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CALCULATIONS OF DRUG RELEASE RATES FROM CONTROLLED RELEASE DEVICES. THE SLAB

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SUMMARY

Mathematical expressions have been derived to describe rates of drug release from controlled release devices. The devices have been limited to those of a non-degradable nature and which have the geometry of a plane sheet. Full solutions to Ficks' Laws of diffusion have been compared with the approximate solutions in general use. Multiphase layers have been considered and equations show the effect of slow interfacial transfer between these layers.

INTRODUCTION

During recent years much work has been concentrated on the development of controlled release devices. These drug delivery systems provide release rates which are determined by the device itself and should thus be insensitive to biological variations. One of the most successful means of producing such a dosage form has been to use the diffusion process as the rate-determining step.

It is the purpose of this paper to present a simple account of the solutions to the diffusion equations used in this type of problem and to compare some of the complete solutions with the approximate solutions which are in common use. Initially, devices in which there is only one phase present, will be considered. For such a configuration the solutions to Fick's Laws of diffusion are simplified and this provides an easier understanding of the mathematics involved.

In the second half of the paper more complex multiphase systems will be considered in which the drug crosses an organic–aqueous interface. The effects of slow interfacial rate constants will be discussed.

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Two major categories of release device are available. First when the slab is full of drug (the burst effect) and second when the sheet is initially free of drug but supplied by a drug reservoir (the lag effect). Simultaneous dissolution of the inert matrix will not be considered and difussion coefficients will be considered to be concentration independent.

(1) THE BURST EFFECT

Fick's second law of diffusion is expressed mathematically as:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \tag{1}$$

where c is concentration, x is distance, t is time and D is diffusion coefficient. Equation 1 can be stated in terms of dimensionless variables:

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

in which

$$u = c/c_0 \tag{3}$$

$$\chi = x/\ell \tag{4}$$

$$\tau = Dt/\ell^2 \tag{5}$$

and c_0 is the initial concentration of drug in the sheet and ℓ is the thickness of the sheet.

The concentration profiles of the drug in the sheet at different times are shown in Figs. 1 and 2. It is now necessary to define the boundary conditions for these types of experiments.

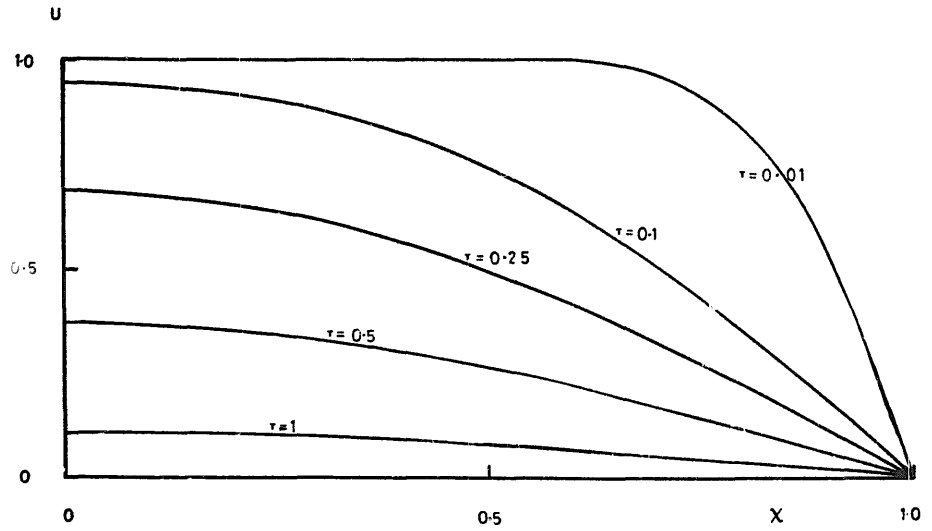

Fig. 1. Concentration profile in the sheet for Case IB calculated using Eqn. 62 given in the Appendix.

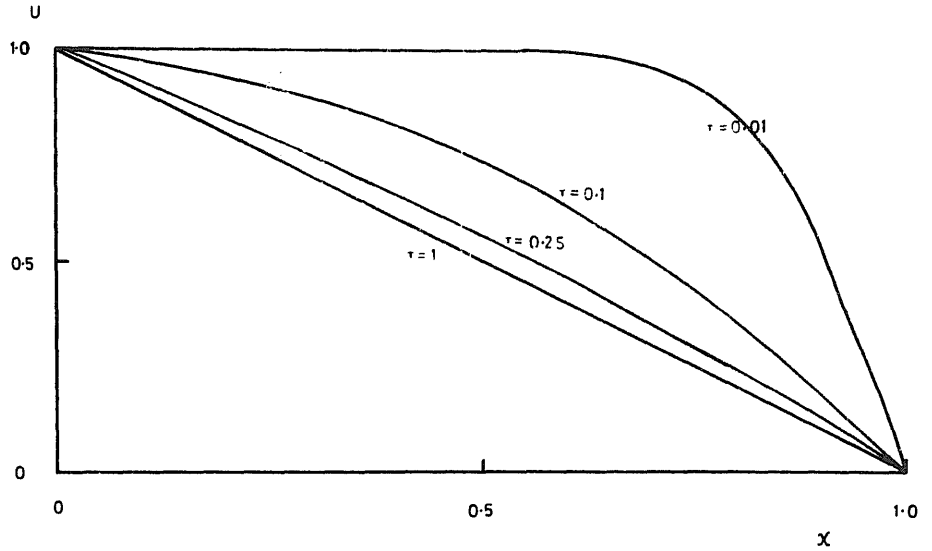

Fig. 2. Concentration profile in the sheet for Case IIB calculated using Eqn. 64 given in the Appendix.

