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A THEORETICAL DESCRIPTION RELATING SKIN PENETRATION TO THE THICKNESS OF THE APPLIED MEDICAMENT

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SUMMARY

Mathematical expressions have been derived which relate the degree of percutaneous penetration to the thickness of the applied base. The relative importance of simple physicochemical parameters is discussed and theoretical release curves provided to show the way in which optimum dosage regimens may be achieved.

INTRODUCTION

When dermatological preparations are applied topically there will always be some variation in the thickness of the cream or ointment that is used. In some instances reproducible dosage is facilitated by the design of the product. One example is Haelan Tape in which flurandrenolone is evenly distributed on a thin transparent plastic tape (Goldman et al., 1967).

In this paper a mathematical model is developed in order to show the effect of applying different thicknesses of medicament to the skin and how the dosage may be optimized. We treat both the case of the intact skin and also abraded skin where different factors become important. The expression obtained will also be of use in the interpretation of results where thin polymeric films are applied to the epidermis (Iyer and Vasavada, 1979).

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CASE I. APPLICATION TO NORMAL SKIN

In this case we assume that transport in the base and the stratum corneum is relatively slow compared to the transport in the viable epidermis and subsequent removal by the capillaries and lymphatic system. This will produce the condition, which simplifies the mathematical treatment, that there are sink conditions at the junction of the stratum corneum and the viable epidermis. For most compounds this will be a valid approximation but there will be certain limitations in the treatment for drugs such as potent vasoconstrictors where the rate of elimination may be slow.

The concentration profile of the drug after the base has been in contact with the skin for a short period of time is given in Fig. 1. The different physicochemical constants relevant to the transport process are given in Fig. 2.

The total amount of drug that penetrates the stratum corneum at time t is given by

$$M_t = -D_s A \int_0^t \left(\frac{dc_s}{dx}\right)_{x=l_s} dt \tag{1}$$

In order to calculate M_t it is necessary to solve the differential equations that describe the transport of the drug in the ointment and in the stratum corneum. Solution of these equations is facilitated by the use of normalized variables (Hadgraft, 1979). The following variables are defined accordingly:

$$u = c/c_\infty \tag{2}$$

$$\lambda = D_s l_0/D_0 l_s \tag{3}$$

$$p = D_0 l_s^2/D_s l_0^2 \tag{4}$$

$$\tau = D_s t/l_s^2 \tag{5}$$

We assume that diffusion occurs in only one dimension and that the diffusion coefficients

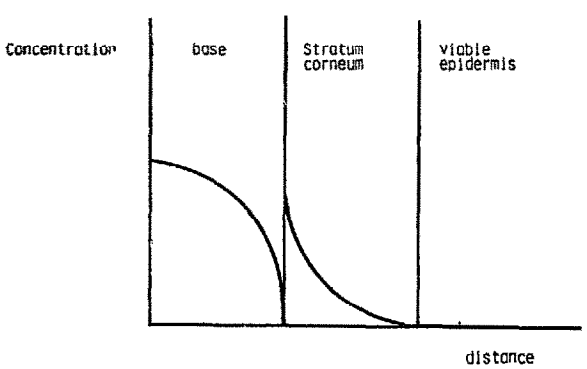


Fig. 1. Concentration profile of drug in base and stratum corneum.

