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pH, pK_a and dermal delivery

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Abstract

The effect of pH on the permeation of ibuprofen and lignocaine through human skin has been modelled using a modification to the equation derived by Potts and Guy, which is normally applied to unionized entities. The results show that permeation is related to the distribution coefficient. The physicochemical properties have been predicted ab initio using commercially available software and compared to literature values. The approach is successful and shows that there is significant permeation of the ionized drugs through a lipophilic pathway, possibly as a result of ion pairing. Since the aqueous solubility of the ionized material is significantly higher than the unionized, the maximum flux through the skin may occur at a pH where ionization is high. Optimum topical or transdermal formulations may not therefore be for the free acid or free base.

Keywords: Dermal delivery; Ibuprofen; Lignocaine; pH partition

1. Introduction

The pH partition theory is well documented for the general absorption of ionizable drugs across the gastro-intestinal tract but it is less well described in the dermal and transdermal delivery of drugs. This is perhaps surprising given the number of medicines that are delivered to the skin and which would be ionized over the normal physiological pH range of the dermal tissues (4–7.4). It is generally accepted that, where possible, the free acid or free base should be used, however perhaps this premise should be questioned. This fact has been alluded to in a publication on the transdermal penetration of a series of non-steroidal anti-inflammatory agents (Cordero et al., 1997).

The total flux (J_{tot}) of a permeant through the skin is a composite term, which can be attributed to transport of both the ionized and unionized moieties. The transport properties can be described by the permeabilities of the ionized and unionized species and the respective concentrations k_{pion}, k_{punion}, c_{ion}, and c_{union} respectively.

$$J_{tot} = k_{punion} * c_{union} + k_{pion} * c_{ion} \quad (1)$$

The ambient pH and the pK_a of the permeant will give the relative amounts of ionized and unionized species. For a base, the fraction of the permeant that is ionized (f_{ion}) is given by the well-described equation:

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$$f_{ion} = 100/[1 + 10^{(pH - pK_a)}] \quad (2)$$

For any given pH, pK_a and total applied concentration, it is therefore possible to calculate the amounts of c_{union} and c_{ion}. What is less clear is the value of k_{punion} and k_{pion}. The former permeability can be estimated using the equation provided by Potts and Guy (1992).

$$\log k_p \text{ (cm/h)} = -2.7 + 0.71 \log K_{oct} - 0.0061 \text{ MW} \quad (3)$$

where K_{oct} is the octanol water partition coefficient and MW is the molecular weight. The question arises, can a similar equation be used to predict the permeability of the ionized species? The value will be considerably less than for the unionized species but it must be remembered that the overall flux is a composite term that includes the concentration of the species. The solubility of the ionized species will be considerably higher than for the unionized species. It may therefore, be possible that, given a set pH or permeant concentration, the amounts of drug permeating will be dominated by the diffusion of the ionized moieties. Results in the literature for both an acid and a base, ibuprofen and lignocaine have been analysed to show the relative permeation of the two species. Predictive software (ACD, Toronto, Canada), which can estimate the distribution coefficients of the different species present between octanol and water, has been used to show its utility in formulation design. This software was chosen as it has an integrated suite of programs that allow calculation of log P, log D and pK_a and aqueous solubility. P is the partition coefficient of the unionized species between octanol and water; D is the distribution coefficient between octanol and water (i.e. allowing for the partitioning of ionized species which will change with pH).

2. Methodology

A representative acid (ibuprofen) and base (lignocaine) were chosen for analysis since values of the permeation of these two materials, over a range of pH, through human skin are available in the literature (Watkinson et al., 1993; Valenta et al., 2000). The distribution behaviour of these two compounds between octanol and water was predicted using ACD software and compared to that in the literature (Avdeef et al., 1998). In this paper, there are also values for another partitioning media, liposomes made from dioleylphosphatidyl choline (DOPC). The latter may be a solvent more representative of the skin since the intercellular channels in the stratum corneum, into which the permeant will partition, contain an array of structured lipid bilayers.

3. Ibuprofen

Ibuprofen is a non-steroidal anti-inflammatory agent that has been formulated into a number of topical preparations. Its transfer across skin is well documented and Watkinson et al. (1993) have examined its solubility and diffusion properties as a function of pH. Table 1 summarizes the properties.

As expected, as pH increases the solubility increases with the degree of ionization, but the permeability decreases. ACD software predicts a pK_a for ibuprofen of 4.41, a measured value of 4.45 (Avdeef et al., 1998) is in very good agreement. At the extremes of the pH range in Table 1, the values for the permeabilities therefore represent the values for the unionized and ionized species.

