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THE EPIDERMAL RESERVOIR; A THEORETICAL APPROACH

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SUMMARY

Mathematical expressions have been derived to describe the rates of release of drugs forming a reservoir in the stratum corneum. The different physicochemical constants incorporated into the expressions and their significance in the formation of a reservoir are discussed. Theoretical release curves are given which show how the oil/water partition coefficient of the drug affects the storage capacity of the stratum corneum.

INTRODUCTION

When corticosteroids are applied to the intact skin a reservoir of the drug accumulates in the stratum corneum. The reservoir was first postulated by Malkinson and Ferguson (1955) in order to explain the prolonged urinary excretion of hydrocortisone after skin application. It has been shown that skin sites blanch up to 15 days after steroid application when they are re-occluded (McKenzie et al., 1962; Vickers, 1963; Winkelmann, 1969). This shows the existence of a significant depot or reservoir located in the epidermis.

Results show that intradermal injection of the corticosteroids produces no depot formation and thus the reservoir appears to be located in the stratum corneum. Stoughton (1965) provided evidence for this location by a radiochemical technique and further confirmation was produced by the removal of the reservoir by stripping the area of application.

In this paper a mathematical model of the skin will be developed. The different physicochemical properties of the skin and drug will be considered and their effects on the formation of a reservoir discussed. In studies of the percutaneous penetration of steroids and in their clinical usage the drug is left in contact with the skin for periods of several hours and then removed. This allows a build up of the drug in the epidermis which will be released into the dermis both during and after the topical application is removed. The equations derived show what happens to the steroid after the application is removed.

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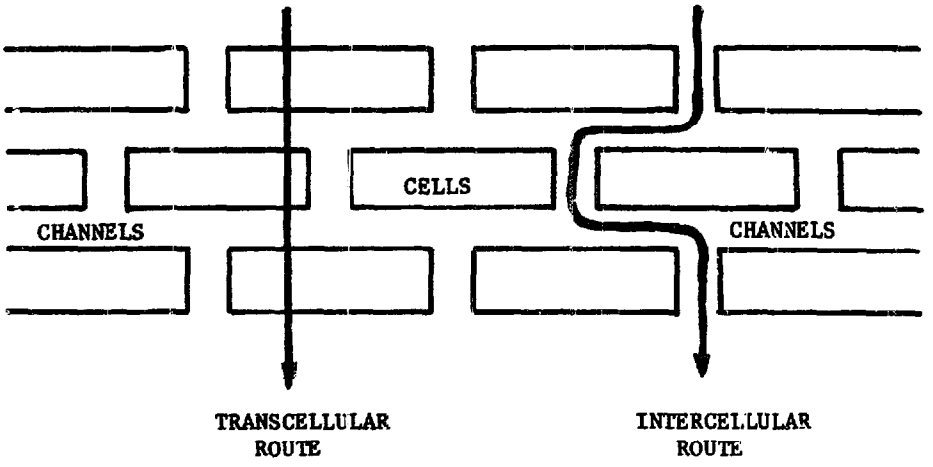

Fig. 1. Idealized model of the stratum corneum.

Expressions for the rates of uptake by the epidermis have been derived (Albery and Hadgraft), but these do not show what happens in the case of reservoir formation.

THE PHYSICAL MODEL

The skin has such a complex structure that in order to characterize its properties algebraically an idealized model has to be used. The model chosen is based on a structure given by Michaels et al. (1975) and is shown in Fig. 1. Two routes of penetration are possible, first when the drug diffuses through the cells and second when the drug travels through the channels surrounding the cells. Taking typical data for the cellular dimensions, thickness of the stratum corneum and lipid/proteinaceous volume fraction ratio (Tregear, 1966; Katz and Poulsen, 1971, Michaels et al., 1975), estimates of the dimensional parameters for the two different routes of penetration may be calculated. These are given in Table 1.