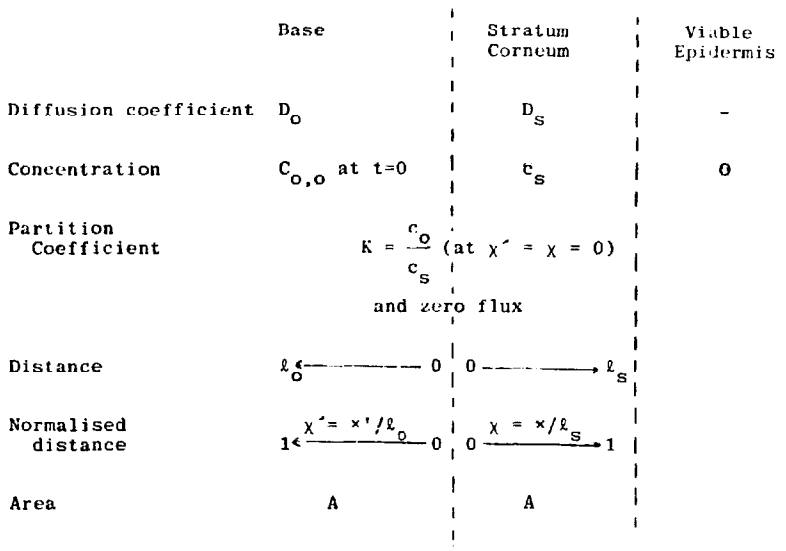


Fig. 2. Schematic representation of the mathematical model.

are concentration independent. We also assume that there exist fast interfacial kinetics at the two interfaces (Albery and Hadgraft, 1979) and that there is no significant variation in area as the drug diffuses from the ointment to the capillary network. It has been shown previously that if there are area variations the form of the equation derived in this type of treatment does not change (Hadgraft, 1979b). Thus the final expression obtained may be easily modified to account for the possibility of an intercellular mechanism.

Using the normalized variables we express the differential equations describing the diffusion process in the two regions as follows. In the base

$$\frac{\partial u_0}{\partial \tau} = p\left(\frac{\partial^2 u_0}{\partial \chi'^2}\right) \tag{6}$$

and in the stratum corneum

$$\frac{\partial u_s}{\partial \tau} = \left(\frac{\partial^2 u_s}{\partial \chi^2}\right) \tag{7}$$

At the boundary between the base and the stratum corneum

$$\left(\frac{\partial u_0}{\partial \chi'}\right)_0 = -\lambda\left(\frac{\partial u_s}{\partial \chi}\right)_0 \tag{8}$$

Eqn. 1 may be written in terms of the normalized parameters

$$M_t = Al_s c_0 \int_0^\tau \left(\frac{\partial u_s}{\partial \chi}\right)_1 d\tau \tag{9}$$

which shows that in order to calculate M_t the concentration gradient at the inner interface must be calculated. In order to obtain this analytically, Eqns. 6 and 7 are solved with the following boundary conditions:

$$\chi' = 1, (\partial u_0/\partial \chi')_1 = 0 \tag{10}$$

$$\tau = 0, u_0 = 1, u_s = 0 \tag{11}$$

Eqn. 10 shows that the base contains only a finite quantity of drug and condition 11 shows its distribution in the two regions at time t = 0.

Laplace transformation is used to simplify solution. In the base, Eqn. 6 transforms to

$$s\bar{u}_0 - 1 = p\left(\frac{\partial^2 \bar{u}_0}{\partial \chi'^2}\right) \tag{12}$$

which has the general solution

$$\bar{u}_0 = A \cosh(s^{1/2}p^{-1/2}\chi') + B \sinh(s^{1/2}p^{-1/2}\chi') + s^{-1} \tag{13}$$

By using condition 10 the coefficients A and B may be eliminated

$$\bar{u}_0 = s^{-1} - p^{1/2}s^{-1/2}\left(\frac{\partial \bar{u}_s}{\partial \chi'}\right)_0 \operatorname{cotanh}(s^{1/2}p^{-1/2}) \tag{14}$$

Since there are fast interfacial kinetics the two concentrations $u_{0,0}$ and $u_{s,0}$ are related by the ointment/skin partition coefficient.

$$K = u_{0,0}/u_{s,0} \tag{15}$$

Using this relationship and Eqn. 8, Eqn. 14 may be rewritten

$$K\,\bar{u}_{s,0} = s^{-1} + \lambda p^{1/2}s^{-1/2}\left(\frac{\partial \bar{u}_s}{\partial \chi}\right)_0 \operatorname{cotanh}(s^{1/2}p^{-1/2}) \tag{16}$$

