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The selection of non-steroidal anti-inflammatory agents for dermal delivery

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Abstract

An analysis has been conducted to show how the penetration of a selection of non-steroidal anti-inflammatory agents (NSAIDs) through the skin may be predicted. The calculations are based on physicochemical parameters that can be predicted using commercially available software. Where available the predictions compare favourably with the literature values. The bio-effectiveness of the NSAID will be a function of both its penetration through the skin and its potency. The variation in potency has also been considered. Most NSAIDs are carboxylic acids, therefore the pK_a will be an important determinant in ionisation and hence permeation. pH partition behaviour into the skin has been considered together with the relative impact of decreased permeation but increased solubility with degree of ionisation.

Keywords: Non-steroidal anti inflammatory; Skin penetration; Modelling; Transdermal delivery

1. Introduction

There has been a proliferation in the number of products that have been designed to deliver non-steroidal anti-inflammatory agents (NSAIDs) to the skin surface for local delivery. These include simple creams, gels and more complex transdermal systems with a range of active drugs. The choice of the most appropriate active depends on a number of factors. These include its potency, its ability to permeate the stratum corneum and its lack of local skin toxicity. Generally drugs have been chosen which have well established safety records following conventional oral delivery and many of the problems can be anticipated from this knowledge base. The dermal absorption of the various compounds can be predicted from physicochemical parameters obtainable from commercially available software. If this information is combined with knowledge of the potency of the NSAID, rational judgements can be made about the suitability of the drug for further development. This publication seeks to examine a num-

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ber of representative NSAIDs to show the utility of this approach in dermal drug screening. It extends some of the concepts described by Cordero et al. (1997).

2. Methods

The chosen drugs are listed in Table 1 together with some of their physicochemical properties. The melting points are from standard texts (such as The Merck Index). The octanol water partition coefficients (P) were predicted together with estimates of their aqueous solubilities using the ACD suite of programmes (Advanced Chemical Development Inc., Toronto, Canada (version 3.5)). This software suite also provides literature log P values for some of the compounds in an in-built database. The database does indicate the various references from where the measured values are available. The solubilities, where available (Table 1), are comparable, with the exception of piroxicam, to those provided by Cordero et al. (1997).

3. Results and discussion

The molecular masses and calculated molar volumes (ACD software) are all very similar suggesting that the diffusion coefficients through the skin will be very similar. However the log P values range over five orders of magnitude and therefore represent a wide spectrum of the various therapeutic NSAIDs available.

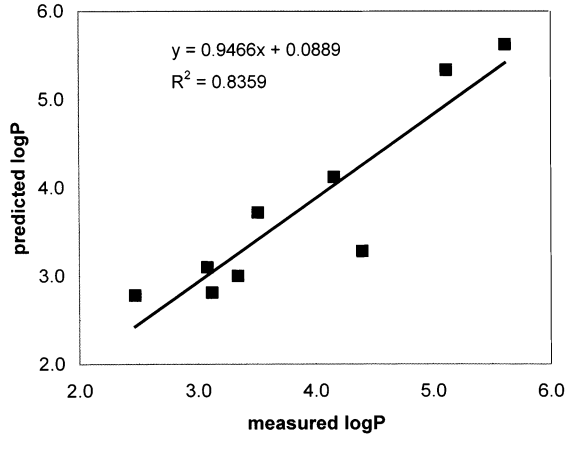

Fig. 1. The relationship between the measured and predicted log P values for the NSAIDS.

