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Aspects of the transdermal delivery of prostaglandins II

A.C. Watkinson [a], A.L. Bunge [b] and J. Hadgraft [a]

[a] *Welsh School of Pharmacy, University of Wales, PO Box 13, Cardiff CF1 3XF (UK) and*
[b] *Colorado School of Mines, Chemical Engineering and Petroleum Refining Department, Golden, CO 80401 (USA)*

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Summary

Two distinct and detailed mechanistic arguments are presented to explain the differing transdermal absorption rates of two types of prostaglandins (the 1- and 2-series). These arguments focus on two areas of basic skin research: (i) the effects of penetrant-skin interactions on rates of permeation; and (ii) the effects of the solubility characteristics of the penetrant *as well as* the partitioning behaviour on relative rates of percutaneous absorption.

Introduction

The prostaglandins are a large and much studied group of compounds whose medicinal potential might be enhanced by delivering them transdermally. The percutaneous route avoids first-pass metabolic transformations that are responsible for the rapid inactivation of orally delivered prostanoids and allows therapy to be terminated quickly where necessary.

Previously published data (Watkinson et al., 1991) have shown that the prostaglandins E_2 and $F_{2\alpha}$ were much more readily absorbed by human skin than E_1 and $F_{1\alpha}$. This difference between the 1- and 2-series behaviour was tentatively explained in terms of differing interactions between the penetrants and the constituent molecules of the stratum corneum (sc). It was proposed that the 2-series compounds might interact with lipid molecular packing in the sc channels in such a manner as to facilitate their own passage through them. These suggestions were based on results that indicated the 2-series compounds disrupted the packing of structured lipids in model monolayers and bilayers to a much greater extent than those of the 1-series.

The results presented here consider an interfacial kinetic transfer model which has general relevance to the interpretation of skin penetration mechanisms. Additionally, the flux ratios of the 1- and 2-series prostaglandins are considered using thermodynamic principles and may be related to their relative stratum corneum solubilities.

Correspondence: J. Hadgraft, Welsh School of Pharmacy, University of Wales, PO Box 13, Cardiff CF1 3XF, U.K.

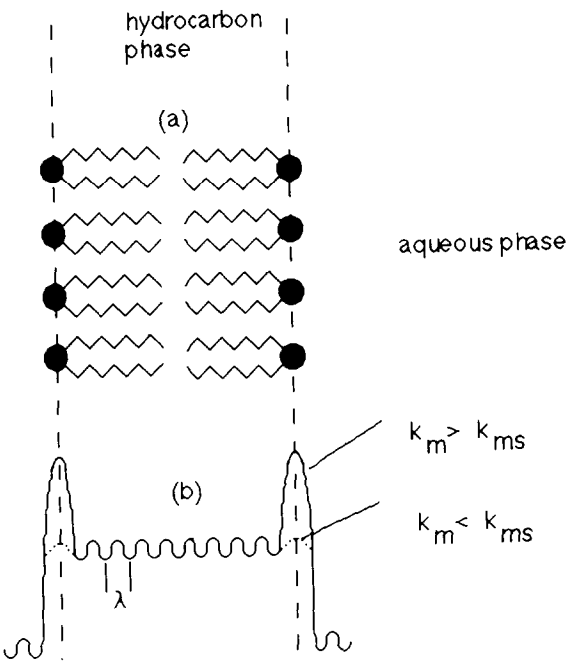

Fig. 1. (a) A schematic representation of membrane interfaces and the phases involved in solute transfer; (b) possible potential energy profile for a solute molecule diffusing through a membrane.

Theoretical and Discussion

Application of absolute reaction rate theory in describing the diffusional process and locating a permeability barrier

Fick's laws of diffusion view permeation as a rate process that contains two contributions from both an equilibrium and a nonequilibrium step, however, the assumption that is made, of instantaneous partitioning of a solute, is not always valid and a treatment based on Eyring's absolute reaction rate theory attempts to account for this (Zwolinsky et al., 1949).