THE MATHEMATICAL MODEL

The model taken is essentially similar to that described by Albery and Hadgraft and is shown schematically in Fig. 2. In the model the rate of removal of the steroid by the

TABLE 1

ESTIMATES OF THE PHYSICAL PARAMETERS CALCULATED USING AN IDEALIZED MODEL OF THE STRATUM CORNEUM FOR THE TWO DIFFERENT ROUTES OF PENETRATION

	Transcellular	Intercellular
Diffusional path length/μm	25	350
Area ratio	1	7×10^{-3}
Volume ratio	1	0.1
Thickness of viable epidermis/μm	150	150

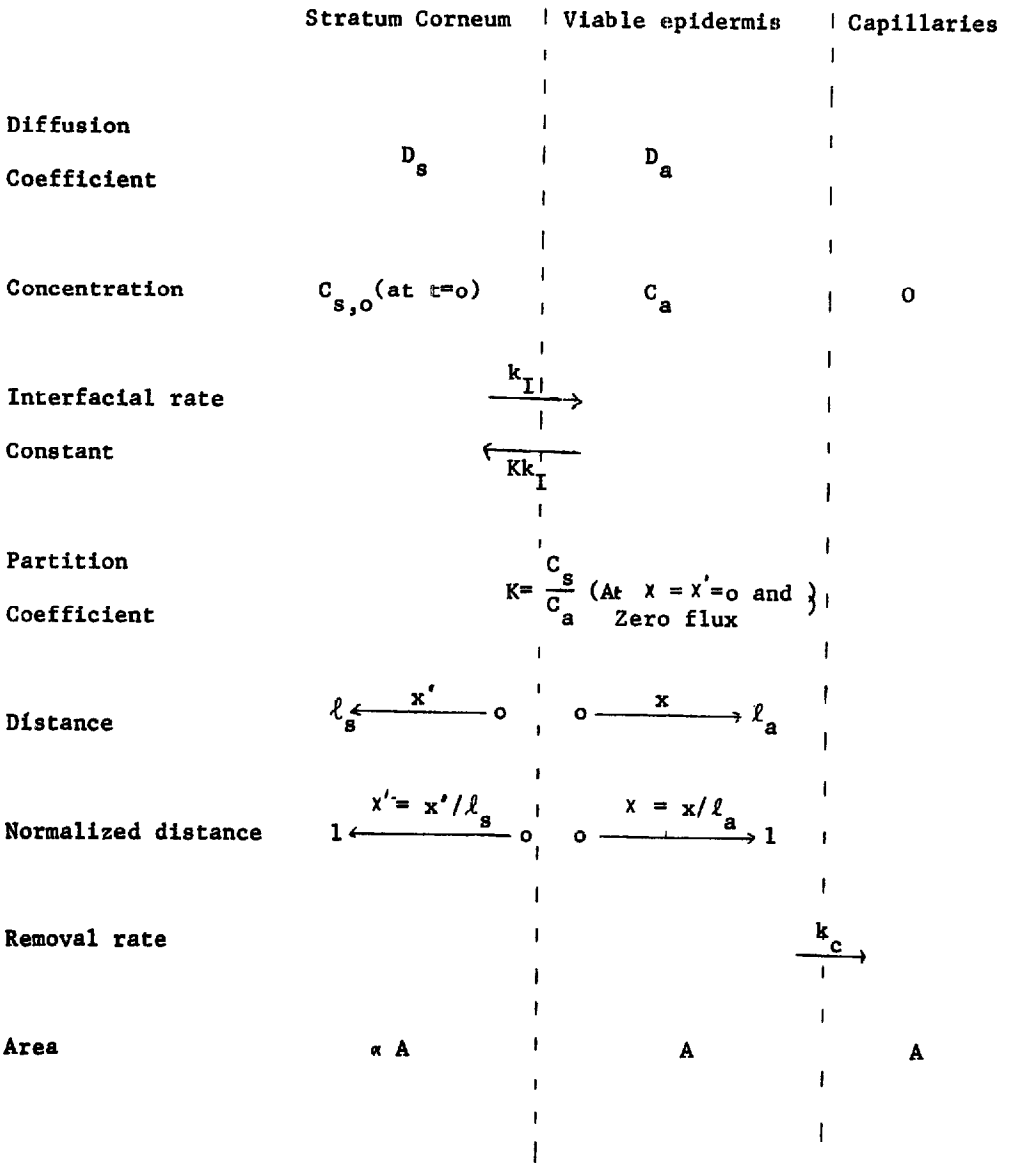

Fig. 2. Schematic representation of the mathematical model of the epidermis.

capillaries at the dermal–epidermal junction is given by a first order rate constant, k_c. Thus the total amount (M_t) of drug removed at time, t, is given by

$$M_t = A\ell_a \int_0^t k_c C_{a(x=1)}\, dt \qquad (1)$$

The following normalized variables are used in order to simplify the solution of the differential equations.