Fig. 1 shows the correlation between the predicted and measured log P values (where available). The regression line on the graph has a gradient close to unity and the agreement shows that the software is good at predicting values for this class of medicines. The reason that two values are provided for piroxicam (Table 1 and Table 2) is that the ACD software identifies that two tautomeric forms can exist. The predominant form will be dependent on the solvent conditions. There is a considerable difference between the predicted log P and solubility properties of the two tautomers. Both have therefore been included for completeness. The data provided in Table 1 can be used to estimate the permeability coefficients of the various NSAIDs through the skin. The equation used for this is the one given by Potts and Guy (1992) (Eq. (1)):

$$\log k_p(\mathrm{cm/h}) = -2.7 + 0.71 \log P - 0.0061\ \mathrm{MW} \quad (1)$$

Simple molecular weights (MW) were used, as there appears to be no significant advantage in using molecular volume (Potts and Guy, 1992). The values of the calculated permeability coefficients are given in Table 2. It should be remembered that these values are for the unionised permeant in an aqueous formulation. The aqueous phase would have to be sufficiently acidic to suppress ionisation. This will be a function of the pK_a of the NSAID. The pK_a values can also be predicted using the ACD suite of software and are also included in Table 2. The maximum flux through the skin is obtained by taking the predicted permeability coefficient and multiplying it by the predicted aqueous solubility (from Table 1).

Fig. 2 shows the relationship between the calculated and mean literature values for the permeability coefficients. The value for piroxicam appears to give a better fit for the more lipophilic tautomer. In subsequent analyses this has been used as the predominant species in dermal delivery.

Table 1
NSAIDs chosen and their various physicochemical properties

NSAID	Molecular mass (D)	Melting point (°C)	Predicted log P[a]	Literature log P	Predicted aqueous solubility (μg/ml)[a]	Experimental aqueous solubility (μg/ml)[b]
Alclofenac	226.7	92.5	2.78	2.47	150	
Bufexamac	223.3	154	2.43		110	
Diclofenac	296.0	157	3.28	4.4	12	3.5
Felbinac	212.2	164	3.26		8	
Flufenamic acid	281.2	125	5.62	5.62	0.03	
Flurbiprofen	244.3	110.5	4.12	4.16	2.7	
Ibuprofen	206.3	76	3.72	3.51	14	
Indomethacin	357.8	155	3.10	3.08	25	11
Ketoprofen	254.3	94	2.81	3.12	150	294
Mefenamic acid	241.3	230	5.33	5.12	0.01	
Naproxen	230.3	155.3	3.00	3.34	23	
Piroxicam	331.4	199	1.46	1.80	870	53.3
Piroxicam II	331.4	199	−0.02		55300	
Tiaprofenic acid	260.3	96	2.42		450	

[a] calculated using ACD software.
[b] from Cordero et al.

Table 2
pK_a, permeability coefficients, and predicted maximum flux of the NSAIDs

NSAID	pK_a[a]	Permeability coefficient (cm/h)[b]	log k_p predicted	log k_p literature	J_{max} (μg/cm^2/h)
Alclofenac	4.26	7.04×10^{-3}	−2.15		1.06
Bufexamac	9.24	4.16×10^{-3}	−2.38		0.46
Diclofenac	4.18	6.02×10^{-3}	−2.22	−3.0[c]	0.07
Felbinac	4.29	1.89×10^{-2}	−1.72		0.15
Flufenamic acid	3.65	3.40×10^{-1}	−0.47		0.01
Flurbiprofen	4.14	4.91×10^{-2}	−1.31		0.13
Ibuprofen	4.41	4.36×10^{-2}	−1.36	−1.44[c]	0.61
Indomethacin	4.18	1.88×10^{-3}	−2.73	−3.15[d]	0.05
Ketoprofen	4.23	5.01×10^{-3}	−2.30	−2.57[d]	0.75
Mefenamic acid	3.69	3.70×10^{-1}	−0.43		0.002
Naproxen	4.40	9.59×10^{-3}	−2.02	−2.54[d]	0.22
Piroxicam		1.87×10^{-4}	−3.73	−3.18[e]	0.16
Piroxicam II		1.66×10^{-5}	−4.78		0.92
Tiaprofenic acid	4.05	2.44×10^{-3}	−2.61		0.10

[a] calculated by the ACD software.
[b] Predicted from log P and the Potts and Guy equation.
[c] From Degim et al. (1998).
[d] Cordero et al. (ionised form) (1997).
[e] From Wilschut et al. (1995).

