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Percutaneous metabolism with saturable enzyme kinetics

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Summary

Theoretical equations have been formulated to describe the effect of epidermal metabolic processes on the transport of drugs penetrating the skin. Michaelis-Menten kinetics have been assumed and the relative contributions from the kinetic parameters discussed.

Introduction

A recent review article (Wester and Noonan, 1980) has indicated that the enzymes in skin may have real activities in the range 80–120% of those in the liver. In this event, topically applied drugs may be subject to considerable metabolic conversion especially if the drug forms a reservoir in the skin; such compounds as the corticosteroids are known to form substantial reservoirs (McKenzie et al., 1962). It is pertinent to produce mathematical models of skin which describe the metabolic fate of a diffusing drug in order to assess how the metabolism will affect the overall transport rate and disposition of the active species. In certain circumstances the breakdown of the drug may be used to advantage. It is possible to synthesize prodrugs which penetrate the skin more rapidly than the parent molecule but are metabolized to the active form at their site of action (Yu et al., 1979).

Previous publications have considered epidermal metabolism. Fox et al. (1979) produced a complete model which requires computer simulation. Yu et al. (1979)

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derive complex hyperbolic functions which predict the concentration distribution and fluxes of all the metabolites of vidarabine-5′-valerate through the epidermis. The equations in this treatment are complex. An earlier publication (Hadgraft, 1979) has indicated how more simple analytic functions may be derived to describe percutaneous metabolism in which the kinetics are first-order. In this paper a similar treatment is adopted but more complex Michaelis-Menten kinetics are assumed.

Theory

(1) The model

To simplify the mathematical treatment of percutaneous absorption, we adopt an idealized physical model which is schematically presented in Fig. 1 (Albery and Hadgraft, 1979; Hadgraft, 1979; Guy and Hadgraft, 1980). In this particular discussion we have not differentiated between the stratum corneum and the viable epidermis. An earlier publication (Hadgraft, 1979) has already described the mathematics required for treating the skin in this fashion. The theoretical description in this paper therefore deals with a somewhat simpler situation but may be extended, using the procedures outlined by Hadgraft (1979) to the more complicated bilayer case.

In this model it has been assumed that the metabolism of drug follows Michaelis-Menten kinetics and that uptake of drug by the capillaries is described by the first-order rate constant k_c. The latter is related to the total amount of drug (M_t) removed at time t by:

$$M_t = A \int_0^t k_c c_{x=l} \, dt \tag{1}$$

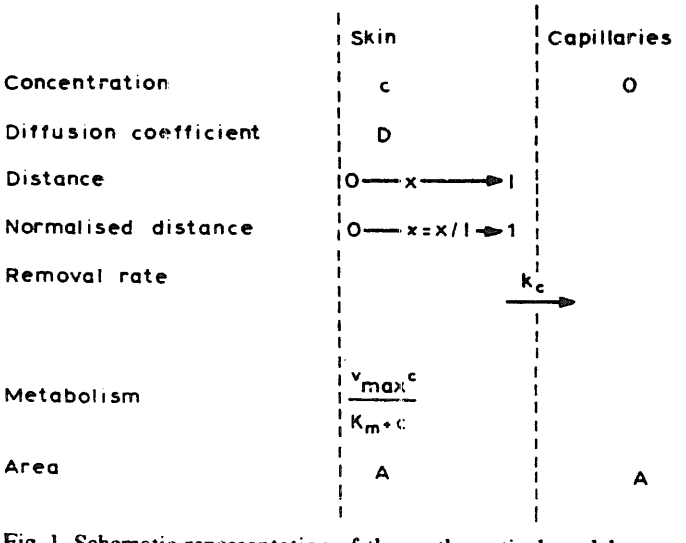

Fig. 1. Schematic representation of the mathematical model.

where $c_{x=l}$ is the concentration of drug at the capillary interface and ℓ is the thickness of the skin.

To simplify solution of the differential equations derived to interpret the transport and kinetic processes, several normalized variables are defined. Firstly,

$$u = c/c_0 \tag{2}$$

where c is the drug concentration in the skin and c_0 is the initial drug concentration applied to the skin surface at $t = 0$. In the mathematics presented below, we deal with two different surface boundary conditions: (a) where there is a constant drug concentration at the surface throughout the experiment (Case A); and (b) where the drug concentration decays exponentially with a first-order rate constant k_d (Case B).