$$u = C/C_{s,0} \tag{2}$$

$$\kappa = k_I \ell_a / D_a \tag{3}$$

$$\lambda = \ell_a / \ell_s \tag{4}$$

$$p = D_s \ell_a^2 / D_a \ell_s^2 \tag{5}$$

$$\omega = k_c \ell_a^2 / D_a \tag{6}$$

$$\tau = D_a t / \ell_a^2 \tag{7}$$

Assuming diffusion occurs in one dimension and the diffusion coefficients are independent of concentration, the following differential equations are obtained. (Fick's second law of diffusion expressed in terms of the normalized variables, Eqns. 2–5.) In the stratum corneum,

$$\frac{\partial u_s}{\partial \tau} = p \frac{\partial^2 u_s}{\partial \chi'^2} \tag{8}$$

and in the viable epidermis,

$$\frac{\partial u_a}{\partial \tau} = \frac{\partial^2 u_a}{\partial \chi^2} \tag{9}$$

At the stratum corneum/viable epidermis barrier

$$\frac{\alpha p}{\lambda}\left(\frac{\partial u_s}{\partial \chi'}\right)_0 = \kappa u_{s,\chi'=0} - K\kappa u_{a,\chi=0} = -\left(\frac{\partial u_a}{\partial \chi}\right)_0 \tag{10}$$

The term $\alpha p/\lambda$ describes the effects of the area ratio differences, the diffusional path length difference and the difference in the diffusion coefficients. The κ terms reflect the finite rate of transport across the interface given by an interfacial rate constant, k_I.

Equation 1 may be rewritten in terms of the dimensionless variables

$$M_t = C_{s,0} A l_a \int_0^\tau \omega u_{a,\chi=1}\, d\tau \tag{11}$$

Thus to calculate M_t it is necessary to show how u_a varies with time. This is achieved by solution of Eqns. 8 and 9 with the following boundary conditions:

$$\chi' = 1\,, \quad (\partial u/\partial \chi')_1 = 0 \tag{12}$$

$$\tau = 0\,, \quad u_s = 1 \tag{13}$$

$$\tau = 0\,, \quad u_a = 0 \tag{14}$$

The condition given by Eqn. 14 is not entirely correct. Some steroid will have diffused into the viable epidermis during the time of application thus $u_a \neq 0$. However in the time scale of application, and considering the low aqueous solubilities of the corticosteroids, the amount is very small and can be considered as being negligible, $u_a \approx 0$.

The differential equations are solved using Laplace Transforms. In the stratum corneum, the differential Eqn. 8 is transformed to give,

$$s\bar{u}_s - 1 = p \frac{\partial^2 \bar{u}_s}{\partial \chi'^2} \tag{15}$$

which has the general solution

$$\bar{u}_s = A \cosh(s^{1/2}p^{-1/2}\chi') + B \sinh(s^{1/2}p^{-1/2}\chi') + s^{-1} \tag{16}$$

The coefficients A and B may be eliminated using the boundary condition 12,

$$\bar{u}_{s,\chi'=0} = s^{-1} - p^{1/2}s^{-1/2}\left(\frac{\partial \bar{u}_s}{\partial \chi'}\right)_0 \operatorname{cotanh} s^{1/2}p^{-1/2} \tag{17}$$

Similarly in the viable epidermis, from Eqn. 9,

$$s\bar{u}_a = \frac{\partial^2 \bar{u}_a}{\partial \chi^2} \tag{18}$$

which has the general solution,

$$\bar{u}_a = A' \cosh(s^{1/2}\chi) + B' \sinh(s^{1/2}\chi) \tag{19}$$

Eliminating the coefficients A' and B' by using the boundary conditions,

$$\bar{u}_a = \bar{u}_{a,\chi=0} \cosh(s^{1/2}\chi) + s^{-1/2}\left(\frac{\partial \bar{u}_a}{\partial \chi}\right)_0 \sinh(s^{1/2}\chi) \tag{20}$$

and

$$\left(\frac{\partial \bar{u}_a}{\partial \chi}\right)_1 = \bar{u}_{a,\chi=0}\, s^{1/2} \sinh s^{1/2} + \left(\frac{\partial \bar{u}_a}{\partial \chi}\right)_0 \cosh s^{1/2} = -\omega \bar{u}_{a,\chi=1} \tag{21}$$

Combining Eqns. 20 and 21 with $\chi = 1$, followed by rearrangement,

$$\bar{u}_{a,\chi=1} = -\omega^{-1}\left(\frac{\partial \bar{u}_a}{\partial \chi}\right)_0 (\cosh s^{1/2}(1 + s^{1/2} \tanh s^{1/2}/\omega))^{-1} \tag{22}$$