Fig. 3 shows the relationship between the maximum predicted flux and the calculated log P. Previous work by Yano et al. showed that there was maximum percutaneous absorption for a series of NSAIDs and salicylates where the log P was between 2 and 3 (Yano et al. 1986). The data in Fig. 3 are in general agreement with this. At low log P, the permeability coefficient is low but the aqueous solubility is high. At high log P, the permeability coefficient is high but the aqueous solubility is low. The optimum value appears to be in the log P range 2–3. However there is a paucity of data for compounds having a log P less than 2.

The other factor that needs to be taken into account when considering the effectiveness of the NSAID is its potency. Information is available in the literature for some of the compounds mentioned in Table 1. The prostaglandin synthesis IC_{50} values for a mouse macrophage model are given in Table 3 (Brune et al. 1981) together with the normal oral doses used in clinical practice. The mouse macrophage model obviously has limitations but it does appear to be related to the human potency as determined, crudely, by the daily oral dose. As can be seen from Table 3, and as expected, the lower the IC_{50}, the higher the daily clinical dose.

From the calculations, the largest predicted flux is for ketoprofen. This value is comparable to that for ibuprofen, however the relative potencies of these two NSAIDs are significantly different. To obtain an idea of the relative topical effectiveness expected, the ratio of J_{max}/IC_{50} should be considered. The larger the ratio, the more likely the

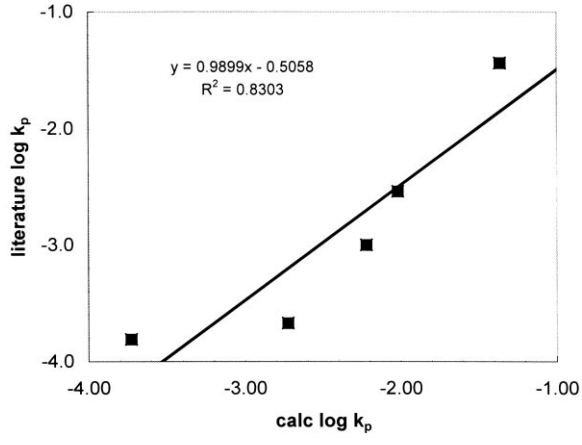

Fig. 2. The correlation between calculated and literature permeability coefficients (where available).

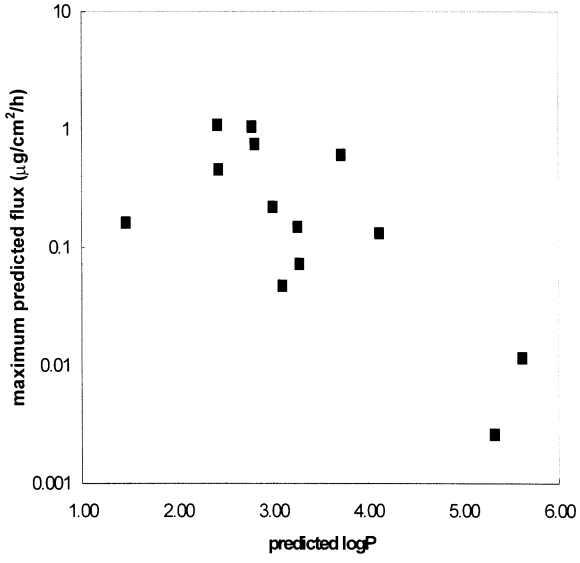

Fig. 3. The variation in maximum predicted flux with the calculated log P of the unionised species.

bio-effectiveness of the compound following topical administration. In Table 3 the ratio has been normalised (ketoprofen = 1) to provide more manageable numbers. Ketoprofen appears to be the most effective with indomethacin being very similar. Considering the variability found in skin permeation it is unlikely that it would be possible to distinguish between these two and possibly also between these and diclofenac. However there is a very large difference between these three and the other two NSAIDs considered, ibuprofen and naproxen. This is largely a result of the higher IC_{50}s for these two compounds.