In the stratum corneum, Laplace transformation of Eqn. 7 produces

$$s\,\bar{u}_s = \left(\frac{\partial^2 \bar{u}_s}{\partial \chi^2}\right) \tag{17}$$

which has a general solution

$$\bar{u}_s = A' \cosh(s^{1/2}\chi) + B' \sinh(s^{1/2}\chi) \tag{18}$$

The coefficients A' and B' are eliminated using straightforward algebraic manipulations of Eqns. 16, 18 and 11 to give

$$\left(\frac{\partial \bar{u}_s}{\partial \chi}\right)_1 = -[s^{1/2} \cosh s^{1/2}\{K \tanh s^{1/2} + \lambda p^{1/2} \operatorname{cotanh}(s^{1/2}p^{-1/2})\}]^{-1} \tag{19}$$

M_t can then be found by substitution into Eqn. 9 producing

$$M_t = AC_0 l_s \mathcal{L}^{-1} [s^{3/2} \cosh s^{1/2} \{K \tanh s^{1/2} + \lambda p^{1/2} \operatorname{cotanh} (s^{1/2} p^{-1/2})\}]^{-1} \quad (20)$$

It is not possible to invert this equation to produce a simple analytic function showing the variation of M_t with time. Different approximations are considered which are correct for the period before steady-state conditions have been established in the stratum corneum ($\tau < 1$) and for the period after ($\tau > 1$). There will be a small interval when $\tau \simeq 1$ where neither approximation is valid.

(i) Short-time approximation when $\tau < 1$, $s > 1$, the hyperbolic expressions in Eqn. 20 may be simplified (Abramowitz and Stegun, 1970) to produce,

$$M_t = 2Al_s c_0 (K + \lambda p^{1/2})^{-1} \mathcal{L}^{-1} s^{-3/2} \exp(-s^{1/2}) \quad (21)$$

Inverting this transformed expression (Abramowitz and Stegun, 1970)

$$M_t = 4Al_s c_0 \tau^{1/2} (K + \lambda p^{1/2})^{-1} \operatorname{ierfc}(1/2\, \tau^{1/2}) \quad (22)$$

A similar expression has previously been derived and a further simplification suggested by approximating the ierfc term (Hadgraft, 1979a):

$$M_t = 8Al_s c_0 (K + \lambda p^{1/2})^{-1} \pi^{-1/2} \tau^{3/2} \exp(-1/4\tau) \quad (23)$$

$Al_0 c_0$ is the total amount of drug present M_∞ which may be incorporated to give

$$M_t = 8\, M_\infty \lambda p (K + \lambda p^{1/2})^{-1} \pi^{-1/2} \tau^{3/2} \exp(-1/4\tau) \quad (24)$$

(ii) Long-time approximation. After steady-state conditions have been established, $\tau > 1$ and $s < 1$. For small values of s, the hyperbolic functions in Eqn. 20 may be simplified (Hadgraft, 1979a) producing

$$M_t = Al_s c_0 \mathcal{L}^{-1} [Ks(s + \lambda p/K)]^{-1} \quad (25)$$

which may be inverted to give

$$M_t = \frac{Al_s c_0}{\lambda p} (1 - \exp(-\lambda p \tau / K)) \quad (26)$$

or

$$M_t = M_\infty (1 - \exp(-\lambda p \tau / K) \quad (27)$$

Eqns. 22 and 24 show that during short time intervals the thickness of the applied medicament has no effect on the rate of penetration. The parameters that are significant