(a) Drug present exists only in the sheet, no reservoir.

In this case the following boundary conditions exist

$$\tau = 0\,, \quad u = 1 \tag{6}$$

$$\chi = 1\,, \quad u = 0 \tag{7}$$

$$\chi = 0\,, \quad \left(\frac{\partial u}{\partial \chi}\right)_0 = 0 \tag{8}$$

Equation 7 shows that the receptor phase is acting as a perfect sink by maintaining zero concentration at the outside surface of the sheet. The boundary condition expressed in Eqn. 8 shows that there is no drug reservoir at the inner surface of the slab.

Equation 2 may be solved by a variety of techniques but the method used in this paper is to use Laplace transforms.

$$s\bar{u} - 1 = \frac{\partial^2 \bar{u}}{\partial \chi^2} \tag{9}$$

This differential equation has the general solution

$$\bar{u} = A \cosh\sqrt{s}\,\chi + B \sinh\sqrt{s}\,\chi + \frac{1}{s} \tag{10}$$

Differentiating

$$\frac{\partial \bar{u}}{\partial \chi} = \sqrt{s}\, A \sinh\sqrt{s}\,\chi + \sqrt{s}\, B \cosh\sqrt{s}\,\chi \tag{11}$$

The boundary conditions in Eqns. 7 and 8 may now be substituted to eliminate the coefficients A and B from Eqns. 10 and 11. Thus,

$$\frac{\partial \bar{u}}{\partial \chi} = -s^{-1/2} \operatorname{sech}\sqrt{s} \sinh\sqrt{s}\,\chi \tag{12}$$

The total amount of drug that has passed through the plane $\chi = 1$ at time t, M_t, is given by

$$M_t = -DA \int_0^t \left(\frac{dc}{dx}\right)_{x=\ell} dt \tag{13}$$

In terms of the dimensionless variables defined in Eqns. 3, 4 and 5

$$M_t = -Alc_0 \int_0^\tau \left(\frac{\partial u}{\partial \chi}\right)_1 d\tau \tag{14}$$

But Alc_0 is the total amount of diffusant contained initially in the sheet and is thus the amount that would be released after an infinite amount of time, M_∞. Substituting Eqn. 12 when $\chi = 1$

$$M_t = M_\infty \int_0^\tau \ell^{-1}\, s^{-1/2} \tanh\sqrt{s}\, d\tau \tag{15}$$

The inverse transform in this equation is given by Spiegel,

$$\ell^{-1}\, s^{-1/2} \tanh\sqrt{s} = 2 \sum_{n=1}^{\infty} (-1)^{n-1} \exp\left(\frac{-(2n-1)^2\pi^2\tau}{4}\right) \frac{\sin(2n-1)\tau}{2} \tag{16}$$

Integrating between the limits 0 and τ

$$M_t = M_\infty \left[1 - \frac{8}{\pi^2}\left(\sum_{n=1}^{\infty} \frac{1}{(2n-1)^2} \exp\left(-\frac{(2n-1)^2\pi^2\tau}{4}\right)\right)\right] \tag{17}$$

This is the full solution for the burst effect without a reservoir and may be applied over the complete time range of an experiment. Simplifications are possible by making approximations which are valid for the initial and final periods of release, i.e. at short and long times.

(i) Short time approximation

Equation 15 can be integrated with respect to τ by division by the Laplace time variable s, thus

$$M_t = M_\infty \ell^{-1}\, s^{-3/2} \tanh\sqrt{s} \tag{18}$$

At short times $\tau << 1$ $s >> 1$ and $\tanh\sqrt{s} \approx 1$

$$M_t \approx M_\infty \ell^{-1} s^{-3/2} \tag{19}$$

$$\approx 2M_\infty(\tau/\pi)^{1/2} \tag{20}$$

(ii) Long time approximation

At long times $s << 1$ and $\tanh\sqrt{s} \approx \sqrt{s}$ (2)

$$M_t = M_\infty \ell^{-1} s^{-1} \tag{21}$$

$$M_t = M_\infty \tag{22}$$

and all the drug that is contained in the slab is released.

(b) Drug reservoir maintained at inner slab surface.

The problem is similar to that described above but the boundary conditions are different. Equation 10 describes the variation in $\bar{u}$ with χ and s but the coefficients A and B are determined by using the boundary conditions in Eqn. 7 and:

$$\chi = 0, u = 1, \bar{u} = 1/s \tag{23}$$

Equation 23 gives the requirement that a constant reservoir is maintained at the inner surface of the sheet. Thus the equations derived here are only applicable where there is insignificant depletion of drug concentration in the reservoir.