The time variable is normalized with respect to the thickness of the skin and the drug diffusion coefficient therein,

$$\tau = Dt/\ell^2 \tag{3}$$

The Michaelis-Menten parameters and capillary uptake rate constant are similarly normalized.

$$V = V_{max}\ell^2/Dc_0 \tag{4}$$

$$K = K_m/c_0 \tag{5}$$

$$\omega = k_c\ell^2/D \tag{6}$$

and we further define

$$\kappa = V_{max}\ell^2/K_mD \tag{7}$$

In order to describe transport through the skin, Fick's second law of diffusion is modified to take into account the metabolic process. This may be expressed mathematically

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - \frac{v_{max}c}{K_m + c} \tag{8}$$

or, in terms of the normalized parameters

$$\frac{\partial u}{\partial \tau} = \frac{\partial^2 u}{\partial \chi^2} - \frac{Vu}{K + u} \tag{9}$$

To produce specific solutions to this second-order differential equation the following

boundary conditions are set:

Case A: $\tau = 0, u = 0$ (10)

$\tau > 0, \chi = 0, u_0 = 1$ (11)

Case B: $\tau = 0, u = 0$ (12)

$\tau > 0, \chi = 0, u_0 = \exp(-\gamma\tau)$ (13)

where γ is the normalized rate constant describing the exponential depletion of drug at the skin surface.

$$\gamma = k_d \ell^2 / D \tag{14}$$

The physical interpretations of these boundary conditions are that Eqns. 10 and 12 show that initially the skin is free of any drug. Condition 11 shows that there is a constant source of drug at the skin surface for Case A and Condition 13 shows how the surface concentration varies for Case B.

In both cases there is a third boundary condition applicable at the capillary interface ($x = \ell$, $\chi = 1$) to describe the first-order removal of the drug by the capillary vasculature,

$$\left(\frac{\partial u}{\partial \chi}\right)_1 = -\omega u_1 \tag{15}$$

A complete simple analytical solution to Eqn. 9 cannot be obtained. However, various approximations can be made and we concentrate on the two limiting situations. At low concentrations, where the rate of enzymatic metabolism is linear with concentration, the Michaelis constant K_m is dominant ($u < K$) and Eqn. 9 reduces to

$$\frac{\partial u}{\partial \tau} = \frac{\partial^2 u}{\partial \chi^2} - V \tag{16}$$

The second approximation is for the region where the metabolic rate is independent of concentration ($u > K$) and Eqn 9 becomes

$$\frac{\partial u}{\partial \tau} = \frac{\partial^2 u}{\partial \chi^2} - \kappa u \tag{17}$$

We now solve Eqns. 16 and 17 for the two cases A and B having the corresponding boundary conditions 10, 11 and 12, 13.

(2) Case A

(i) $u > K$. Eqn. 16 is solved using Laplace transforms. The transform is

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

which has the general solution

$$\bar{u} = A\cosh s^{1/2}\chi + B\sinh s^{1/2}\chi - Vs^{-1} \tag{19}$$

Elimination of the coefficients A and B using the boundary conditions 11 and 15 gives

$$\bar{u}_1 = [V(1 - \cosh s^{1/2}) + 1]/[s\cosh s^{1/2}(1 + \omega s^{-1/2}\tanh s^{1/2})] \tag{20}$$

The number of moles of drug reaching the blood in the capillary network at time t may be calculated by using the normalized version of Eqn. 1.

$$M_t = A\ell c_0 \int_0^{\tau} \omega u_1 d\tau \tag{21}$$

$$= A\ell c_0 \mathcal{L}^{-1}\omega\bar{u}_1/s \tag{22}$$

Substitution of Eqn. 20 into Eqn. 22 gives

$$M_t = A\ell c_0 \omega \mathcal{L}^{-1}[V(1 - \cosh s^{1/2}) + 1]/[s^2\cosh s^{1/2}(1 + \omega s^{-1/2}\tanh s^{1/2})] \tag{23}$$