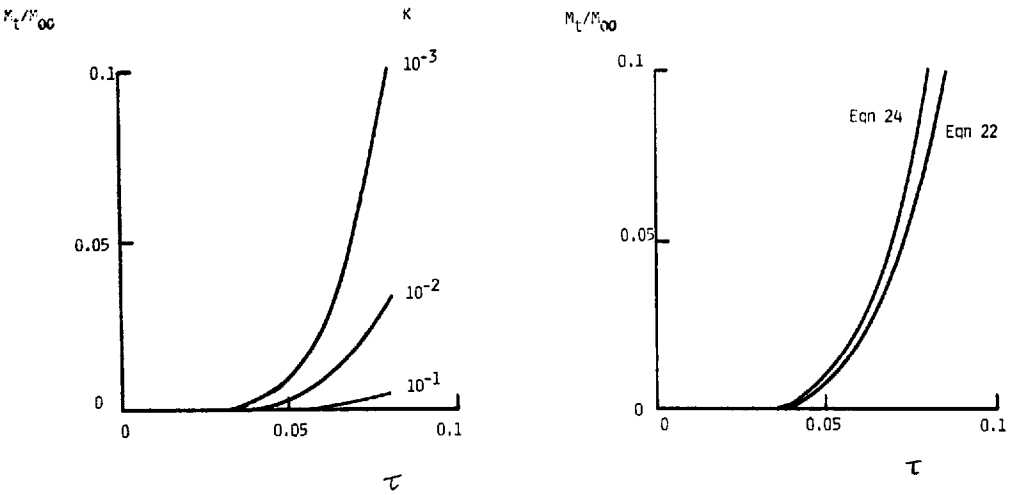


Fig. 3. Release profiles given by Eqn. 24 showing the pattern for short periods of time in non-abraded skin and different K values ($\lambda p^{1/2} = 3.2 \times 10^{-3}$).

Fig. 4. Comparison of Eqns. 22 and 24.

are the partition coefficient K and the ratio of the diffusion coefficients ($D_s^{1/2}/D_0^{1/2} = \lambda p^{1/2}$). In general we would expect $\lambda p^{1/2}$ to be small since the stratum corneum is the rate-limiting barrier and $D_s << D_0$. K, the base–skin partition coefficient is also likely to be small since most drug designs favour distribution into the skin. It is not possible to generalize which term is likely to be dominant. Fig. 3 shows the release profile calculated using Eqn. 24 with fixed values of ($K + \lambda p^{1/2}$). Typical values for the parameters used in the release profiles are given in Table 1. Fig. 4 compares Eqns. 22 and 24 with a single value of ($K + \lambda p^{1/2}$). It shows that for the short time period shown, the approximation of the ierfc term produces sufficient accuracy to describe the release profile.

The long-time expression is shown graphically in Fig. 5 and is seen to be a simple first-order kinetic process with a rate constant (D_s/Kl_0l_s). After sufficient time has elapsed for establishment of steady-state conditions the thickness of the applied base does become

TABLE 1

VALUES FOR THE DIFFERENT PARAMETERS USED TO CALCULATE THE RELEASE PROFILES

Parameter	Normal skin	Abraded skin
K	variable	variable
$l_0/\mu m$	variable	variable
$l_s/\mu m$	25	150
D_0/m^2s^{-1}	10^{-10}	10^{-10}
D_s/m^2s^{-1}	10^{-15}	10^{-11}
k_c/s^{-1}	10^{-4}	10^{-4}

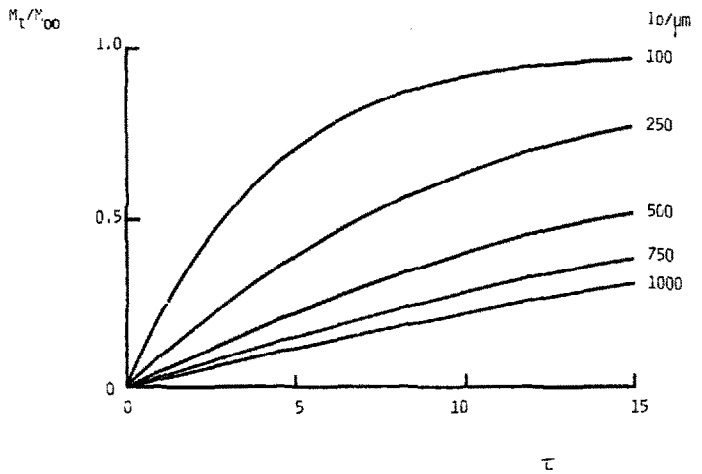


Fig. 5. Release profiles for long-time approximation (Eqn. 27) in non-abraded skin. The effect of varying base thickness is shown.