The partial differential, $(\partial u_a/\partial \chi)_0$, is given by the boundary condition 10 and Eqn. 17,

$$\left(\frac{\partial \bar{u}_a}{\partial \chi}\right)_0 = K\kappa \bar{u}_{a,\chi=0} - \frac{\kappa}{s} - \frac{\lambda\kappa}{\alpha}\sqrt{\frac{1}{sp}}\left(\frac{\partial \bar{u}_a}{\partial \chi}\right)_0 \operatorname{cotanh} s^{1/2}p^{-1/2} \tag{23}$$

$\bar{u}_{a,\chi=0}$ is eliminated from this equation by substitution of Eqn. 20 with a value of $\chi = 1$,

$$\left(\frac{\partial \bar{u}_a}{\partial \chi}\right)_0 = (K\kappa \bar{u}_{a,\chi=1}/\bar{g} \cosh s^{1/2}) - \bar{g}^{-1}s^{-1} \tag{24}$$

where

$$\bar{g} = 1 + K\kappa s^{-1/2} \tanh s^{1/2} + \lambda\kappa\alpha^{-1}s^{-1/2}p^{-1/2} \operatorname{cotanh} s^{1/2}p^{-1/2} \tag{25}$$

Using these two expressions an expression for $\bar{u}_{a,\chi=1}$ is obtained by substitution into Eqn. 22,

$$\bar{u}_{a,\chi=1} = \bar{f}(s) =$$

$$\left[s^{1/2} \sinh s^{1/2}\left(\frac{s^{1/2}\omega}{\kappa \tanh s^{1/2}} + K\omega + \frac{\omega\lambda}{\alpha p^{1/2}} \frac{\operatorname{cotanh} s^{1/2}p^{-1/2}}{\tanh s^{1/2}} + \frac{s}{\kappa} + \frac{s^{1/2}K}{\tanh s^{1/2}}\right.\right.$$

$$\left.\left. + \frac{s^{1/2}\lambda \operatorname{cotanh} s^{1/2}p^{-1/2}}{\alpha p^{1/2}}\right)\right]^{-1} \tag{26}$$

Thus from Eqn. 11 an expression for M_t is obtained

$$M_t = C_{s,0}Al_a \mathcal{L}^{-1}\omega\bar{f}(s)/s \tag{27}$$

The steroid reservoir exists in the stratum corneum for such a long time that steady state conditions will be established in the viable epidermis where difussion is compartively rapid. Since the time, τ, has been normalized with respect to transport in this layer, solutions for M_t are required when $\tau >> 1$. For large values of τ, s will be very small and the hyperbolic functions of s alone in Eqn. 26 may be approximated to give,

$$\frac{\omega\bar{f}(s)}{s} = \left[s^2\left(\frac{1}{\kappa} + K + \frac{\lambda}{\alpha s^{1/2}p^{1/2} \tanh s^{1/2}p^{-1/2}} + \frac{s}{\omega\kappa} + \frac{K}{\omega} + \frac{s^{1/2}\lambda}{\alpha\omega p^{1/2} \tanh s^{1/2}p^{-1/2}}\right)\right]^{-1} \tag{28}$$

There is no simple inversion of this equation and in order to find how M_t varies with time it is necessary to make further approximations. Using the idealized model of the skin, different values for the normalized variables given by Eqns. 2–7 will arise for the two routes of penetration. Estimates for the variables for both routes will be made.

The diffusion coefficients of some steroids in the stratum corneum have been measured (Scheuplein et al., 1969; Foreman and Kelly, 1976). The calculations are based on the penetration of drug straight through the membrane and average values are $\sim 10^{-15}$ m^2 s^{-1}. If the steroid diffuses round the cells, through a longer path length and smaller area fraction, the true diffusion coefficients would need to be very much faster to give

TABLE 2

ESTIMATED AVERAGE VALUES FOR THE NORMALIZED VARIABLES GIVEN BY EQNS. 3–6.

	Transcellular	Intercellular
κ	38	38
λ	6	0.4
p	4×10^{-3}	2×10^{-2}
ω	2×10^{-2}	2×10^{-2}

the same overall flux. Correcting for the path length and area fraction differences (given in Table 1) the average values would be increased to be of the order of 10^{-12} m^2 s^{-1}. The diffusion coefficient in the viable epidermis will probably be similar to a hindered diffusion coefficient in an aqueous environment, e.g. a gel of some 75–95% water content. A value of 10^{-11} $m^2 s^{-1}$ has been taken as being typical (Scheuplein, 1967).