3.1. Ionisation effects

One of the factors that is very often ignored in dermal formulation design and the prediction of skin permeability is that many potential permeants are weak acids or weak bases and will therefore be ionised. The surface pH of the skin is around 5.0 and often a pH between 4 and 7 will be chosen for the aqueous phase of a dermal formulation. The question needs to be asked; how will this affect the amount of permeant that can be delivered? There have been very few systematic studies conducted on pH permeation profiles through the epidermis. The role of pK_a and ionisation has been discussed, in part, by Cordero et al. for a series of NSAIDS (Cordero et al., 1997). The partition of the ionised component will be significantly smaller than that for the unionised species. However it must be remembered that the maximum flux is the product of the permeability (directly related to partition coefficient) and the aqueous solubility. The aqueous solubility will increase as partition decreases. These two effects are shown in Fig. 4 for ketoprofen (as a general example) with values calculated using the ACD software.

Recent evaluations of the skin permeation of ibuprofen and lignocaine have shown that it is possible to use the Potts and Guy equation (Eq. (1)) with log D rather than log P (Hadgraft and Valenta, 2000). The generated permeability coefficients can be combined with the aqueous solubilities to estimate maximum fluxes of the combination of ionised and unionised entities. The simulations are given in Fig. 5.

For all NSAIDs shown except bufexamac there is an increase in flux with pH. The solubilities of

Table 3
Predicted maximum flux, daily clinical dose, IC_{50} and the relative ratio, J_{max}/IC_{50}

NSAID	J_{max} (μg/cm²/h)	Daily dose (mg)	PG synthesis IC_{50}(mol/kg)[a]	Relative J_{max}/IC_{50}[b]
Diclofenac	0.07	100	9.6×10^{-9}	0.22
Ibuprofen	0.61	1600	5.5×10^{-7}	0.03
Indomethacin	0.05	100	1.7×10^{-9}	0.81
Ketoprofen	0.75	150	2.2×10^{-8}	1.00
Naproxen	0.22	750	2.8×10^{-7}	0.02

[a] Mouse macrophage assay for prostaglandin synthesis (Brune et al., 1981).
[b] Normalised to the value of the maximum ratio (that for ketoprofen).

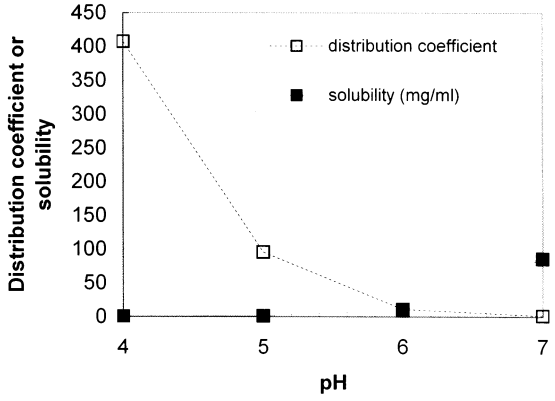

Fig. 4. The calculated octanol water distribution coefficient and aqueous solubilities for ketoprofen as a function of pH.

the compounds appear to increase more than the distribution coefficients (and hence permeabilities) decrease. Bufexamac has an estimated pK_a of 9.24 and over the pH range quoted the partition and solubility behaviour is essentially pH independent. For compounds where ionisation is possible it may be better to buffer the formulation such that the solubility is improved but the permeability may be compromised. In addition the IC_{50} should be taken into account since the relative effectiveness will be a function of both the amount that reaches the target site and its potency. Where the IC_{50} is not available a more simple approach would be to use the daily human dose as an indicator of potency. Table 4 shows the predicted relative bio-effectiveness where a value of 1 has been given to unionised ketoprofen.