TABLE 2

THE RATIOS OF DRUG RELEASED COMPARED TO M_∞ FOR THE THICKEST APPLICATION (1000 μm) AT DIFFERENT TIME INTERVALS

$l_o/\mu m$	τ				
	1	2	5	10	15
100	0.022	0.039	0.071	0.092	0.098
250	0.024	0.045	0.098	0.158	0.194
500	0.024	0.048	0.111	0.197	0.269
750	0.024	0.048	0.114	0.211	0.294
1000	0.024	0.049	0.118	0.221	0.313

important. The effect that different thicknesses have on the penetration rates of the drug is also seen in Fig. 5.

It is also instructive to compare the total amount of drug penetrating the skin relative to M_∞ for the thickest application, 1000 μm. The results are given in Table 2. The table shows that at short times there is no significant difference in the quantity penetrating but as time progresses the deviation becomes more apparent.

CASE II. APPLICATION TO ABRADED SKIN

In this case the stratum corneum has been damaged by disease or physical injury and offers no resistance to transport. Drug penetration occurs through the viable epidermis/dermis and is removed at a finite rate by the blood vessels and lymphatics.

The treatment of this case is identical to that previously described and the relevant

physicochemical constants are given in Table 1. Capillary removal is characterized by a 1st-order rate constant, k_c, and the amount of drug removed at time t is given by

$$M_t = Al_e \int_0^t k_c c_{e(\chi=1)}\, dt \tag{28}$$

The normalized variables for this case are slightly different:

$$\tau' = D_e t / l_e^2 \tag{29}$$

$$\lambda' = D_e l_0 / D_0 l_e \tag{30}$$

$$p' = D_0 l_e^2 / D_e l_0^2 \tag{31}$$

$$K = u_{0,0} / u_{e,0} \tag{32}$$

$$\kappa = k_c l_e^2 / D_e \tag{33}$$

Expressing M_t in terms of these variables

$$M_t = c_0 Al_e \int_0^{\tau'} \kappa u_{e,1}\, d\tau' \tag{34}$$

It may also be found using an analogous equation to Eqn. 9

$$M_t = -c_0 Al_e \int_0^{\tau'} \left(\frac{\partial u_e}{\partial \chi}\right)_1 d\tau' \tag{35}$$

The differential equations describing transport in the base are identical to those previously described in Case I and Eqn. 16 may be transposed directly;

$$K\bar{u}_{e,0} = s^{-1} + \lambda' p'^{1/2} s^{-1/2} \left(\frac{\partial \bar{u}_e}{\partial \chi}\right)_0 \operatorname{cotanh}(s^{1/2} p'^{-1/2}) \tag{36}$$

In the viable epidermis

$$s\bar{u}_e = \frac{\partial^2 \bar{u}_e}{\partial \chi^2} \tag{37}$$

which has a general solution

$$\bar{u}_e = A' \cosh(s^{1/2}\chi) + B' \sinh(s^{1/2}\chi) \tag{38}$$

The coefficients A' and B' may be eliminated using Eqn. 36 to give

$$\bar{u}_{e,1} = \frac{\cosh s^{1/2}}{Ks} + \left(\frac{\partial \bar{u}_e}{\partial \chi}\right)_0 f_1(s) \tag{39}$$

where

$$f_1(s) = \lambda' p'^{1/2} K^{-1} s^{-1/2} \{\cosh s^{1/2} \operatorname{cotanh} s^{1/2} p'^{-1/2} + s^{-1/2} \sinh s^{1/2} \tag{40}$$

and

$$\left(\frac{\partial \bar{u}_e}{\partial \chi}\right)_1 = \frac{\sinh s^{1/2}}{Ks^{1/2}} + \left(\frac{\partial \bar{u}_e}{\partial \chi}\right)_0 f_2(s) \tag{41}$$