Equation 11 with conditions 7, 23 and $\chi = 1$ gives

$$\left(\frac{\partial \bar{u}}{\partial \chi}\right)_1 = -s^{-1/2} \coth\sqrt{s} \tag{24}$$

Substitution of Eqn. 24 into Eqn. 14 followed by the inversion of the transform (Spiegel), gives

$$M_t = M_\infty\left[\tau + \tfrac{1}{3} + \frac{2}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp(-n^2\pi^2\tau)\right] \tag{25}$$

In this case M_∞ is not a finite quantity of drug since c_0 is the concentration contained in the reservoir which is not being depleted.

The short time approximation for this configuration is the same as Eqn. 20 since $\coth\sqrt{s} \approx 1$ for $s \gg 1$. At long times, the exponential term in Eqn. 25 will become very small and

$$M_t = M_\infty(\tau + 1/3) \tag{26}$$

or

$$M_t = \frac{Ac_0Dt}{\ell} + \frac{A\ell c_0}{3} \tag{27}$$

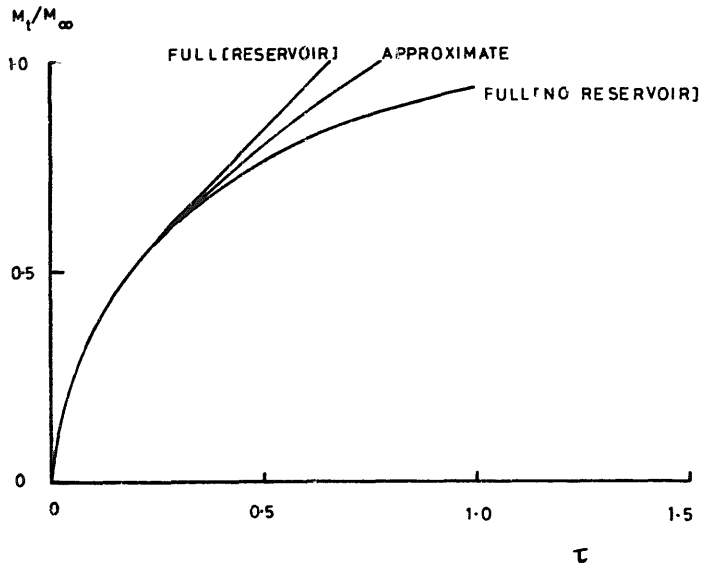

Fig. 3. Comparison of full and approximate solutions for Cases IB and IIB using Eqns. 17, 20 and 25.

The first term in Eqn. 27 expresses the accumulated material from the steady state flux (Fick's 1st law) and the second term gives the displacement due to the initial non-steady state period.

Comparision of full and approximate solutions

Fig. 3 shows theoretical curves plotted using Eqns. 17, 20 and 25. The variation of the ratio M_t/M_∞ with τ is shown. The graphs show that the approximate solution, Eqn. 20 is very good at describing release rates up to the time when 60% of the drug contained in the sheet has been released. This corresponds to a value of $\tau \sim 0.3$. It is thus possible to calculate how long the controlled release device will release drug at a rate proportional to $t^{1/2}$ from a knowledge of the diffusion coefficient of the drug and the thickness of the slab.

It is interesting to note that many authors have used expressions similar to Eqn. 20 to explain drug release rates from ointments and creams (e.g. Chowhan and Pritchard, 1975; Ostrenga et al. 1971). In these circumstances the full diffusion equation has been approximated to that given in Eqn. 20 and the results show that the experimental release rates are predicted satisfactorily by this simplified formula.

(2) THE LAG EFFECT

The concentration profiles at different τ values for lag experiments are shown in Fig. 4. At a value of $\tau = 1$, the concentration drop across the slab is linear and steady state diffusion has been established. The rates of transfer are given by Fick's 1st law.

In order to understand the rates of diffusion before the steady state exists it is necessary to solve Eqn. 2, Fick's 2nd law of diffusion expressed in dimensionless variables. For the lag experiments a new set of boundary conditions must be applied. The appropriate

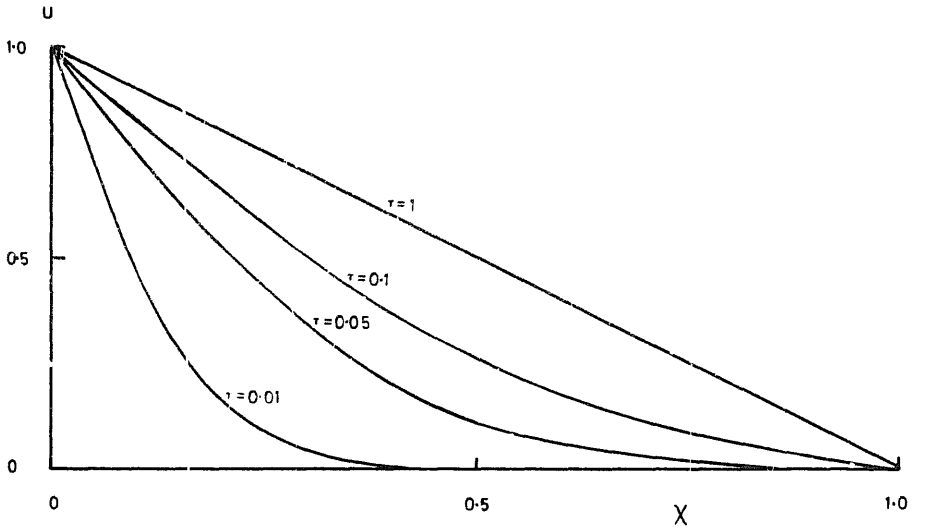

Fig. 4. Concentration profile in the sheet for Case IL calculated using Eqn. 66 given in the Appendix.

