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A theoretical description of the effects of volatility and substantivity on percutaneous absorption

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Summary

Substances applied to the skin may be removed from the skin surface by evaporation, washing or simple physical abrasion. These losses may be simulated by assuming that they are zero- or first-order processes. In this paper we present theoretical equations to describe the distribution of drugs within the skin allowing for concomitant loss from the surface. The solutions to the diffusion equations show the relative contributions of the loss processes to the overall fate of the applied drug.

Introduction

When any substance is applied to the surface of the skin, it is subject to many removal processes. In general, calculations in the past have assumed that all the drug applied to the skin is available for penetration. In an ideal state this would be true. However, in reality, the skin is exposed to the atmosphere and thus volatile materials will evaporate from the formulation. This may be at a rate comparable to percutaneous penetration (Reifenrath and Robinson, 1982). The problem will be particularly acute for those compounds which have a high vapour pressure, e.g insect repellents and those liable to be removed by washing, e.g. sun-screen agents. In addition all topically applied formulations will be subject to physical abrasion which will lower the applied dose.

In our previous publications (e.g. Hadgraft, 1979; Guy and Hadgraft, 1980 and 1982) we have not accounted for the loss of penetrant from the skin surface by any

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means other than the passive diffusion through the stratum corneum. In this publication we address this problem and, for modelling purposes, assume that the surface loss may be considered as being either zero- or first-order with simultaneous diffusion through the skin.

Theory

The model

We have previously presented an idealized model of the skin which has been successful in describing the complex diffusion equations required to interpret percutaneous absorption and diffusion through the topical base (Guy and Hadgraft, 1980). A schematic representation of this model is given in Fig. 1.

In order to assess the effect of surface loss it is convenient to calculate the amount of drug that resides at the outer layers of the stratum corneum at time t.

This problem is solved by considering the differential equations which describe transport in the topical base and in the epidermis. The solutions to these equations are made easier by the use of the following normalised variables.

$$u = c/c_\infty \tag{1}$$

$$\lambda = D_s l_v / D_v l_s \tag{2}$$

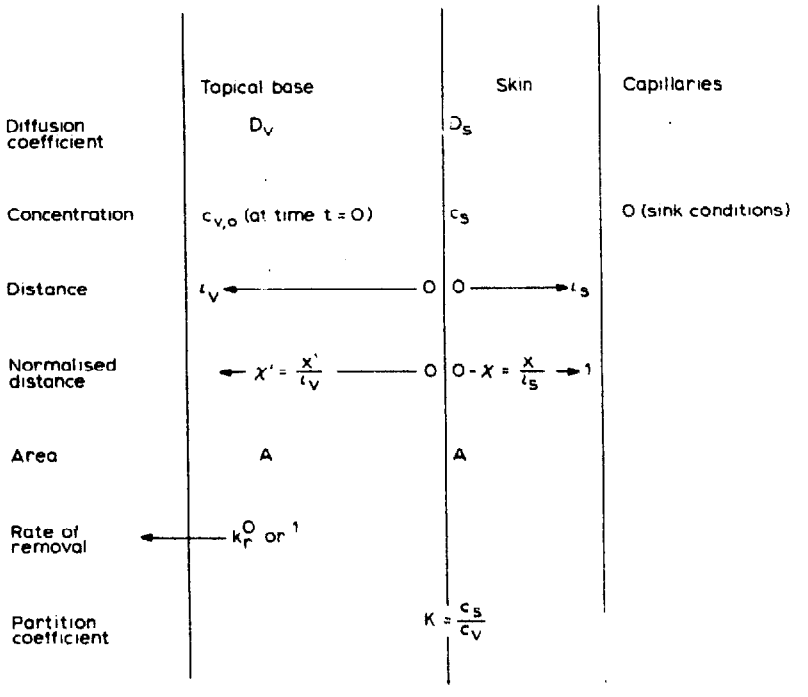

Fig. 1. Schematic representation of the mathematical model.

$$p = D_v l_s^2 / D_s l_v^2 \tag{3}$$

$$\tau = D_s t / l_s^2 \tag{4}$$

Assuming that the diffusion processes may be expressed in terms of Fick's second law of diffusion we can write differential equations to describe transport in the base

$$\frac{\partial u_v}{\partial \tau} = p \cdot \frac{\partial^2 u_v}{\partial \chi'^2} \tag{5}$$

and in the skin

$$\frac{\partial u_s}{\partial \tau} = \frac{\partial^2 u_s}{\partial \chi^2} \tag{6}$$

At the interface between the formulation and the skin

$$\left(\frac{\partial u_v}{\partial \chi'}\right)_0 = -\lambda \left(\frac{\partial u_s}{\partial \chi}\right)_0 \tag{7}$$

To calculate the concentration at the skin–base junction it is necessary to solve Eqns. 5 and 6 with the following boundary conditions.

