They are used in the treatment of osteo and rheumatoid arthritis (Chi and Jun, 1990; Lin et al., 1994). Oral therapy of NSAIDs is very effective, but the clinical use is often limited because of its potential to cause adverse effects such as irritation and ulceration of the gastro-intestinal (GI) mucosa. Patient noncompliance is also a common therapeutic problem in the management of chronic inflammatory diseases, because most NSAIDs must be administered in multiple daily doses to maintain therapeutic blood levels (Jacobs et al., 1988). 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 (Okabe et al., 1994; Fang et al., 1995; Jiang et al., 1995; Lu et al., 1995; Valenta and Almasi, 1995; Singh et al., 1996). However, none of these have investigated the correlation of the transdermal absorption and the physicochemical and pharmacokinetic parameters.

A number of drugs readily passes through the skin, and the rate and extent to which this happens are influenced by the physicochemical properties of the drug (Beckett, 1982). Other factors may also have an influence, but if they are kept constant, it should be possible to determine which physicochemical properties are most important in determining the rate and extent of absorption through or into the skin (Lien and Tong, 1973). The physicochemical properties investigated 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.

## 2. Materials and methods

### 2.1. Chemicals

Indomethacin was purchased from Adcock Ingram Pharmaceuticals (Johannesburg, RSA). Ketoprofen was obtained from Sigma (St. Louis, MO) and piroxicam from Secifarma (Milan, Italy). Acetonitrile (BDH, Pool, England) and acetic acid (Saarchem, Johannesburg, RSA) used for the HPLC assay were of analytical grade. Water was HPLC grade deionized with a Milli-Q 50 purification system (Millipore, Milford, MA).

Eutha-naze® solution (sodium pentobarbitone) was obtained from the Premier Pharmaceutical Company Ltd. (Bryanston, RSA) and used to sacrifice the rats. Halothane obtained from Zeneca (Woodmead, RSA) was used for anesthetic purposes.

### 2.2. Chromatography

High performance liquid chromatography (HPLC) analysis was performed with a Spectraseries P100 isocratic pump (Spectra Physics Analytical, Fremont), a Rheodyne injection valve fitted to a 50-$\mu$l loop and a Spectra System UV 1000 variable wavelength UV detector. A Nova Pak (Millipore) C18 column (150 $\times$ 3.9 $\mu$m I.D. 4 mm), together with a LiChroCart® guard column were used and the mobile phase was a mixture of acetonitrile/water/acetic acid (50:46:4). The flow rate was 1.5 ml/min and the detection wavelength was 254, 264 and 365 nm for indomethacin, ketoprofen and piroxicam respectively. Data handling

was performed using an EZChrom Chromatographic data system (Scientific Software Inc., San Ramon).

### 2.3. Standard solutions and calibration curves

Stock solutions of indomethacin, ketoprofen and piroxicam (500 $\mu$g/ml) were made by dissolving pure drug and diluting to volume with 50% acetonitrile solution. A working solution of the internal standard piroxicam or indomethacin (30 $\mu$g/ml) was prepared in acetonitrile by dilution from the stock solution. All stock solutions were stored in the dark at 4°C. Indomethacin was used as internal standard in the assay of piroxicam, piroxicam was used for the assay of indomethacin and indomethacin was used as internal standard in the assay for ketoprofen.

For the establishment of calibration curves, blank plasma samples (1 ml) were spiked with piroxicam, indomethacin or ketoprofen at concentrations within the studied range (0.5–20 $\mu$g/ml). The internal standard concentration was maintained at 10 $\mu$g/ml for every sample.

### 2.4. Preparation and assay of gel formulae

In order to compare the transdermal absorption of the different NSAIDs the same gel formulae was used. The gels were prepared by dissolving the NSAID (0.25 g equivalent) in ethyl alcohol (19.58 g). The following materials were then added in the following sequence while mixing continuously: distilled water (12.02 g), propylene glycol (3 g), glycerin (2.5 g), dipropylene glycol (2 g) and hydroxypropyl cellulose (0.25 g). After mixing for 2 min, carbomer (0.65 g) was added very slowly and the mixture was left to stir thoroughly for 6 h. Finally tetrahydroxypropylethylenediamine (1.25 g) was added to the final mixture in order to change the consistency of the mixture to that of a gel by neutralizing the carbomer. The resulting gels were stored at room temperature.

The assay of each formula complied with the general criteria of 90–110% as stated in the USP monograph.

### 2.5. Preparation of rats prior to application

Five male BD IX rats (weighing between 160 g and 200 g) were used for each time interval. Halothane (0.8 ml) was sprayed onto a paper towel inside the container to establish a 0.025% halothane-air mixture. Each rat was separately sedated by placing it in a 4-l glass container. As soon as the rat was calm it was coupled to an anaesthesia apparatus (see Section 2.6). While the rat was coupled to the anaesthesia apparatus, the hair on the dorsal surface was shaved, taking care not to injure the skin. The shaved area was marked by means of a $8 \times 4$-cm$^2$ template and indelible ink to facilitate dosing uniformity. The temperature in the animal laboratory was $21 \pm 2$°C and the humidity $55 \pm 10$%.