conditions are:

$$\tau = 0, \quad u = 0 \tag{28}$$

$$\chi = 0, \quad u = 1, \bar{u} = 1/s \tag{29}$$

$$\chi = 1, \quad u = 0, \bar{u} = 0 \tag{30}$$

Equations 29 and 30 are the conditions used for the burst effect with reservoir (Eqns. 7 and 23) and their significance has been discussed. The important difference is condition 28 which shows that initially the sheet is free of drug. Taking the Laplace transform of Eqn. 2 and using 28,

$$s\bar{u} = \frac{\partial^2 \bar{u}}{\partial \chi^2} \tag{31}$$

which has the general solution

$$\bar{u} = A \cosh\sqrt{s}\,\chi + B \sinh\sqrt{s}\,\chi \tag{32}$$

Using the same techniques as previously, the coefficients A and B may be eliminated and

$$\left(\frac{\partial \bar{u}}{\partial \chi}\right)_1 = s^{-1/2} \sinh\sqrt{s} - s^{-1/2} \cosh\sqrt{s} \coth\sqrt{s} \tag{33}$$

Substituting into Eqn. 14 to find M_t

$$M_t = M_\infty \int_0^\tau \mathcal{L}^{-1}\, s^{-1/2} \operatorname{cosech}\sqrt{s}\, d\tau \tag{34}$$

Spiegel gives the inverse transform

$$\mathcal{L}^{-1}\frac{\cosh x\sqrt{s}}{\sqrt{s}\sinh a\sqrt{s}} = \frac{1}{a} + \frac{2}{a}\sum_{n=1}^{\infty}(-1)^n \exp(-n^2\pi^2\tau) \tag{35}$$

Using values a = 1, x = 0,

$$\mathcal{L}^{-1}\, s^{-1/2}\,\mathrm{cosech}\sqrt{s} = 1 + 2\sum_{n=1}^{\infty}(-1)^n \exp(-n^2\pi^2\tau) \tag{36}$$

Integrating between the limits 0 and τ gives

$$M_t = M_\infty\left[\tau - \tfrac{1}{6} - \frac{2}{\pi^2}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2}\exp(-n^2\pi^2\tau)\right] \tag{37}$$

(i) Short time approximation

At short times $\tau \ll 1$, $s \gg 1$ and the cosech $\sqrt{s}$ term in Eqn. 34 may be approximated (Abramowitz and Stegun, 1970, p. 85),

$$\mathrm{cosech}\sqrt{s} \approx 2\exp(-\sqrt{s}) \tag{38}$$

Thus from Eqn. 34

$$M_t = 2M_\infty \mathcal{L}^{-1}\, s^{-3/2}\exp(-\sqrt{s}) \tag{39}$$

Inverting (Abramowitz and Stegun, 1970, p. 1026) gives an expression for M_t in terms of a repeated integral of the error function complement:

$$M_t = 4M_\infty\sqrt{\tau}\ \mathrm{ierfc}(1/2\sqrt{\tau}) \tag{40}$$

It is possible to express ierfc (z) as a power series (Abramowitz and Stegun, 1970, p. 300), and, taking the first term only in this expansion

since $\tau \ll 1$, $z = 1/2\sqrt{\tau} \gg 1$,

$$\mathrm{ierfc}\ z \approx \frac{2}{\sqrt{\pi}}\frac{\exp(-z^2)}{(2z)^2} \tag{41}$$

Hence,

$$M_t = 8M_\infty\pi^{-1/2}\tau^{3/2}\exp(-1/4\tau) \tag{42}$$

Similar expressions have been obtained by Fourier Analysis (Rodgers et al. 1954; Short et al. 1970).

(ii) Long time approximations

At long times $s \ll 1$ and cosech $\sqrt{s}$ may be approximated (Abramowitz and Stegun, 1970, p. 85)

$$\text{cosech}\sqrt{s} \approx s^{-1/2} - s^{1/2}/6 \tag{43}$$

From Eqn. 34

$$M_t = M_\infty \mathcal{L}^{-1}(s^{-2} - (6s)^{-1}) \tag{44}$$

$$M_t = M_\infty(\tau - 1/6) \tag{45}$$

This is the same as the first two terms in the bracketed expression in Eqn. 37. In this equation the long time approximation is given since the exponential term becomes negligible.

Comparison of full and approximate solutions

Fig. 5 shows the theoretical release curves from plotting Eqns. 37 and 42. The short time approximation deviates from the full expression at fairly short times and remains within 10% of the true value up to $\tau \sim 2 \times 10^{-2}$. At $\tau = 10^{-1}$ there is a 50% error. The agreement is not as good as that for the burst effect which is caused by taking only the first term in the ierfc expansion. For work where an accurate expression is required, Eqn. 42 should only be used for very small values of τ.