(a) For zero-order loss from the formulation surface

$$\chi' = 1, \quad (\partial u_v / \partial \chi')_1 = -\kappa p^{-1} \tag{8}$$

where

$$\kappa = k_r^0 l_s^2 / D_s c_{v,0}$$

(b) For first-order loss from the formulation surface

$$\chi' = 1, \quad (\partial u_v / \partial \chi')_1 = -\omega u_{v,1} / p \tag{9}$$

where

$$\omega = k_r^1 l_s^2 / D_s$$

and

$$\tau = 0, \quad u = 1, \quad u_s = 0 \tag{10}$$

Eqns. 8 and 9 represent, respectively, the rate of removal by a zero-order process k_r^0 and a first-order process k_r^1. Condition 10 shows the substrate disposition in the two regions at time $t = 0$.

Zero-order loss

Solution of the differential equation is achieved using the technique of Laplace transformation. Eqn. 5 transforms to

$$s\bar{u}_v - 1 = p \cdot \frac{\partial^2 \bar{u}_v}{\partial \chi'^2} \tag{11}$$

which has a general solution

$$\bar{u}_v = A \cosh(s^{1/2}p^{-1/2}\chi') + B \sinh(s^{1/2}p^{-1/2}\chi') + s^{-1} \tag{12}$$

The coefficients A and B may be eliminated using the transformed boundary condition 8

$$\left(\frac{\partial \bar{u}_v}{\partial \chi'}\right)_1 = \frac{-\kappa}{ps} \tag{13}$$

This yields

$$\frac{-\kappa}{ps} = (\bar{u}_{v,0} - s^{-1})s^{1/2}p^{-1/2} \sinh(s^{1/2}p^{-1/2}) + \left(\frac{\partial \bar{u}_v}{\partial \chi'}\right)_0 \cosh(s^{1/2}p^{-1/2}) \tag{14}$$

Turning to diffusion within the skin, the general solution to Eqn. 6 is:

$$\bar{u}_s = A' \cosh(s^{1/2}\chi) + B' \sinh(s^{1/2}\chi) \tag{15}$$

Using the condition

$$u_{s,1} = 0$$

i.e. there are sink conditions imposed by the removal of drug by the capillaries, the coefficients A′ and B′ may be eliminated to give

$$\bar{u}_{s,0} = -s^{-1/2} \tanh s^{1/2}\left(\frac{\partial \bar{u}_s}{\partial \chi}\right)_0 \tag{16}$$

Eqns. 14 and 16 may now be combined using the relationship in Eqn. 7 and the partition coefficient of the drug between the skin and the formulation

$$K = u_{s,0}/u_{v,0}$$

By simple algebraic manipulation it may be shown that

$$\bar{u}_{s,0} = \frac{s^{1/2}p^{-1/2} \sinh(s^{1/2}p^{-1/2}) - \kappa p^{-1}}{s[s^{1/2}p^{-1/2}K^{-1} \sinh(s^{1/2}p^{-1/2}) + \lambda s^{1/2} \coth s^{1/2} \cosh(s^{1/2}p^{-1/2})]} \tag{17}$$

In order to simplify the inverse transformation of this equation we use a short time approximation.

Short time

For small values of τ ($\tau = 0.1$ corresponds to 17 h with the diffusion parameters used) the hyperbolic terms in Eqn. 17 may be simplified as follows:

$$\begin{aligned}
\sinh(s^{1/2}p^{-1/2}) &\rightarrow \tfrac{1}{2}\exp(s^{1/2}p^{-1/2}) \\
\coth s^{1/2} &\rightarrow 1 \\
\cosh(s^{1/2}p^{-1/2}) &\rightarrow \tfrac{1}{2}\exp(s^{1/2}p^{-1/2})
\end{aligned}$$

This provides the following expression for u

$$u_{s,0} = \mathscr{L}^{-1}\left[s(K^{-1} + \lambda p^{1/2})\right]^{-1} - \mathscr{L}^{-1}\frac{2\kappa \exp(-s^{1/2}p^{-1/2})}{s^{3/2}p^{1/2}(K^{-1} + \lambda p^{1/2})} \tag{18}$$