Log D (octanol–water) for ibuprofen as a function of pH has been simulated and is shown in

Table 1
The solubility and permeability properties of ibuprofen as a function of pH (data from Watkinson et al., 1993)

pH	2.2	2.3	4.0	5.0	6.0	7.0	9.0	9.2
Solubility (mg/ml)	0.024	0.027	0.029	0.096	0.52	3.70	7.83	14.8
Permeability coefficient (cm/h)	0.06	0.053	0.045	0.036	0.019	0.0066	0.0024	0.0012

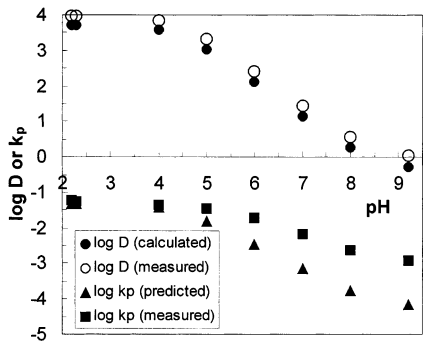

Fig. 1. The variation, for ibuprofen, in the predicted (and measured) log D, and the predicted (and measured) log k_p with pH.

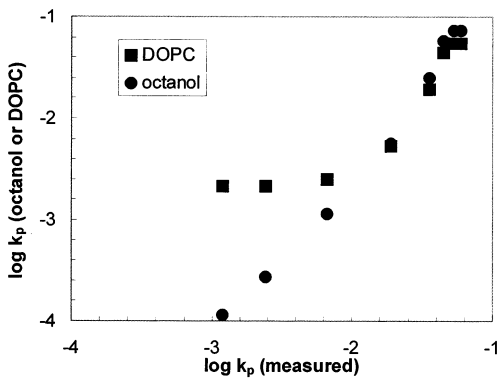

Fig. 2. A comparison between the measured log k_p for ibuprofen and that estimated using log D values for octanol or DOPC as the partition medium.

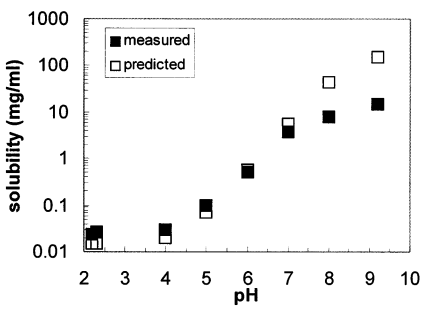

Fig. 3. The relationship between measured and calculated solubility and pH.

Fig. 1. Measured values for log D are available in the literature (Avdeef et al., 1998) and have, in addition, been plotted. There is a very good agreement between the predicted and measured values. Since the partitioning will be a function of the ionic strength and the nature of the counter-ions present the agreement can be considered to be excellent.

Also shown are the calculated k_p values using log D in Eq. (3) and the measured k_p values from Table 1.

Avdeef et al. (1998) also provide log D values for DOPC. These can also be used to estimate k_p. If DOPC represents a more appropriate partitioning medium to represent skin lipids, the correlation should be better. Fig. 2 shows a comparison between measured and predicted k_p values using both log D for octanol and DOPC.

For the pH range 2.2–6.0 there is good agreement between the predicted values for octanol and DOPC. Where the fraction of the ionized species becomes close to 100%, at pH > 6.0, there is a discrepancy between the two values. DOPC does not appear to mimic the behaviour found for the skin. There is a linear relation between log k_p measured and log k_p predicted from octanol:

$$\log k_p \text{ (predicted)} = 1.72 \log k_p \text{ (measured)} + 0.93 \quad (4)$$

$$R^2 = 0.986$$

There is not a 1:1 correlation, but it should be possible to use this type of relationship to get a more accurate prediction of the permeability coefficients over a range of pH. The predicted value underestimates the actual value, as is seen in Fig. 1.

ACD software also predicts aqueous solubility as a function of pH. The comparison of the predicted values and those quoted by Watkinson et al. (1993) is shown in Fig. 3.

There is good agreement between the predicted and measured values with the largest discrepancy occurring at the higher values of pH where ionisation is at its highest. The predicted values overestimate the measured ones.

The maximum steady state flux at each of the pHs is obtained by multiplying the permeability coefficient by the solubility. The results are shown graphically in Fig. 4.

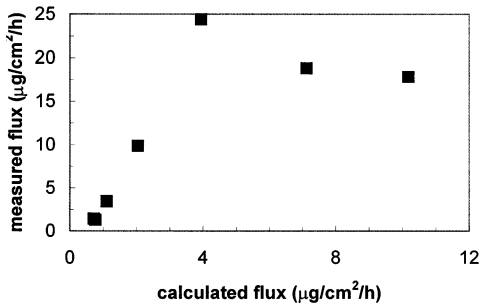

Fig. 4. The relationship between the calculated and measured flux of ibuprofen through human skin from saturated solutions at various pHs. The pH values range from 2.2 on the left-hand side of the figure to 9.2 at the right-hand side.

A number of comments can be made about Fig. 4. It is interesting that the calculation, purely from predicted values using the ACD software gives fluxes that are of the same order of magnitude as the experimental ones. The maximum flux that can be achieved is at the higher pH values. This suggests that lower permeability of the ionized species is more than compensated for by the increased solubility.