where

$$f_2(s) = \cosh s^{1/2} + \lambda' p'^{1/2} K^{-1} \sinh s^{1/2} \operatorname{cotanh} s^{1/2} p'^{-1/2} \tag{42}$$

combining Eqns. 39, 41, 34 and 35

$$M_t = c_0 A l_e \mathcal{L}^{-1} g(s) \tag{43}$$

where

$$g(s) = [s^{3/2} \sinh s^{1/2} \{K s^{1/2} \kappa^{-1} \operatorname{cotanh} s^{1/2} + \lambda' p'^{1/2} s^{1/2} \kappa^{-1} \operatorname{cotanh} s^{1/2} p'^{-1/2} + K + \lambda' p'^{1/2} \operatorname{cotanh} s^{1/2} \operatorname{cotanh} s^{1/2} p'^{-1/2}\}]^{-1} \tag{44}$$

This equation is identical in form to Eqn. 26 (Hadgraft, 1979b) except that in this case there are no terms describing interfacial transfer since fast interfacial kinetics are assumed.

As previously, no simple equation exists for the inversion of Eqn. 43 and appropriate approximations are considered.

Case IIa. Slow removal by capillaries

For this process, κ is small and at short times the first two terms in Eqn. 44 dominate. At short times, $s > 1$, the hyperbolic terms may be approximated (Abramowitz and Stegun, 1970).

$$2g(s) = [s^2 \exp(s^{1/2}) \{K\kappa^{-1} + \lambda' p'^{1/2} \kappa^{-1}\}]^{-1} \tag{45}$$

which may be inverted and substituted into Eqn. 43 to produce

$$M_t = \frac{M_\infty \lambda' p'}{(K\kappa^{-1} + \lambda' p'^{1/2} \kappa^{-1})} \operatorname{erfc}(1/2\, \tau'^{1/2}) \tag{46}$$

The way in which M_t varies with t is shown in Fig. 6. The typical values for the variables chosen are given in Table 1. Examination of Eqn. 46 shows that for this case, at short times, there is no dependence on l_0, the thickness of the applied medicament. The rate is solely limited by the slow systemic removal.

At long times $\tau > 1$, $s < 1$, and due to the form of the hyperbolic terms in Eqn. 44, the first and last terms become dominant and may be approximated to give

$$g(s) = \left[\frac{Ks}{\kappa}\left(s + \frac{\kappa\lambda' p'}{K}\right)\right]^{-1} \tag{47}$$

which may be substituted into Eqn. 43 and inverted.

$$M_t = M_\infty (1 - \exp(-\kappa\lambda' p' \tau'/K)) \tag{48}$$

Inspection of this equation shows that the amount released will be dependent on the thickness of ointment applied. Fig. 7 shows M_t as a function of time and the effect of different thicknesses of base.

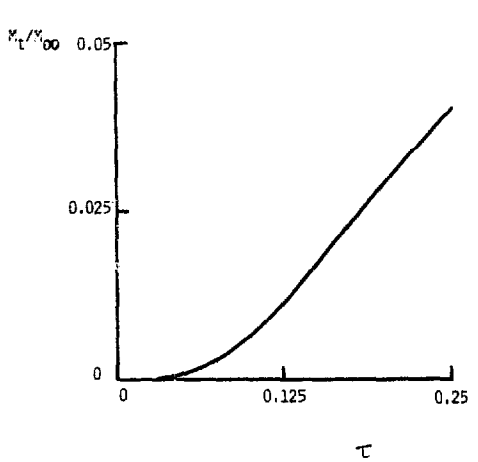
Case IIb. Fast removal by the capillaries