The inverse of this equation may be found (Oberhettinger and Badii)

$$u_{s,0} = \frac{1}{(K^{-1} + \lambda p^{1/2})}\left[1 - \frac{2\kappa}{p^{1/2}}\left\{\frac{2\tau^{1/2}}{\pi^{1/2}}\exp - \left(\frac{1}{4p\tau}\right) - \frac{1}{p^{1/2}}\operatorname{erfc}\left(\frac{1}{2p^{1/2}\tau^{1/2}}\right)\right\}\right] \tag{19}$$

First-order loss

For this situation the coefficients in Eqn. 12 are eliminated using the transformed boundary condition 9

$$\chi' = 1, \quad (\partial \bar{u}_v/\partial \chi')_1 = -\omega \bar{u}_{v,1}/p \tag{20}$$

to give

$$\begin{aligned}
&(\bar{u}_{v,0} - 1/s)\left[s^{1/2}p^{-1/2}\sinh(s^{1/2}p^{-1/2}) + \omega p^{-1}\cosh(s^{1/2}p^{-1/2})\right] \\
&+\left(\frac{\partial \bar{u}_v}{\partial \chi'}\right)_0\left[\cosh(s^{1/2}p^{-1/2}) + \omega p^{-1/2}s^{-1/2}\sinh(s^{1/2}p^{-1/2})\right] = -\omega p^{-1}s^{-1}.
\end{aligned} \tag{21}$$

Using Eqns. 7, 16 and the partition coefficient as before, an expression for $\bar{u}'_{s,0}$ is obtained.

$$\begin{aligned}
\bar{u}'_{s,0} = &\left[s^{1/2}p^{-1/2}\sinh(s^{1/2}p^{-1/2}) + \omega p^{-1}\cosh(s^{1/2}p^{-1/2}) - \omega p^{-1}\right] \\
&\times \left\{s\left[K^{-1}\left\{s^{1/2}p^{-1/2}\sinh(s^{1/2}p^{-1/2}) + \omega p^{-1}\cosh(s^{1/2}p^{-1/2})\right\}\right.\right. \\
&\left.\left.+\lambda s^{1/2}\coth s^{1/2}\left[\cosh(s^{1/2}p^{-1/2}) + \omega p^{-1/2}s^{-1/2}\sinh(s^{1/2}p^{-1/2})\right]\right]\right\}^{-1}
\end{aligned} \tag{22}$$

The similarities in form between Eqns. 17 and 22 should be immediately apparent. However, in the latter case there are two terms in the numerator describing the effect of surface loss. Again, only considering the solution at small τ values, it is possible to simplify Eqn. 22.

$$\bar{u}'_{s,0} = \frac{1}{K^{-1} + \lambda p^{1/2}} \left[\frac{\omega}{p^{1/2} s(s^{1/2} + \omega p^{-1/2})} - \frac{2\omega \exp(-s^{1/2} p^{-1/2})}{p^{1/2} s(s^{1/2} + \omega p^{-1/2})} + \frac{1}{s^{1/2}(s^{1/2} + \omega p^{-1/2})} \right] \tag{23}$$

which may be inverted (Oberhettinger and Badii):

$$u'_{s,0} = \frac{1}{(K^{-1} + \lambda p^{1/2})} \left\{ 1 - 2\,\mathrm{erfc}\left(\frac{1}{2p^{1/2}\tau^{1/2}} \right) + 2 \exp\left(\frac{\omega^2 \tau}{p} + \frac{\omega}{p} \right) \mathrm{erfc}\left(\frac{1}{2p^{1/2}\tau^{1/2}} + \frac{\omega \tau^{1/2}}{p^{1/2}} \right) \right\} \tag{24}$$

It is possible to simplify further Eqns. 19 and 24 by making the approximations that for small values of z

$$\mathrm{erfc}(Z) \rightarrow 1 - 2\pi^{-1/2} Z$$

$$\exp(Z) \rightarrow 1 + Z$$

Using these two approximations, Eqns. 19 and 24 become, respectively:

$$u_{s,0} = \frac{1}{(K^{-1} + \lambda p^{1/2})} \left\{ 1 + \frac{2\kappa}{p} - \frac{2\kappa}{\pi^{1/2} p^{3/2} \tau^{1/2}} - \frac{4\kappa \tau^{1/2}}{\pi^{1/2} p^{1/2}} \right\}$$

$$u'_{s,0} = \frac{1}{(K^{-1} + \lambda p^{1/2})} \left\{ 1 + \frac{2\omega}{p} + \frac{2\omega^2 \tau}{p} - \frac{4\pi\tau^{1/2}}{\pi^{1/2} p^{1/2}} + \frac{6\omega^2 \tau^{1/2}}{\pi^{1/2} p^{3/2}} - \frac{4\omega^3 \tau^{3/2}}{\pi^{1/2} p^{3/2}} \right\}$$