4. Lignocaine

Similar analyses can be made for basic permeants such as lignocaine. Valenta et al. (2000) give the log D values at pH 4.0; 6.0; 6.8; 7.0 and 8.0

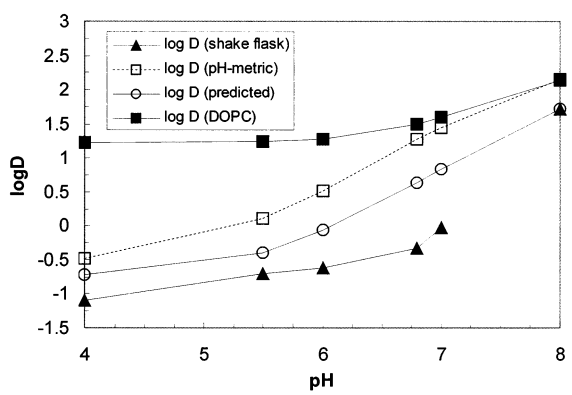

Fig. 5. The variation, for lignocaine, in log D for octanol water both measured and predicted and for DOPC (measured) with pH.

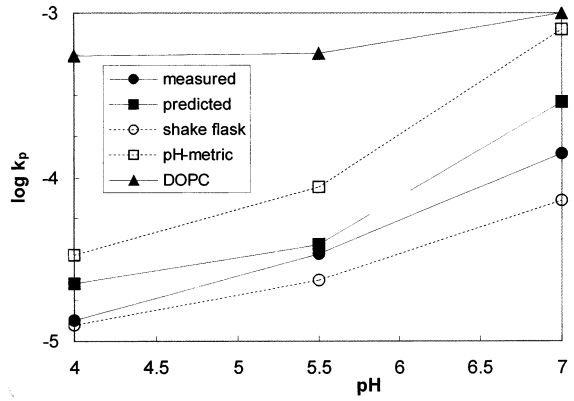

Fig. 6. The relationship between the measured k_p and those calculated using Eq. (3) and the various log D values (predicted using ACD software, measured (shake flask and pH-metric)) and log D measured for DOPC.

using the shake flask method. Avdeef et al. (1998) give similar values measured using a pH metric procedure; they also give values for the DOPC system. Values were also estimated using the ACD software. The calculated pK_a for lignocaine is 8.53 which can be compared to a measured value of 7.96 (Avdeef et al., 1998). The variation in log D with pH is shown in Fig. 5.

The predicted log D values lie between those that have been measured. The difference in the measured values may be a result of the difficulties involved in the shake flask determinations and variations in the ionic strengths and components of the buffers used. The degree of ion pairing and hence partition will be very sensitive to these parameters. There is good correlation between the result for the value at high pH where there is a higher fraction of the unionized species. It is recognized that distribution of the ionized fraction is considerably less than the unionized and it is impressive that the agreement is good. At low pH, where the fraction of lignocaine ionized is highest, there is a significant difference between DOPC and octanol. This is similar behaviour to that observed in the case of ibuprofen.

The log D values were used to estimate the permeabilities at the three pH values used in human skin diffusion studies (Valenta et al., 2000). The results are provided in Fig. 6.

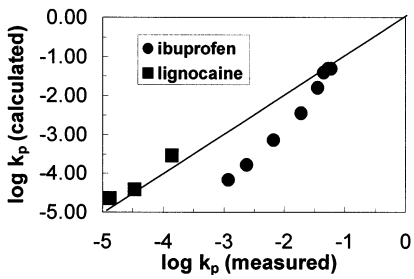

Fig. 7. The relationship between the estimated permeabilities (calculated using ACD software) and those measured experimentally. The graph also shows the line of equality.

Apart from the DOPC estimates, the other values correspond rather well with the values obtained experimentally which again demonstrates the utility of the approach and the usefulness of Eq. (3) despite the fact that it was developed using data from unionized species.

5. Conclusions

Ionized organics can penetrate the stratum corneum and their permeability can be modelled with equations similar to that given by Potts and Guy (1992). The ability to model the permeation using this equation suggests there is no specific aqueous pathway through which the organic cations and anions transfer. It is possible that there is an ion pairing mechanism as proposed in previous publications (Hadgraft et al., 1985, 1986; Green and Hadgraft, 1987). The partition characteristics of these charged permeants in the lipids of the stratum corneum can be approximated using octanol as the solvent. It is possible that other solvent systems may be more appropriate. Despite the structured bilayers found in DOPC, which have similarities to the ceramides, found in the intercellular channels, DOPC does not appear to be a good model.

The estimated permeabilities, as determined ab initio using the ACD software are shown together with the experimental values for both ibuprofen and lignocaine in Fig. 7.

The values for the calculated permeabilities of lignocaine are very close to those measured and there is almost a 1:1 relationship (however, only three experimental points are available). For the anionic ibuprofen, the experimental values are underestimated, the deviation being more marked the greater the degree of ionisation.

It is difficult to explain the precise reasons for this and whether or not it is a general phenomenon found for both anionic and cationic species. One of the problems with skin permeability measurements is the inherent variability between samples, although, for a given permeant, the data presented in Fig. 7 appear to be self-consistent. It is always difficult estimating the role of ion pairing in the skin with the possibility existing that this process may involve endogenous counter ions. Further experiments on a wider range of ionized permeants should answer these questions.

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