If the flow of molecules through a membrane is viewed as a series of successive molecular jumps of length λ from one energy minimum to another, the whole diffusion process can be seen in terms of an energy profile (Fig. 1). Thus, a third factor is introduced into the mathematical approach to diffusion, i.e., the activation energy required, ΔG_a that prevents spontaneous partitioning from occurring. If C_i is the concentration (molecules per ml) at the i-th position in the membrane, then the amount of material in 1 cm^2 cross-section and length λ_i (the distance between equilibrium maxima) is $C_i\lambda_i$ and the velocity of forward diffusion is:

$$V_f = k_i C_i \lambda_i \tag{1}$$

where k_i represents the rate constant for crossing barrier i. Similarly, the rate of backward diffusion over the barrier i will be:

$$V_b = k'_{i+1} C_{i+1} \lambda_{i+1} \tag{2}$$

If it is assumed that $k_i = k'_{i+1} = k$ and $\lambda_i = \lambda_{i+1} = \lambda$, then the net rate of diffusion, or flux, is expressed as:

$$J = k_i C_i \lambda_i - k'_{i+1} C_{i+1} \lambda_{i+1} \tag{3}$$

$$J = k\lambda(C_i - C_{i+1}) = -k\lambda^2(C_{i+1} - C_i)/\lambda$$

$$J = -k\lambda^2 \, dC/dx \tag{4}$$

where the diffusion coefficient, $D = k\lambda^2$.

The diffusional process can be viewed as five resistances in series, two at the interfaces, one in the membrane, and two due to the bulk solvent phase on either side of the membrane. If it is now assumed that diffusion in the bulk solvent phase is much faster than in the membrane phase or at the interfaces and that the energy barriers within the membrane are the same height as are those on either side of it (Lakshminarayanaiah, 1969),

$$P = \lambda k_{sm} k_m / (2k_m + mk_{ms}) \tag{5}$$

where λ denotes the mean jump distance, m is the number of jumps in the membrane and k_{sm}, k_{ms} and k_m represent the rate constants of adsorption and desorption at interfaces and diffusion in the membrane, respectively. However, the ratio k_{sm}/k_{ms} can be defined as the partition coefficient, K, and since $m\lambda = \Delta x$, the membrane thickness, and $D = k\lambda^2$, then:

$$1/P = 2\lambda/D_{sm} + \Delta x/D_m K \tag{6}$$

If diffusion in the membrane is the rate-limiting step ($k_m \ll k_{ms}$), then:

$$P = D_m K/\Delta x \quad (7)$$

(i.e., the same equation as produced by Fick's first law) and if the slowest step is diffusion through the interface, then $k_m \gg k_{ms}$ and:

$$P = D_{sm}/2\lambda \quad (8)$$

i.e., the permeability constant will be independent of the partition coefficient and the membrane thickness. If this is the case the rate of diffusion will be controlled by the nature of the interface. The thermodynamics of transfer can be examined since

$$k_{sm} = (kT/h) \cdot e^{-\Delta G_{sm}/RT} \quad (9)$$

Therefore:

$$P = (\lambda kT/2h) \cdot e^{-\Delta G_{sm}/RT} \quad (10)$$

where ΔG_{sm} is the free energy of activation necessary for crossing the interface. This will be dependent on the physicochemical relationship between penetrant and barrier. Thus, a compound that interacts in a such a way as to reduce the value of ΔG_{sm} will increase the rate of permeation, i.e., act as a penetration enhancer. Where the membrane is rate limiting, ΔG_m becomes rate determining, and the creation of free volumes within the acyl chain region by an enhancer may reduce its value.

If it is assumed that the differences in penetration rates of the 1- and 2-series of prostaglandins are due solely to a difference in interaction of the two series with the structured lipids, it is possible to examine different contributions by the use of absolute reaction rate theory, i.e., Eqns 7 and 8.