### 2.6. Anaesthesia apparatus

The anaesthesia apparatus consisted of two 1.19 l plastic bags connected to a three way valve. Two plastic bags were connected to two exits of the valve and latex rubber to the middle exit (filled with medicinal oxygen and halothane respectively). An initial dose of 4% (0.24 ml) and a maintenance dose of 2% (0.12 ml) halothane were used. Sodium lime (10 mg) was also placed in the bags to absorb the exhaled carbon dioxide. The rat was connected to the apparatus by placing the free end of the latex rubber over the rat's head. The valve was used to direct the 2% or the 4% halothane-oxygen mixture to the rat, thereby regulating the level of anaesthesia (Marais, 1992).

### 2.7. Gel application

An accurately weighed 1 g gel sample (equivalent to 5 mg NSAID) was spread uniformly over the prepared dorsal areas of the rats with a weighed spoon in order to determine the exact dose. After application the rats were released from the anaesthesia apparatus to recover and housed in individual containers where restricted movements were allowed, preventing loss of gel from the dorsal surface.

### 2.8. Blood sampling and sample preparation

The rats were sacrificed at 2, 4, 8, 24, 30, 48 and 96 h after gel administration, by overdosing with an intraperitoneal injection of 0.8 ml Eutha-nase® solution (200 mg/ml sodium pentobarbitone). Blood samples (4.5 ml) were taken by cardiac puncture and placed in veneject tubes containing heparin. Plasma was immediately separated by centrifugation and kept frozen at −20°C until analysed. One ml of internal standard was added to 1 ml plasma in a glass-stoppered centrifuge tube (5 ml). Precipitation of plasmaproteins was accomplished by the addition of 1 ml acetonitrile to the plasma. The tubes were stoppered and vortexed for 1 min using a Heidolph type Reax 1 DR shaking apparatus (Germany). After 10 min equilibration, it was vortexed again for 1 min and left to equilibrate for another 10 min. The samples were then centrifuged in a Model TJ-6 centrifuge (Beckman – RIIC Ltd., Glenrothes-Fife Scotland) for 30 min at 3000 rpm at 4°C temperature. A 50-$\mu$l aliquot of the supernatant was injected onto the HPLC column.

### 2.9. Calculation of pharmacokinetic parameters

From the mean NSAID concentration-time curve, the AUC was calculated by using a method described by Jawién (1992). The difference between the AUC values was evaluated using the same method for statistical comparison of bioavailability when one concentration-time point per individual is available. The difference was considered significant when $P$ values of 0.05 or less were obtained.

The half-lives ($t1/2$) for the NSAIDs in humans were obtained from the literature (Ritschel, 1992). We assumed that these values could be an indication for those found in rats.

### 2.10. Physicochemical properties

The solubility constraint in the stratum corneum was calculated by the following equation:

$$\log \sigma_{sc} = 1.911\ (10^3/\mathrm{mp}) - 2.956 \quad (1)$$

where mp is the melting point (Kelvin).

The Henderson-Hasselbalch equation (Eq. (2)) was used to calculate the ratio of the concentration of the ionized form ($A^-$) and the unionized form ($HA^-$) of the drug when they reached the skin (Proudfoot, 1988).

$$\mathrm{pH} - \mathrm{p}K_a = \frac{\log\ [\text{ionized form}]}{[\text{unionized form}]} \quad (2)$$

In this case, the pH of the skin was taken as the acid mantle of the skin.

The melting point, molecular mass $\mathrm{p}K_a$ and $\log P$ values for all three drugs were obtained from the literature (Ritschel, 1992).

## 3. Results and discussion

Table 1 provides a summary of the physicochemical properties of interest as well as relevant pharmacokinetic parameters for indomethacin, piroxicam and ketoprofen respectively. Significally differences ($P < 0.05$) were indicated for the AUC parameter between all of the drugs. Piroxicam showed the highest bioavailability followed by ketoprofen and indomethacin. In order to determine whether the physicochemical properties of these drugs played a role in the absorption process through the skin, the following parameters were taken into account, namely, the molecular mass, the state of ionization, the lipid/water partition coefficient and the solubility constraint of the drugs in the stratum corneum.

### 3.1. Molecular mass

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.

Table 1
The physicochemical and pharmacokinetic properties of piroxicam, ketoprofen and indomethacin after transdermal application

| Properties | Piroxicam[a] | Ketoprofen[b] | Indomethacin[c] | References |
|---|---|---|---|---|
| Physicochemical formula | $C_{15}H_{13}N_3O_4S$ | $C_{16}H_{14}O_3$ | $C_{19}H_{16}ClNO_4$ | Lund, 1994 |
| Molecular mass | 331.40 | 254.29 | 357.80 | Lund, 1994 |
| Log *P* | 1.8 | 0.97 | 3.8 | Mihalic et al., 1986[a]; Liversidge, 1981[b]; Hansch and Leo, 1997[c] |
| pKa | 5.3 | 4.45 | 4.5 | Lund, 1994 |
| % Unionised at acid mantle of skin pH 4.8 | 75.97 | 30.88 | 33.39 | Ritschel, 1988 (Eq. 2) |
| Solubility constraint | 12.38 | 175.38 | 28.67 | Eq. 1 |
| Melting point | 199°C | 94.5°C | 160°C | Lund, 1994 |
| Pharmacokinetic AUC ($\mu$g/ml/h)* | 527.00 | 269.45 | 243.22 | |
| t1/2 (h) | 40.80 | 1.80 | 6.10 | Ritschel, 1992 |

*In order of decreasing bioavailability.