There is no simple inversion of this equation. However, it is reasonable to assume that metabolism will be insignificant over short periods of time (Hadgraft, 1979). We therefore consider times for which $\tau > 1$ which corresponds approximately to $t > 1$ h and rewrite the hyperbolic expressions in Eqn. 23 using the first terms of their asymptotic power series since $s < 1$ (Abramowtiz and Stegun, 1970). Hence Eqn. 23 becomes

$$M_t = A\ell c_0 \omega \mathcal{L}^{-1}(2 - Vs)/2s^2(1 + s/2 + \omega + \omega s/6) \tag{24}$$

A further simplification may be made, that is $2(\omega + 3) > 4\omega$ since $\omega < 1$ to give

$$M_t = 3A\ell c_0 \omega/(\omega + 3)\mathcal{L}^{-1}(2 - Vs)/s^2(s + 2) \tag{25}$$

Inversion of this equation is possible by separation into partial fractions to produce

$$M_t = \frac{3A\ell c_0 \omega}{2(\omega + 3)}[(V + 1)\exp(-2\tau) + 2\tau - (V + 1)] \tag{26}$$

Direct inversion of Eqn. 24 gives a more complex expression for M_t values of which

do not differ by more than 2% from those determined using Eqn. 26.

(ii) $u < K$. For this case, Eqn. 17 is solved using the technique outlined above and the corresponding boundary conditions. The long-time solution only is considered and the simplification $2(\omega + 3) > 4\omega$ is again used. In this way it is found that

$$M_t = \frac{6A\ell c_0}{(\omega + 3)} \mathcal{L}^{-1}\left[s^2(s + (2 + \kappa))\right]^{-1} \tag{27}$$

which on inversion gives

$$M_t = \frac{6A\ell c_0 \omega}{(\omega + 3)(2 + \kappa)^2}\left[\exp - (2 + \kappa)\tau + (2 + \kappa)\tau - 1\right] \tag{28}$$

Eqns. 26 and 28 are somewhat similar in form which is reasonable and both reduce to the same expression if we postulate no metabolism and therefore effectively set κ and V to zero.

3. Case B

For these solutions we allow the surface concentration of drug to deplete as given by Eqn. 13. This boundary condition when differentiated inverts to

$$\chi = 0, \quad \left(\frac{\partial u}{\partial \chi}\right)_0 = -\lambda\gamma/(s + \gamma) \tag{29}$$

where $\lambda = h/\ell$ and corrects for the difference in thickness of the applied vehicle (h) and the skin (ℓ).

(i) $u > K$. Solution of Eqn. 16 with the boundary conditions 15 and 29 gives

$$u_1 = \frac{\lambda\gamma s^{1/2} - \lambda V(s + \gamma)\sinh s^{1/2}}{s(s + \gamma)\sinh s^{1/2}(1 + \omega s^{-1/2}\coth s^{1/2})} \tag{30}$$

Approximation of the hyperbolic functions for large values of τ followed by substitution into Eqn. 22 gives on inversion

$$M_t = M_\infty\left\{\left[1 - \frac{\gamma\exp(-\beta\tau) + \beta\exp(-\gamma\tau)}{\gamma - \beta}\right] - V(1 - \exp(-\beta\tau))\right\} \tag{31}$$

where $\beta = 3\omega(3 + \omega)$ and M_∞ is the total amount of drug available in the vehicle at $t = 0$.

(ii) $u < K$. Eqn. 17 is solved with the boundary conditions 15 and 29 and gives

$$M_t = M_\infty\omega\gamma\mathcal{L}^{-1}\left[s(s + \gamma)(s + \kappa)^{1/2}\sinh(s + \kappa)^{1/2} \times \left\{1 + \omega(s + \kappa)^{-1/2}\coth(s + \kappa)^{1/2}\right\}\right]^{-1} \tag{32}$$

Approximating the hyperbolic functions, as before, and inverting, produces the following expression for M_t

$$M_t = M_\infty\left(\frac{\omega}{\kappa+\beta}\right)\left\{1 - \frac{\gamma \exp[-(\kappa+\beta)\tau] + (\kappa+\beta)\exp(-\gamma\tau)}{\gamma-(\kappa+\beta)}\right\} \tag{33}$$