Commercial software can be used to predict the physicochemical properties that control the percutaneous absorption of the NSAIDs. If the relative potency of the NSAID is known it is possible to make estimations of the relative bio-effectiveness of the formulated drug. The calculations show that significant absorption of the ionised species can occur. This is in agreement with published data on the effect of pH on the percutaneous absorption of ibuprofen (Watkinson et al., 1993). In this study they showed that although the permeability coefficient of ibuprofen at higher pH's was low, the flux of a saturated solution was greatest at the high pH's. This was due to the increased solubility of the ionised permeant. It is perhaps surprising that the number of studies on the pH permeability relationships in dermal penetration is limited. There are some reports on

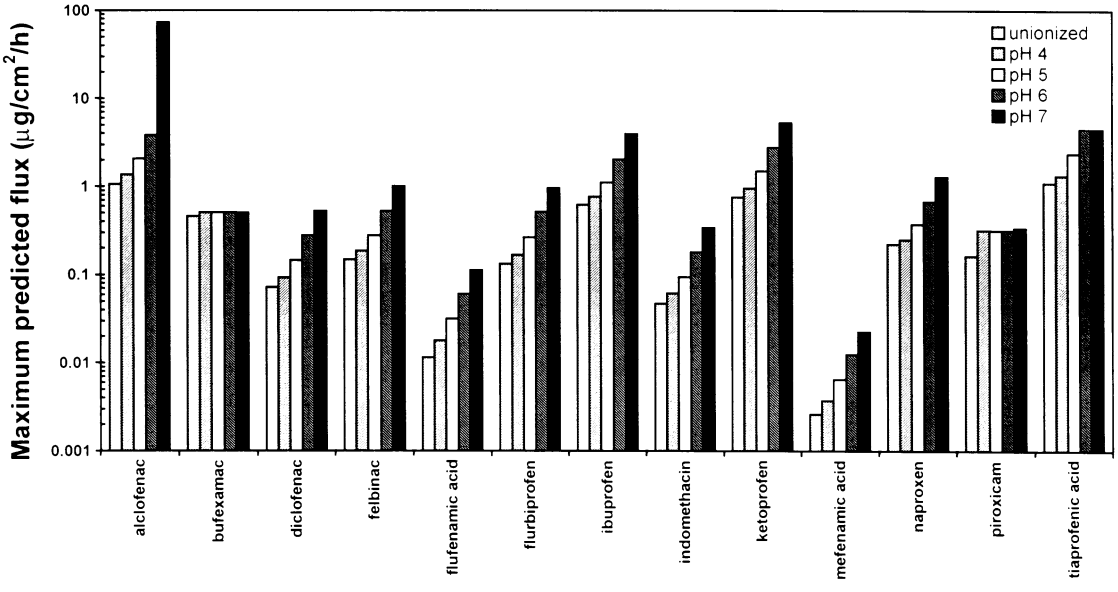

Fig. 5. The maximum fluxes predicted for the different NSAIDs showing the effect of ionisation at pH 4, 5, 6 and 7.

Table 4
The relative predicted bio-effectiveness (dividing maximum flux by IC_{50}) of saturated solutions of different NSAIDs; unionised ketoprofen has been given a value of unity

NSAID	Unionised	pH 4	pH 5	pH 6	pH 7
Diclofenac	0.22	0.38	0.44	1.11	2.11
Ibuprofen	0.03	0.05	0.06	0.14	0.28
Indomethacin	0.81	1.40	1.61	4.11	7.78
Ketoprofen	1.00	1.70	1.99	4.92	9.44
Naproxen	0.02	0.03	0.04	0.09	0.18

animal studies where the results may have parallels in human absorption. One such example is that from Inagi et al. (1981). In this investigation the absorption of indomethacin across guinea pig skin was studied as a function of pH. There was a general correlation between flux and fraction of unionised indomethacin (the concentration of the drug in the different formulations was held constant). At the higher pH the flux however was higher than anticipated, possibly as a result of ion pairing. Since the skin appears to be able to buffer its outer layers to a pH around 5.0 it is important to appreciate the role of ionisation on skin permeability; further studies are clearly warranted.

There may be significant differences when in vivo studies are conducted where active processes may be involved in maintaining the pH balance of the skin. Also when aqueous solutions are applied to the skin in vitro for estimations of the permeability coefficient, ionisation effects and the pK_a of the permeant should be taken into consideration. These findings extend the work by Cordero et al. who also have taken into account the ionisation of a series of non steroidal anti-inflammatory agents when they are applied transdermally (Cordero et al., 1997).

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