### 3.2. Lipid/water partition coefficient

Drugs would preferably have a balanced lipophilic/hydrophilic character and a drug with a log *P* value of $\leq 2$ 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, indomethacin 3.8), it is evident that the transdermal absorption of these drugs should be piroxicam > ketoprofen > indomethacin. This correlated with the AUC values found for these NSAIDs.

Yano et al. (1986) stated that the optimum log *P* value for NSAIDs is $\sim 2.5$. They found that below this optimum log *P* values, the absorption rate increases, while a decrease in the absorption rate occurred above this value. The latter possibly due to unfavourable solubility properties. Due to this, one could assume that piroxicam and ketoprofen would show the best absorption while indomethacin would not be such a good candidate for transdermal absorption (log *P* value $> 3$). Indomethacin is a more lipophilic drug and therefore may form a reservoir in the stratum corneum and be more susceptible to enzymatic degradation.

The use of the water/lipid partition coefficient as a physicochemical parameter in predicting the transdermal absorption of NSAIDs was found to be useful. However, the log *P* value can only be used in combination with other indicative parameters.

### 3.3. $pK_a$ (Ionization at physiological pH)

An ionizable drug will be present in both charged and uncharged form depending on its $pK_a$ and pH of the environment (Smith, 1990). The nonionised moiety of a drug is more lipid soluble and may dissolve more rapidly in the lipid material of the skin, thereby facilitating transport by passive diffusion (Abdou, 1989; Jack et al., 1991). The ionized moiety, on the other hand, is usually less lipid soluble, limiting transdermal permeation (Ritschel, 1988).

The $pK_a$ values of all the drugs investigated ranged from 4.5 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 and indomethacin = 33.39). Since it can be expected that the nonionised moiety of a drug will penetrate the skin best, one can assume that piroxicam would be the better candidate, followed by indomethacin and ketoprofen. The AUC values did not follow this pattern, however, only a difference of less than 3% between the state of ionization of indomethacin and ketoprofen was

found. The AUC of piroxicam showed that the large fraction of unionized drug benefitted the bioavailability of the drug.

### 3.4. Solubility constraint

The solubility constraint of a drug in the stratum corneum can be defined as the potential a compound may have to form a reservoir in the stratum corneum. The higher the value of the solubility constraint of the drug, the lower the ultimate systemic availability thereof. The solubility of a drug in the stratum corneum is of utmost importance in order for the drug to become sufficiently bioavailable (Hadgraft and Wolff, 1993). Therefore, knowledge of the solubility constraint of a drug would enable one to predict the rate and extent of absorption into the skin. By making use of the melting point of the drugs, as based on the efforts by Hadgraft and Wolff (1993) the solubility constraint of piroxicam, ketoprofen and indomethacin was calculated and is shown in Table 1.

According to the values obtained, ketoprofen will be retained in the stratum corneum to a greater extent than indomethacin and piroxicam. One could therefore expect that the amount of drug that is finally bioavailable would decrease in the following order, namely piroxicam > indomethacin > ketoprofen. When the latter was compared with the AUC values of the different NSAIDs, a correlation only existed for piroxicam. Thus, the solubility constraint by itself can therefore not be used as a reliable enough physicochemical parameter in the prediction of the transdermal absorption of the NSAIDs.

### 3.5. Physicochemical and pharmacokinetic parameters

Piroxicam showed the best bioavailability with an AUC value of 527.0 $\mu$g/ml/h because all the factors considered, favoured the bioavailability of this drug. The percentage unionized moiety, the lipid/water partition coefficient, the solubility constraint, the half-life, all of them are favourable 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. Since piroxicam has a half-life of 40.8 h, it is slowly eliminated resulting in higher blood plasma levels.

The bioavailibility of ketoprofen and indomethacin as indicated by their AUC values (Table 1) fell within a narrow range (269.45–243.22 $\mu$g/ml/h) and could be explained as follows. The percentage unionized moiety of both these drugs did not differ much, while the lipid/water partition coefficient for ketoprofen is more favourable for absorption than that of indomethacin. Concerning the solubility constraint, ketoprofen will tend to have a stronger depot effect in the stratum corneum than indomethacin while it also has the shortest half-life. One would thus expect that indomethacin should have better bioavailability than ketoprofen (which is not the case). When one considers the log $P$ values, ketoprofen tends to be the closest to the optimum value indicated for NSAIDs. The latter thus overshadows the aforementioned parameters leading to a slightly better bioavailibility for ketoprofen. This also strengthens the conclusion drawn that the log $P$ value of a drug is a reliable parameter in the prediction of a suitable candidate for transdermal drug delivery.

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