(iii) Special cases. There are two subdivisions of Case B where: (a) $\gamma = \beta$, $(u > K)$; and (b) $\gamma = (\kappa+\beta)$, $(u < K)$. This essentially corresponds to the cases where: (a) depletion and capillary uptake kinetics are equal; and (b) depletion kinetics are equal to the sum of capillary uptake and enzymatic degradation. The correct expressions for these two special cases are respectively given by Eqns. 34 and 35. Case Bi (a):

$$M_t = M_\infty[(1-V)(1-\exp(-\gamma\tau)) - \tau\gamma\exp(-\gamma\tau)] \tag{34}$$

Case Bii (b):

$$M_t = M_\infty\beta\gamma^{-1}[1-(1+\gamma\tau)\exp(-\gamma\tau)] \tag{35}$$

Discussion

We now use the various equations derived to plot release profiles for the different cases considered. In Fig. 2 we present the results for Case A. The profiles are

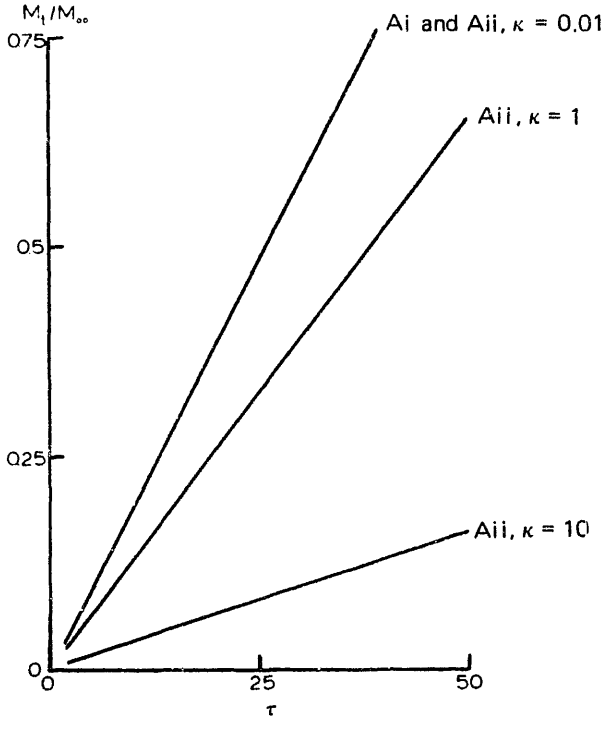

Fig. 2. Release profiles for Cases Ai and Aii as given by Eqns. 26 and 28.

essentially linear with τ as would be expected from the forms of Eqns. 26 and 28. To obtain these curves we have used a value for ω of 2×10^{-2} (Hadgraft, 1979), values of V in the range 0.01–0.95 and κ values between 0.01 and 10. The curve shown for Case Ai corresponds to $V = 0.5$ and is correct over the whole range of V values to within 5% for $\tau > 10$. For Case Aii the release profiles are sensitive to changes in κ as illustrated; this is consistent with the $(2 + \kappa)$ term premultiplying τ in Eqn. 28.

Fig. 3A, B and C show the profiles for Case Bi (Eqn. 31) where we indicate the relative effects of changing γ and V with β maintained constant at 2×10^{-2}. We observe that the faster drug is depleted from the skin surface, the more rapidly is the maximum value of M_t/M_∞, i.e. $(1 - V)$, reached.

Corresponding release profiles for Case Bii (Eqn. 33) are presented in Fig. 4A, B and C. For $\beta = 2 \times 10^{-2}$ again we show the manner in which release is modified by