Lag time experiments have been used to measure diffusion coefficients in excised skin (Foreman and Kelly, 1976; Foreman et al., 1977). In this work computer simulations using the full expression, Eqn. 37, were used successfully. Little data to date has

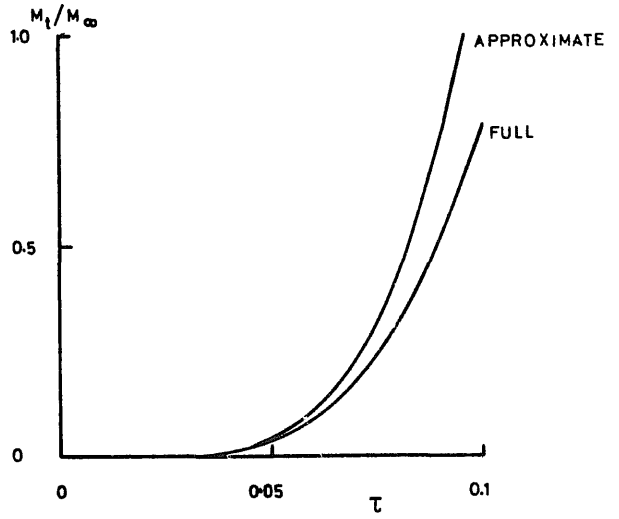

Fig. 5. Comparison of the full and approximate solutions for short time experiments in Case IL (Eqns. 37 and 42).

been analysed using the approximate solution, Eqn. 42, apart from the two references previously cited.

(3) EFFECT OF INTERFACIAL TRANSFER KINETICS ON RATES OF RELEASE

Usually it has been assumed that in a two phase system, equilibration by partitioning is fairly rapid. However experiments with such systems (Albery et al., 1974, 1976) have shown that there are significant free energy barriers for transport across a liquid–liquid interface. For drug release from multiphase devices it is necessary to investigate the significance of interfacial kinetics on release rates.

As in the previous section it is more convenient to use dimensionless variables for the solution of the differential equations. The same notation will be used for the cases involving interfacial transfer but a new normalised variable is introduced, κ, which describes the rate of transport across the interface. For an interfacial rate constant k_I/ $m \cdot s^{-1}$, κ is defined

$$\kappa = k_I \ell / D \qquad (46)$$

where k_I is the process of transfer of the substrate from the organic to the aqueous environment.

$$C_{organic} \underset{k_{-I}}{\overset{k_I}{\rightleftharpoons}} C_{aqueous} \qquad K$$

For transport from a laminated sheet, the different combinations of burst (B) and lag (L) effects and position(s) of the interface(s) are shown in Table 1. Cases IB, IIB and IL are the single phase systems discussed initially. The rest of the cases shown in Table 1 involve at least one two phase boundary.

The solutions to the diffusion equations for the remaining cases (III B, L; IV B, L; IIL) are found by using the techniques described in the previous section. The different

TABLE 1

POSITIONS OF THE PHASES IN THE DIFFERENT CASES

Case	Reservoir	Sheet	Receptor
	(Concentrations in compartments at $\tau = 0$)		
IB	–	aqueous (c_0)	aqueous (0)
IIB	aqueous (c_0)	aqueous (c_0)	aqueous (0)
IIIB	–	organic (c_0) [a]	aqueous (0)
IVB	organic (c_0)	organic (c_0) [a]	aqueous (0)
IL	aqueous (c_0)	aqueous (0)	aqueous (0)
IIL	organic (c_0)	organic (0) [a]	aqueous (0)
IIIL	organic (c_0) [a]	aqueous (0)	aqueous (0)
IVL	aqueous (c_0) [a]	organic (0) [a]	aqueous (0)

[a] Denotes the location of an interface

TABLE 2

THE BOUNDARY CONDITIONS FOR THE DIFFERENT CASES

Case	$\tau = 0$	$\tau = 0$	$\chi = 1$	$(\partial u/\partial \chi)_0$	$(\partial u/\partial \chi)_1$
IB	$u = 1$	–	$u_1 = 0$	0	–
IIB	$u = 1$	$u_0 = 1$	$u_1 = 0$	–	–
IIIB	$u = 1$	–	–	0	$-\kappa u_1$
IVB	$u = 1$	$u_0 = 1$	–	–	$-\kappa u_1$
IL	$u = 0$	$u_0 = 1$	$u_1 = 0$	–	–
IIL	$u = 0$	$u_0 = 1$	–	–	$-\kappa u_1$
IIIL	$u = 0$	–	$u_1 = 0$	$(\kappa u_0/K) - \kappa$	–
IVL	$u = 0$	–	–	$\kappa u_0 - \kappa/K$	$-\kappa u_1$

TABLE 3

VALUES OF $\bar{f}(s)$ FOR THE DIFFERENT CASES

Case	Burst effect (B)	Lag effect (L)
I	$\tanh \sqrt{s}/s^{3/2}$	$s^{-3/2}$ cosech $\sqrt{s}$
II	$s^{-3/2}$ cotanh $\sqrt{s}$	$\kappa/s^{3/2} \sinh \sqrt{s}(\kappa + \sqrt{s}$ cotanh $\sqrt{s})$
III	$\kappa \tanh \sqrt{s}/s^{3/2}$ $(\sqrt{s} \tanh \sqrt{s} + \kappa)$	$\kappa/s^{3/2} \cosh \sqrt{s}(\sqrt{s} + \kappa K^{-1}$ cotanh $\sqrt{s})$
IV	$\kappa/s^{3/2}(\sqrt{s} + \kappa \tanh \sqrt{s})$	$1/Ks^{3/2} \sinh \sqrt{s}\left(1 + \frac{2\sqrt{s}}{\kappa \tanh \sqrt{s}} + \frac{s}{\kappa^2}\right)$