Discussion

Eqns. 19 and 24 describe the concentration of topical agent at the outer stratum corneum surface as a function of time for situations where both zero-order loss and first-order loss from the skin is occurring at the same time as diffusion through the skin. For these two cases it is instructive to show how the concentration varies with

TABLE 1

VALUES FOR THE DIFFERENT PARAMETERS USED TO CALCULATE THE CONCENTRATION PROFILES

Parameters	Value
$c_0/g \cdot dm^{-3}$	1
K	variable (1 → 100)
$D_v/m^2 s^{-2}$	10^{-10}
$D_s/m^2 s^{-1}$	10^{-15}
$l_v/\mu m$	25
$l_s/\mu m$	25
$k_r^0/g \cdot dm^{-3} \cdot s^{-1}$	variable ($1.6 \times 10^{-5} \rightarrow 4 \times 10^{-4}$)
k_r^1/s^{-1}	variable ($1.6 \times 10^{-5} \rightarrow 4 \times 10^{-5}$)

assigned rate constants and partition coefficients that would be experienced in practice. The rate constants and parameters used are shown in Table 1. The rate constants for the zero- and first-order loss have been estimated from the work of Reifenrath et al. (1982) who investigated the evaporation behaviour of insect repellents (e.g. N,N-diethyl-*p*-toluamide, 1-(butylsulphonyl)hexahydro-1H-azepine, N,N'-dicyclohexamethyleneurea, 2-ethyl-1,3-hexanediol and N,N-diethyl-*m*-toluamide). The other parameters are those that have been described previously as being typical for assessing percutaneous penetration (Guy and Hadgraft, 1980).

Figs. 2 and 3 show the concentration of substrate at the skin surface for a system where there is zero-order loss. Fig. 1 shows the loss of material for a substance having a partition coefficient of 1 between the skin and the vehicle. For $\kappa = 10$ the rate of evaporation is slow and the slight decrease shown is a combination of both diffusion through the stratum corneum and loss form the surface. At higher values of κ the surface loss process becomes dominant. At $\kappa = 50$ about 50% of the material has been lost in 9 h which is similar to the value quoted by Reifenrath and Robinson (1982). At higher partitioning (Fig. 3) similar trends are shown but the initial rate of loss is very much faster.

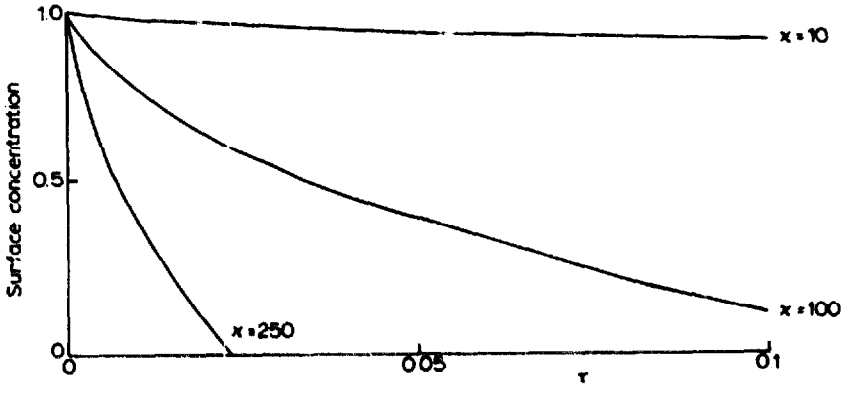

Fig. 2. Skin surface concentration as a function of time for zero-order loss and a skin–vehicle partition coefficient of 1. The effect of the magnitude of the zero-order rate constant is shown.