If the membrane were the rate-determining medium (Eqn 7), one would expect an increase in permeability, P with increasing partition coefficient, K. The opposite is the case with the prostaglandins studied, i.e., in terms of rate $F_{2\alpha} \sim E_2 \gg F_{1\alpha} \sim E_1$ but in terms of partition coefficients (Table 1) $E_1 > F_{1\alpha} > E_2 > F_{2\alpha}$; this seems to indicate that permeability is independent of the partition coefficient. Also, because the 1-series are more lipophilic than the 2-series, they will have lower potential activation barriers to diffusion within the membrane (ΔG_m) and therefore greater values of k_m and consequently D_m, leading to an increased permeability. However, the permeability of the 1-series is lower than that of the 2-series, and taking into account the apparent independence of permeability and partition coefficient, it seems improbable that the membrane interior is the rate-determining barrier.

TABLE 1

Physicochemical properties of prostaglandins E_1, E_2, $F_{1\alpha}$ and $F_{2\alpha}$

Prostaglandin	Log P [a] $(oct/wat)_{calc}$	Log P [b] (cy. hex/buffer)	Aqueous [c] solubility (mg/ml)	~ Lipid [d] solubility (mg/ml)
E_1	2.151	0.642	0.0075	0.03
$F_{1\alpha}$	1.799	–	–	–
E_2	1.607	0.576	1.222	4.6
$F_{2\alpha}$	1.255	0.435	1.478	4.02

[a] Calculated using the Hansch group contribution method with Medchem software (version 3.54, January 1989, Daylight Chemical Information Systems Inc.).
[b] From Uekama et al. (1978).
[c] From Stehle (1982).
[d] Calculated from the cyclohexane/buffer partition coefficient and the aqueous solubility.

If the interface were the rate-limiting barrier (Eqn 8), then an increase in permeability would be expected with an increase in D_{sm} (an increase in D_{sm} implying a decrease in ΔG_{sm}). This seems to be the case as the 2-series compounds will have lower ΔG_{sm} values than those of the 1-series due to their higher hydrophilicity.

It is possible that the main barrier to the percutaneous penetration of prostaglandins may reside in the interfacial regions of the lipid bilayers within the stratum corneum and that the 2-series prostaglandins may interact with polar head-groups in this region in such a way as to enhance their own permeation by decreasing the activation energy barrier that exists here.

Application of regular solution theory as an explanation for the differing rates of penetration of the 1- and 2-series prostaglandins

If it is assumed that the difference in the penetration rates is solely due to differences in skin solubility, the ratio of the fluxes may be approximated to the ratio of the stratum corneum drug solubilities. The solubility of a compound in a given solvent can be described by basic molecular thermodynamics of fluid phase equilibrium. That is, at its solubility limit, the solute's activity in the solvent must equal the activity of the pure solute. Using regular solution theory (Scatchard-Hildebrand) the following equations can be used to produce an expression (involving melting point, temperature and solubility parameter of both solute and solvent) for the solubility of a solid solute 2 in a liquid solvent 1 (Prausnitz, 1969):

$$x_2 = f_{2(\text{pure solid})}/\gamma_2 f_{2,0} \tag{11}$$

$$\ln\left[f_{2,0}/f_{2(\text{pure solid})}\right] = \Delta H^{\text{f}} \cdot \left[(T_{\text{m}} - T)/T\right]/RT_{\text{m}} \tag{12}$$

$$\ln \gamma_2 = \left[\nu_{2,\text{L}} \cdot (\delta_1 - \delta_2)^2 \cdot \Phi_1^2\right]/RT \tag{13}$$

where x_2 is the solubility (mole fraction) of the solute in the solvent, γ_2 the liquid phase activity coefficient of the solute in the solvent, $f_{2,0}$ the standard state fugacity to which γ_2 refers, ΔH^{f} the enthalpy of fusion of solute at its melting temperature, T_{m} the melting point temperature, T the solution temperature, R the gas constant, $\nu_{2,\text{L}}$ the molar volume of the subcooled liquid solute, δ_1 and δ_2 are the solubility parameters of the solvent and solute, respectively, and $\Phi_1 = x_1\nu_1/[x_1\nu_1 + x_2\nu_2]$, the molar volume fraction of the solvent. Substitution of Eqns 12 and 13 into Eqn 11 yields:

$$\ln x_2 = -\Delta H_2^{\text{f}} \cdot ((T_{\text{m}} - T)/T_{\text{m}})/RT_{\text{m}} + \nu_2\Phi_1^2(\delta_1 - \delta_2)^2/RT \tag{14}$$