TABLE 4

APPROXIMATION OF THE HYPERBOLIC FUNCTIONS USED IN LONG AND SHORT TIME SOLUTIONS

Hyperbolic function	Short times $\tau << 1$	Long times $\tau >> 1$
cosh z	exp(z)/2	1
sinh z	exp(z)/2	z
tanh z	1	z

TABLE 5

SOLUTIONS FOR THE DIFFERENT CASES WHEN INTERFACIAL BARRIERS ARE NEGLIGIBLE

Case	Burst effect (B)	Lag effect (L)
I	IB	IL
II	IIB	IL
III	IB	K x IL
IV	IIB	IL/K

boundary conditions which apply to the cases are summarized in Table 2. Solutions for all the cases are given in Table 3. In this table, values of $\bar{f}(s)$ are shown where

$$M_t = M_\infty \mathcal{L}^{-1} \bar{f}(s) \tag{47}$$

Simple solutions for M_t do not exist and it is easier to consider different approximations for short and long time experiments and for large and small values of κ. The different approximations used for the hypobolic terms are summarized in Table 4.

(i) Solutions for fast interfacial transfer.

For large values of κ where the interfacial transfer term is negligble the solutions are simple functions of the single phase results. The solutions are summarized in Table 5. For the two cases where there is an interface established at the inner sheet surface the solution involves the partition coefficient K.

(ii) Solutions for slow interfacial transfer.

(a) Class B, the burst effect. Cases IIIB and IVB for short times, $s \gg 1$, reduce to the same solution:

$$\bar{f}(s) = \frac{K}{s^2} \tag{48}$$

Thus

$$M_t = M_\infty K T \tag{49}$$

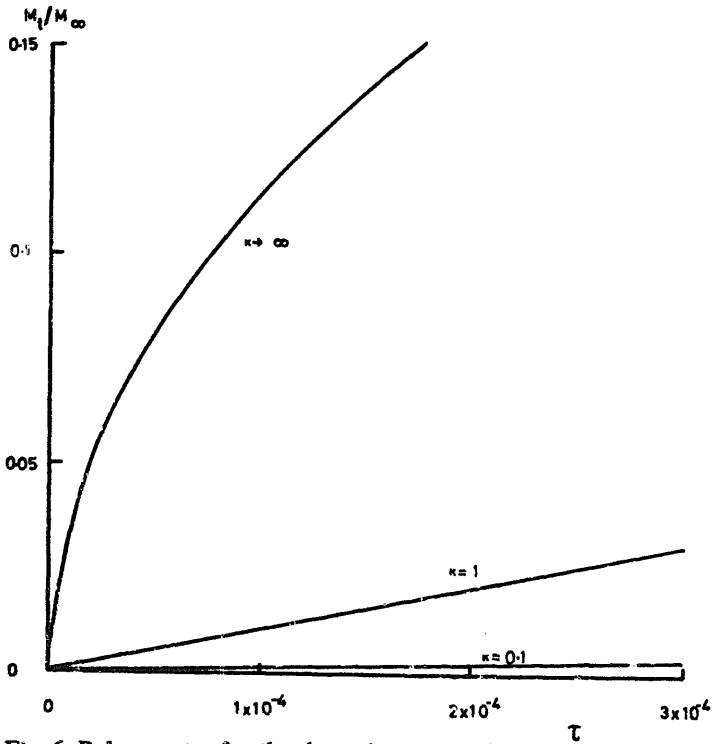

Fig. 6. Release rates for the short time approximations in Cases IIIB and IVB (Eqn. 49).

The rate of release for these types of devices is independent of time, i.e. a zero order process. This is shown in Fig. 6. Also plotted on this graph is the rate of release of material from a similar device in which there is no interfacial barrier. The figure shows that for this case a much faster release rate is given which is not zero order.

Considering long time experiments when $\tau \gg 1$, case IIIB gives the approximation:

$$\bar{f}(s) = \kappa/s(s + \kappa) \tag{50}$$

which, when inverted, gives

$$M_t = M_\infty(1 - \exp(-\kappa\tau)) \tag{51}$$

The slow interfacial rate constant has an exponential effect on the cumulative amount of drug released. Fig. 7 shows this exponential increase in M_t with time. For values of $\kappa \gg 1$, the exponential term is very small and interfacial barriers become insignificant. A very significant effect is observed when $\kappa = 0.1$ where release rates are markedly affected over a wide time range.

Case IVB is interesting in that the same release characteristics apply for both long and short times. Equation 49 holds for all values of τ which is caused by the very slow release rate from a reservoir whose concentration is undepleted.