In this case, κ is large and the second two terms in Eqn. 44 dominate. Using the short time approximations for the hyperbolic terms (Abramowitz and Stegun, 1970),

$$2g(s) = s^{3/2} (K + \lambda' p'^{1/2}) \exp(s^{1/2}) \tag{49}$$

and

$$M_t = 4 M_\infty \lambda' p' \tau'^{1/2} (K + \lambda' p'^{1/2})^{-1} \text{ ierfc } (1/2\, \tau'^{1/2}) \tag{50}$$



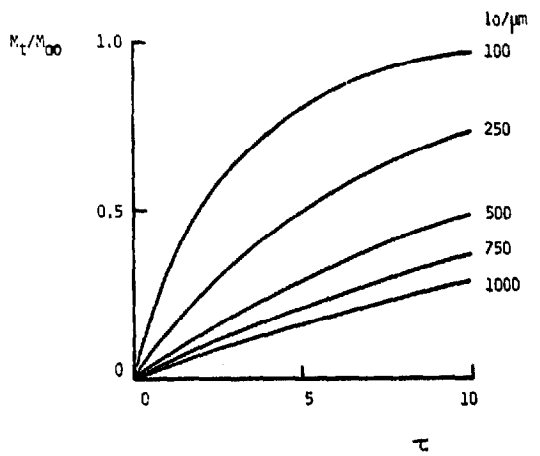


Fig. 6. Short-time release pattern through abraded skin (Eqn. 46).

Fig. 7. Release profiles for long-time approximation (Eqn. 48) for abraded skin and slow capillary uptake. The effect of base thickness is shown.

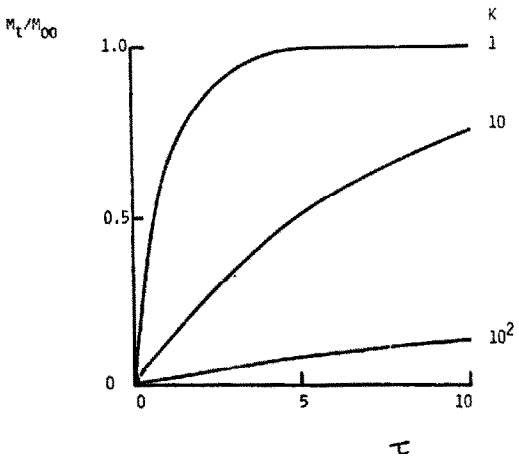


Fig. 8. Release profile for fast uptake by the capillaries (Eqn. 52) and long periods of time. A value for l_0 of 100 μm has been taken and the effect of K is shown.

which is exactly the same form as Case I, Eqn. 22 with the general substitution of D_e for D_s and l_e for l_s. The release profile will be identical to that shown in Fig. 3 with a displaced time scale since τ' represents much shorter real time values than τ.

The long-time approximation is given by simple substitution of the hyperbolic terms when

$$g(s) = \frac{3}{3K + \lambda'(p' + 1)} \left[s\left(s + \frac{3p'\lambda'}{3K + \lambda'(p' + 1)}\right)\right]^{-1} \tag{51}$$

and

$$M_t = M_\infty \left[1 - \exp\left(\frac{3p'\lambda'\tau'}{3K + \lambda'(p' + 1)}\right)\right] \tag{52}$$

The release profile is given in Fig. 8 with typical values of p' and λ' given in Table 1. The effect of varying the partition coefficient is shown and the effect of ointment thickness on the rate of absorption will only be important when $3K >> \lambda'(p' + 1)$.

DISCUSSION

Families of release curves have been produced which show the effects of ointment thickness for a range of experimental conditions. In certain circumstances the thickness of the applied base may be an important consideration in formulation. As drugs become more potent and more efficacious formulations are produced it will probably be desirable to produce dosage forms in which the amount and thickness of the preparation is carefully controlled.

The mathematical expressions derived may also be used in the interpretation of well documented systems (e.g. Iyer et al., 1979). In this work in vitro skin penetration of

triamcinolone acetonide from films was investigated. A simple treatment was used to analyze the results and it is probable that a more rigorous approach as detailed in this paper would give more insight into the mechanisms of percutaneous penetration from films.

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