A more difficult estimate to make is the rate of removal of the steroid by the capillaries. Investigations on the radial diffusion of methyl nicotinate (Albery et al.) indicate a k_c value of 10^{-4} s^{-1}. For the corticosteroids, which produce constriction rather than dilatation of the blood vessels, a significantly lower rate would be expected and 10^{-5} s^{-1} is probably more realistic. Absorption studies of [^{14}C]triamcinoline acetonide (Malkinson and Kirschenbaum, 1963) from stripped skin sites indicate that this estimate is of the correct order of magnitude. Blanching tests by Woodford and Barry (1977) give apparent vasoconstriction half lives of 15 h which also verify the rate constant of 10^{-5} s^{-1}. Thus, this value has been taken in the calculation of the normalized parameters in Table 2.

Interfacial rate constants for a variety of substrates have been measured (Albery et al., 1976). The value for a fluorinated steroid, betamethasone-17-valerate, across an isopropyl myristate/water interface has been found to be 2.5×10^{-6} $m \cdot s^{-1}$ (Albery and Hadgraft). From previous work (Albery et al., 1976) this value is probably fairly typical for all steroids and has thus been used in the subsequent analysis.

In general the fluorinated steroids, which produce large epidermal reservoirs, have large oil/water partition coefficients. It is thus possible to eliminate some of the terms in Eqn. 28 since they will be insignificant in comparison to others. Using values in Table 2 and remembering that since $\tau \gg 1$, $s \ll 1$,

$$\frac{s}{\omega\kappa} \ll \frac{K}{\omega} \gg K \gg \frac{1}{\kappa}$$

Equation 27 then simplifies to,

$$M_t = C_{s,0} A l_a \mathcal{L}^{-1}[s^2(K/\omega + \lambda/\alpha\, s^{1/2} p^{1/2} \tanh s^{1/2} p^{-1/2}]^{-1} \tag{29}$$

Using the values of p given by Table 2 the term $\tanh s^{1/2}p^{-1/2}$ may be approximated to $s^{1/2}p^{-1/2}$ for times greater than two days; this further simplifies Eqn. 29,

$$M_t = C_{s,0} A l_a \mathcal{L}^{-1}[s^2(K\omega^{-1} + \lambda\alpha^{-1} s^{-1}]^{-1} \tag{30}$$

Inverting this transform gives an expression that shows the variation of M_t with the normalized time variable, τ,

$$M_t = C_{s,0}Al_a\alpha\lambda^{-1}(1 - \exp(-\lambda\omega\tau\alpha^{-1}K^{-1})) \quad (31)$$

The quantity $C_{s,0}Al_a\alpha\lambda^{-1}$ is the total amount of steroid stored in the stratum corneum and is the amount that will be released into the blood capillaries after an infinite period, M_∞. Using Eqn. 31 and the parameters given in Table 2 it is possible to show how the steroid will be released over a long period of time as a function of the stratum corneum/water partition coefficient.

Transcellular route

The results for a transcellular route of penetration are shown in Fig. 3. The different curves reflect the effect of the stratum corneum/water partition coefficient on the release rate of the steroid from its reservoir. For even a modest distribution coefficient the results show the possibility of a long residence time in the lipids of the stratum corneum. Considering this length of time it is possible that appreciable metabolism may occur.

It is also possible to see from the curves how the rate of removal by the capillaries affects the reservoir function. If, for example, a partition coefficient of 100 is assumed, a 10-fold increase in the rate constant, k_c, would increase the rate to give the same curve as that plotted for K = 10 in Fig. 3.