(b) Class L, the lag effect. The lag expressions exist where a reservoir of drug is maintained in the device which does not deplete significantly. Considering the short time cases, the two configurations IIL and IIIL reduce to the same approximation

$$\bar{f}(s) = 2\kappa \exp(-\sqrt{s})/s^2 \tag{52}$$

Substitution into Eqn. 47 and inversion (Abramowitz and Stegun, 1970 p. 1026) gives:-

$$M_t = 2M_\infty\kappa\tau \operatorname{erfc}(1/2\sqrt{\tau}) \tag{53}$$

Erfc (z) may be expressed as an asymptotic series (Abramowitz and Stegun, 1970 p. 298)

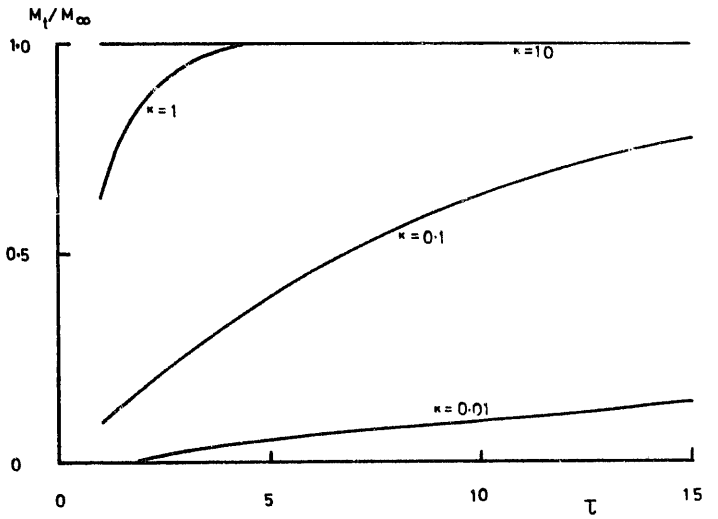

Fig. 7. Long time release rates for Case IIIB calculated using Eqn. 51.

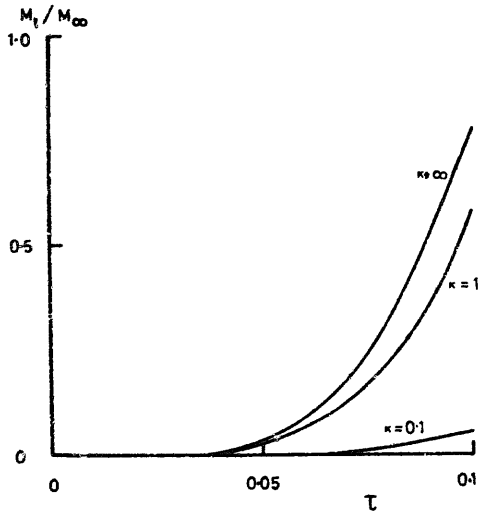

Fig. 8. Release rate at short times for cases IIL and IIIL, Eqn. 55. A plot of the full Eqn. 37, for the case where no interfacial barriers exist, is also shown for comparison.

and the first term taken as an approximation since $(1/2\sqrt{\tau}) \gg 1$;

$$\text{erfc}(z) \approx \pi^{-1/2}\, z^{-1}\, \exp(-z^2) \tag{54}$$

Hence:

$$M_t = 4M_\infty \pi^{-1/2} \tau^{3/2} \kappa \exp(-1/4\tau) \tag{55}$$

Equation 55 is plotted in Fig. 8 with κ values of 1.0 and 0.1. Comparison is possible with the full diffusion solution, Eqn. 37, in which there is no interfacial term ($\kappa \to \infty$). With $\kappa = 1$ there is a slight reduction in the amount of drug released but with $\kappa = 0.1$ there is a very significant decrease.

For case IVL the first two terms in the bracketed expression (Table 3) are insignificant at short times,

$$\bar{f}(s) \approx 2\kappa^2 K^{-1} s^{-5/2} \exp(-\sqrt{s}) \tag{56}$$

Inverting (Abromowitz and Stegun, 1970, p. 1026),

$$M_t \approx 16 M_\infty K^{-1} \kappa^2 \tau^{3/2} i^3\, \text{erfc}(1/2\sqrt{\tau}) \tag{57}$$

The integrated error function may be approximated since $(1/2\sqrt{\tau}) \gg 1$ (Abramowitz and Stegun, 1970, p. 300),

$$M_t \approx 32 M_\infty \pi^{-1/2} K^{-1} \kappa^2 \tau^{7/2} \exp(-1/4\tau) \tag{58}$$

This expression has been plotted in Fig. 9 for different values of κ but maintaining a