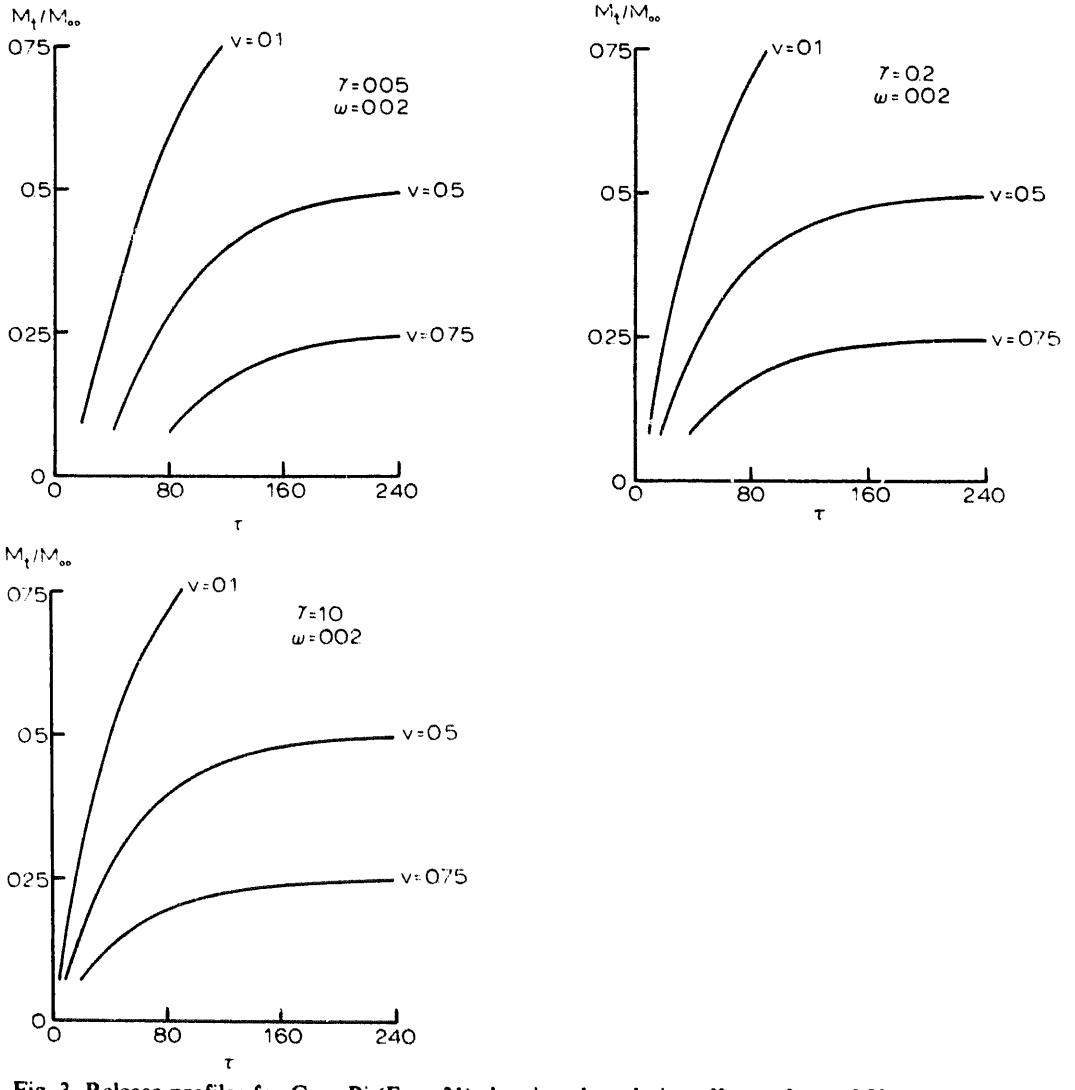

Fig. 3. Release profiles for Case Bi (Eqn. 31) showing the relative effects of γ and V.