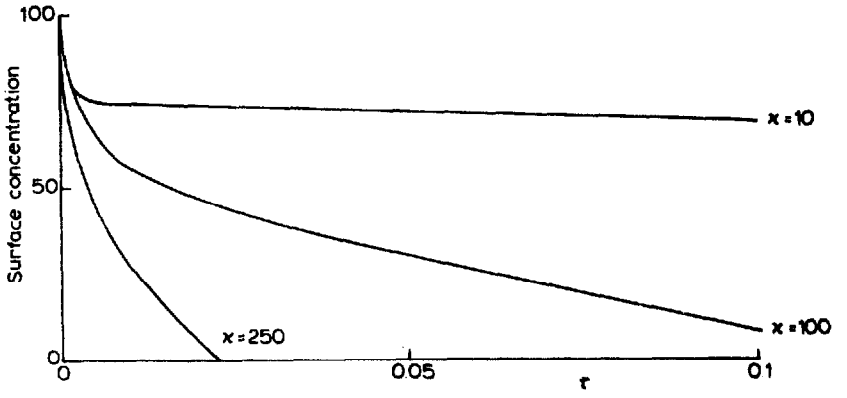

Fig. 3. Skin surface concentration as a function of time for zero-order loss and a skin–vehicle partition coefficient of 100. The effect of the magnitude of the zero-order rate constant is shown.

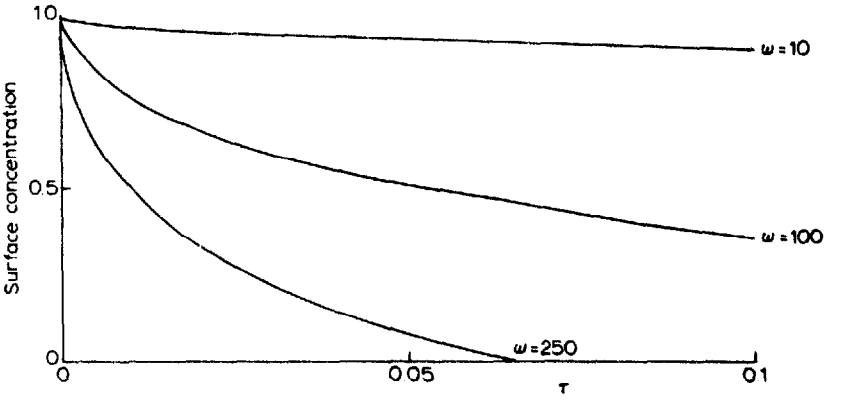

Fig. 4. Skin surface concentration as a function of time for first-order loss and a skin–vehicle partition coefficient of 1. The effect of the magnitude of the first-order rate constant is shown.

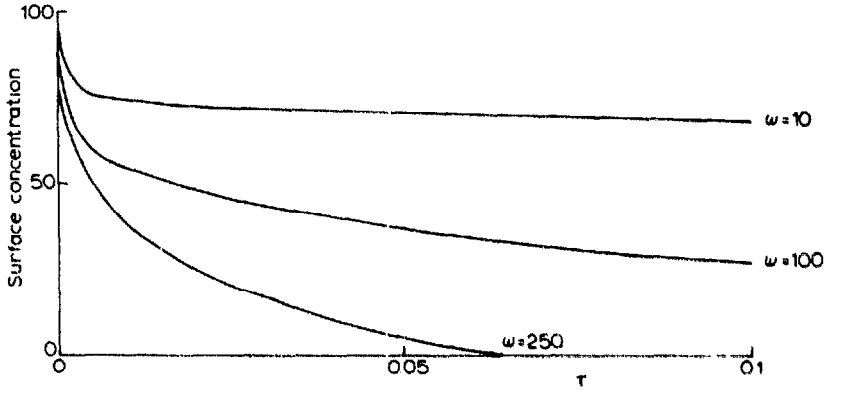

Fig. 5. Skin surface concentration as a function of time for first-order loss and a skin–vehicle partition coefficient of 100. The effect of the magnitude of the first-order rate constant is shown.

Figs. 4 and 5 show similar curves but for the case of first-order loss, and as expected have the same form as Figs. 2 and 3. The most noticeable difference is that the loss process is not as severe at longer periods of time. This is consistent with the behaviour of first- and zero-order kinetics. The approximations given by Eqns. 25 and 26 can be used to produce similar curves. However, errors are introduced. For zero-order loss there is almost perfect correlation between Eqns. 19 and 25 using the range conditions given in Table 1. For first-order loss, Eqn. 26 gives a value to within 10% of the correct value for the following conditions:

$\omega = 10, \quad \tau < 0.1$

$\omega = 100, \quad \tau < 0.05$

$\omega = 250, \quad \tau < 0.01$

Thus for most zero-order cases it is possible to use the approximation but caution should be exercised when considering Eqn. 26.

Surface loss subsequent to topical administration is a process which always occurs and one which is often ignored. The equations presented here show how this process may be modelled. This is useful in the design of new formulations and in estimating how much topically applied drug may be lost and thus be unavailable for therapeutic effect.

Acknowledgements

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