If the skin, or stratum corneum, is now taken as the solvent and designated m (membrane) and the prostaglandin as the solute and designated p, then, assuming that the ratio of the solubilities is approximately equal to the ratio of the fluxes, we obtain (for two prostaglandins a and b):

$$\ln J_{\text{a}} - \ln J_{\text{b}} = \left\{\Delta H_{\text{a}}^{\text{f}}((T_{\text{m,a}} - T)/T)/RT_{\text{m,a}} + \nu_{\text{a}}\Phi_{\text{m}}^2(\delta_{\text{m}} - \delta_{\text{a}})^2/RT\right\} - \left\{\Delta H_{\text{b}}^{\text{f}}((T_{\text{m,b}} - T)/T)/RT_{\text{m,b}} + \nu_{\text{b}}\Phi_{\text{m}}^2(\delta_{\text{m}} - \delta_{\text{b}})^2/RT\right\} \tag{15}$$

The solubility parameters of the prostaglandins studied have been calculated using the method of group contributions (Fedors, 1974) where the expression becomes:

$$\delta = \left[\left(\sum_i \Delta e_i\right)/\left(\sum_i \Delta v_i\right)\right]^{0.5} \tag{16}$$

The incremental group contributions, Δe_i and Δv_i, are listed in the reference quoted. The values found are listed in Table 2 together with the compounds' melting points (in K). It is interesting to note the similarity between the solubility parameters within the 1- and 2-series (reflected in the partition coefficients listed in Table 1) but that the melting points are quite different.

In calculating the flux ratios of E_2/E_1 and $F_{2\alpha}/F_{1\alpha}$, it is possible to simplify Eqn 15 because of the almost identical solubility parameters of E_2 and E_1 and $F_{1\alpha}$ and $F_{2\alpha}$, i.e., the terms involving solubility parameters disappear from the equation to give Eqn 17 where the ratio is dependent

TABLE 2

Prostaglandin solubility parameters and melting points

Prostaglandin	δ	T_{m} (K)
E_1	12.03	388
E_2	12.09	340
$F_{1\alpha}$	12.57	374
$F_{2\alpha}$	12.63	303

only on the differences in melting points of the two species:

$$\ln J_a - \ln J_b = \{\Delta H_a^f((T_{m,a} - T)/T)/RT_{m,a}\} - \{\Delta H_b^f((T_{m,b} - T)/T)/RT_{m,b}\} \quad (17)$$

The value of ΔH^f for E_2 is approx. 29288 J mol^{-1} (Stehle, 1982) and the $\Delta H^f/T_m$ for E_2 of 86.1 J mol^{-1} K^{-1} has been assumed for all the prostaglandins. With $R = 8.314$ J mol^{-1} K^{-1} the following flux ratios (arising simply from differences in melting points) for the unenhanced penetration of the prostaglandins studied can be calculated and compared to the experimental results (these are ratios of drug penetrated at 48 h rather than absolute flux values).

Ratio	Calculated	Experimental
E_2/E_1	5.0	4.9 ± 1.9
$F_{2\alpha}/F_{1\alpha}$	10.7	22.8 ± 8.9
2-series/1-series [a]	7.3	8.3 ± 2.5

[a] The 2/1-series comparisons were calculated by averaging melting points.

The correlation between the calculated and experimental values is good, indicating that it is reasonable to say that solubility differences could explain the difference in the penetration rates of the prostaglandins. The experimental value for $F_{2\alpha}/F_{1\alpha}$ is probably artificially high due to the very low amount of $F_{1\alpha}$ penetrating being extremely hard to detect, i.e., zero figures at 48 h bring down the average markedly.

Conclusions

Of the two theories presented here, the second does seem the more likely to have a dominant effect in creating differing absorption rates but it is possible that some interaction between the stratum corneum lipids and the 2-series prostaglandins may contribute towards their more efficient transdermal absorption. The work presented here indicates that more thought should be given to the two topics discussed (possible skin-penetrant interactions and solubility calculations) when considering the percutaneous absorption of drugs.

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