Intercellular route

The stratum corneum/water partition coefficients measured and quoted in the literature and based on the whole of the skin sample being involved in the distribution process. However, the skin lipids only account for some 10–20% of the total volume, the volume

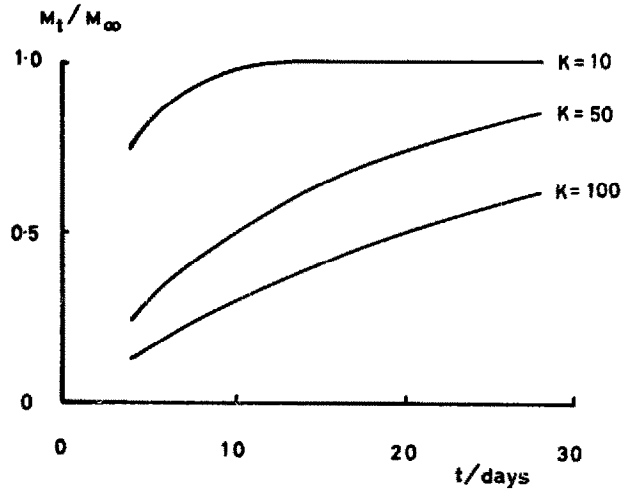

Fig. 3. The release rate of a drug over a 28-day period from the stratum corneum assuming a transcellular route. The effect of partitioning is illustrated.

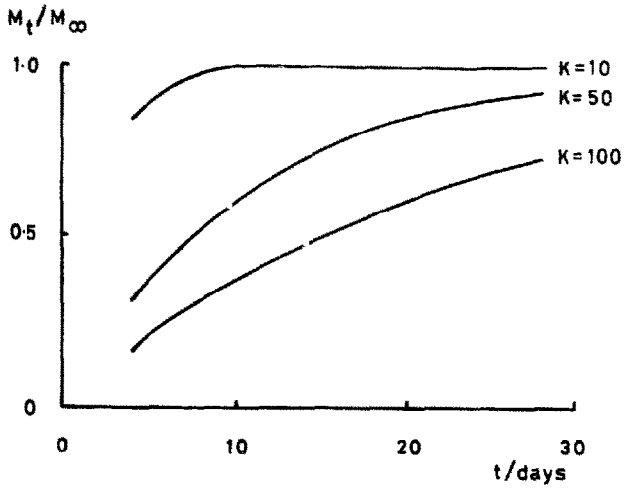

Fig. 4. The releast rate of a drug over a 28-day period from the stratum corneum assuming an intercellular route. The effect of partitioning is shown.

of the intercellular channels (Katz and Poulsen, 1971). Thus if transport is via these channels, and the drug is stored within them, the measured partition coefficients have to be corrected by a volume ratio factor, γ.
Then,

$$K_{channels}/K = V_{total}/V_{channels} = \gamma \tag{32}$$

γ is typically of the order of 7 and this factor has been included in the calculations in Fig. 4. The curves show the release profiles for the intercellular route calculated using the volume ratio corrected equation,

$$M_t/M_\infty = 1 - \exp(-\lambda\omega\tau\alpha^{-1}\gamma^{-1}K^{-1}) \tag{33}$$

The figure shows how the release characteristics vary with partition coefficient.

The same types of curves are given as for the transcellular case (Fig. 3). The results show that it is possible to establish a reservoir with this mode of penetration to nearly the same extent as for the transcellular route. As for the former case, residence times in the stratum corneum for steroids of high lipid solubility are long and metabolism may occur during this period.

DISCUSSION

One of the main causes of the formation of a steroid reservoir in the epidermis is the slow removal rate by the capillary network. Vasoconstriction by the corticosteroids slows down this removal rate and it is this effect that causes the maintenance of a depot in the stratum corneum. Compounds which have no effect on the capillary stream would not be expected to form a significant reservoir and drugs which cause vasodilatation would exhibit no storage characteristics. For formulations of these drugs where residence in the stratum corneum is preferred it may be possible to incorporate long acting vasoconstricting agents into the preparation. These would inhibit the removal of the active material by

lowering the value of k_c and by so doing would increase the storage capacity of the epidermis.

It is also seen that the stratum corneum/water partition coefficient determines the residence time of the drug in the depot. Hydrocortisone, which has a skin/water partition coefficient of approximately 10 (Yotsuyanagi and Higuchi, 1972) would, from Fig. 3, still be present at a level of 10% of the original concentration 6 or 7 days after application. The fluorinated steroids have oil/water partition coefficients approximately 10 times that of hydrocortisone (Katz and Shaikh, 1965) and would be expected to show a more marked reservoir capacity.

Using this information it should be possible to 'tailor' drugs to either improve their storage capability or to increase their rate of removal. For formulations of non-steroidal drugs that do not cause vasoconstriction it may be possible to incorporate long acting vasoconstricting agents into the preparation. This would be adopted for cases in which drug residence in the stratum corneum is preferred and thus may be used for substances which have pharmacological activity in the skin but produce unwanted side effects if absorbed in large doses into the circulatory system.

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