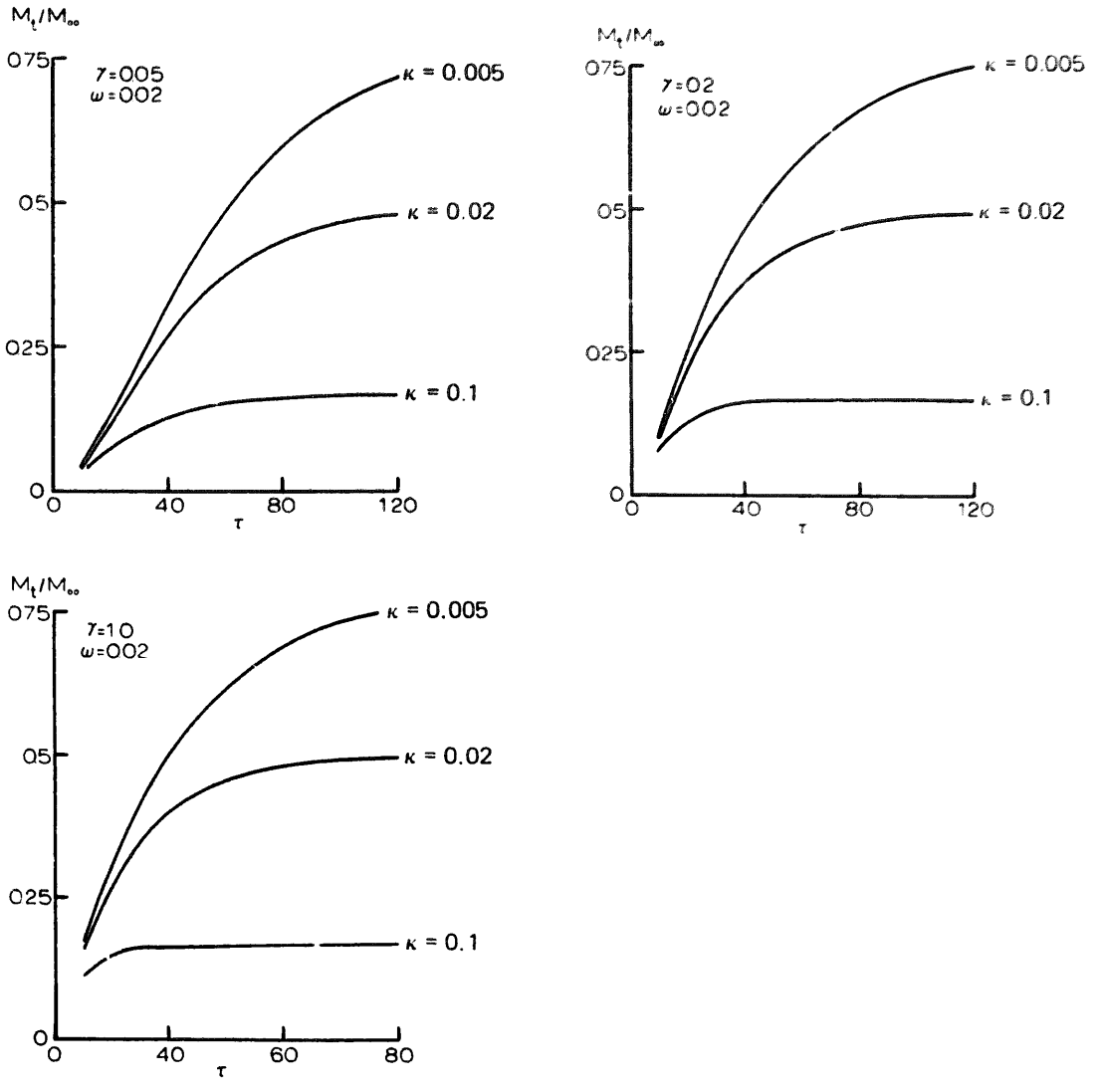

Fig. 4. Release profiles for Case Bii (Eqn. 33) showing the relative effects of γ and κ.

alterating γ and κ. For the higher κ values it is seen that a significantly large amount of drug is metabolized before it reaches the capillary network. At very long times, the ratio M_t/M_∞ tends to a limiting value of $\omega/(\kappa + \beta)$ as predicted by Eqn. 33. As for Case Bi, the greater the value of γ the faster is the limiting value of M_t/M_∞ reached.

The results for the special case solutions, Bi (a), Eqn. 34 and Bii (b), Eqn. 35, are illustrated in Figs. 5A, B and 6A, B, respectively. In the former case release profiles are shown for two values of γ and different values of V. It is apparent that the magnitude of γ is important in determining how quickly the limiting value of M_t/M_∞ is reached. For $\gamma = 0.02$, the ratio reaches 95% of its final value by $\tau \simeq 280$, whereas for $\gamma = 0.1$ the corresponding τ is approximately 50. In Case Bii (b) a similar

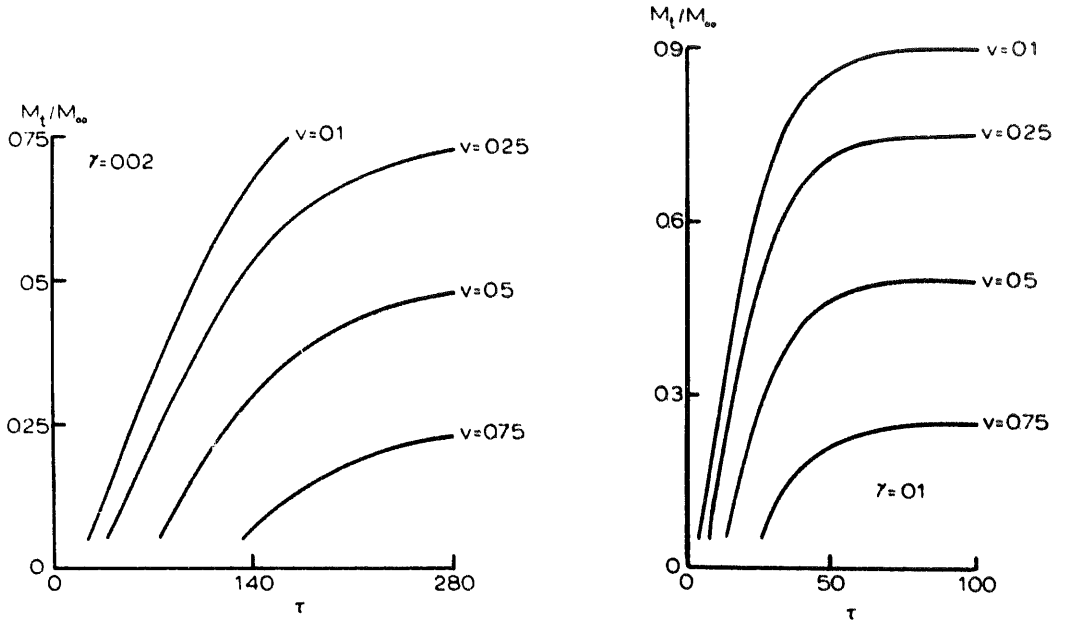

Fig. 5. Release profiles for Case Bi (a) (Eqn. 34) showing the effects of γ and V.

pattern of behaviour is observed and Fig. 6A and B show the effect of varying β for two fixed values of γ.

The metabolic activity of the skin has been shown to be high (Wester and Noonan, 1980). For many drugs that are slowly absorbed by the skin a first-order description of cutaneous metabolism is adequate. On the other hand, for compounds which may be absorbed rapidly in relatively large amounts, saturation of the metabolic processes may be possible. In this event, a different kinetic approach to evaluate the amount of drug reaching the systemic circulation is necessary. In this

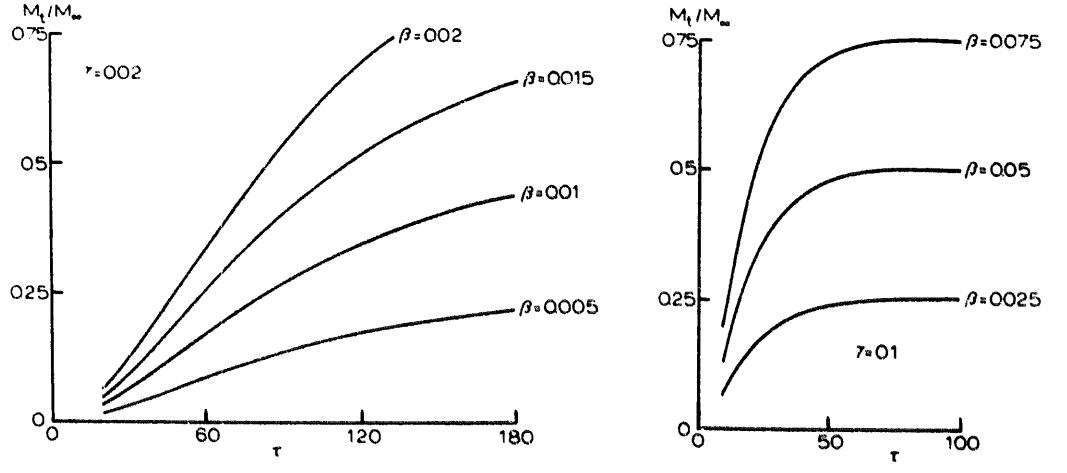

Fig. 6. Release profiles for Case Bii (b) (Eqn. 35) showing the effects of β and γ.

paper we have shown how these two extreme cases may be treated by considering two classical approximations to Michaelis-Menten kinetics. The relatively straightforward equations derived will be useful in predicting the significance of the percutaneous metabolism of drugs and prodrugs and in determining their overall fate.

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