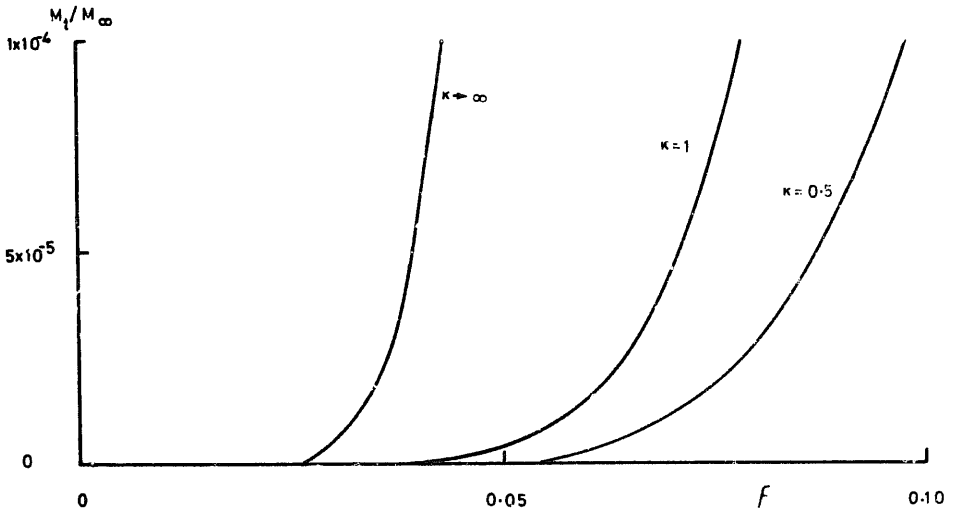

Fig. 9. Short time approximation for Case IVL (Eqn. 58).

partition coefficient of unity. A change in the partition coefficient will have a linear effect on the amount of drug released. Interfacial rate constants have a squared effect on the release rate and thus show a considerable effect.

The long time approximations for cases IIL and IIIL reduce to the same solution as cases IIB and IVB; the release rate is zero order and given by Eqn. 49. A linear plot is

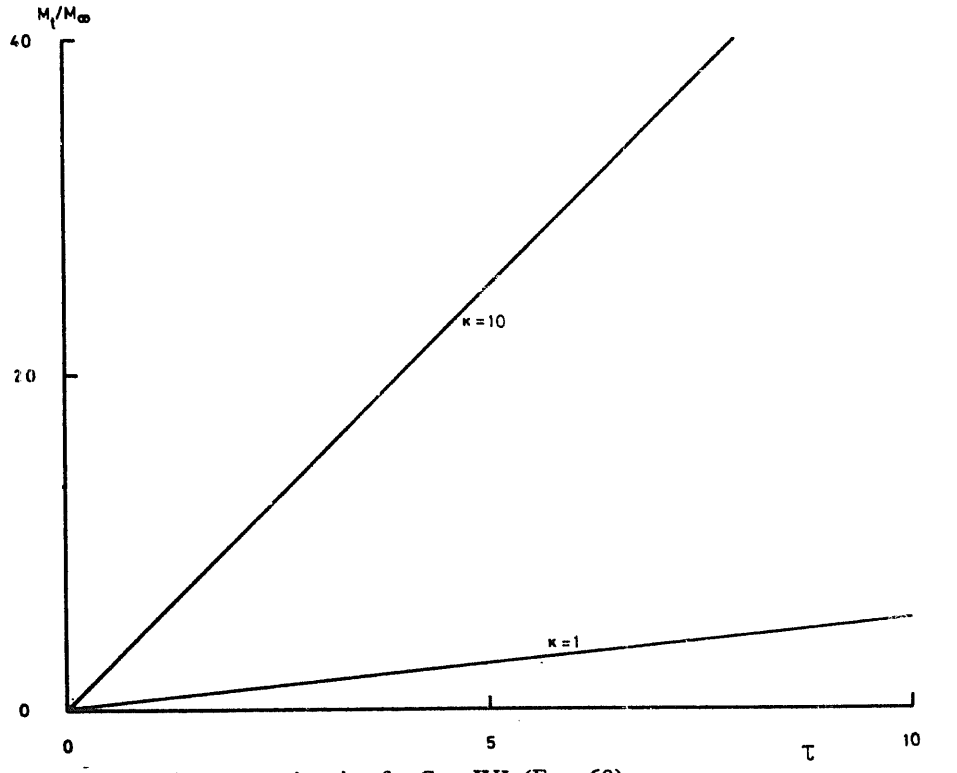

Fig. 10. Long time approximation for Case IVL (Eqn. 60).

obtained as shown in Fig. 6.

Case IVL is more complex. From the solution in Table 3,

$$\bar{f}(s) \approx \frac{\kappa^2}{Ks^2(s + 2\kappa)} \tag{59}$$

which may be inverted and substituted into Eqn. 47 to give

$$M_t = \frac{M_\infty \kappa}{2K} \left[\tau + \frac{1}{2\kappa} [1 - \exp(-2\kappa\tau)]\right] \tag{60}$$

Fig. 10 shows this release rate for different values of the interfacial rate constant but using a partition coefficient of unity. This case is similar to the short time approximation for IVL in which the partition coefficient has a linear effect on the release of drug. The exponential term ($\exp(-2\kappa\tau)$) has little effect at long times and a zero order process is observed.

DISCUSSION

The expressions derived for the different systems in which there are no phase barriers are very familiar and have been treated by many authors (e.g. Crank, 1975; Carslaw and Jaeger, 1959). The derivation of these cases has been given to show one method of solving Fick's laws of diffusion. The mathematical techniques illustrated have then been applied to more complicated systems where interfacial transport is included.

The results show that interfacial kinetics can have a marked effect on the rates of drug release. A typical value of $\kappa = 1$ could dominate transport characteristics. This normalized variable is related to k_I, the interfacial rate constant by Eqn. 46. From previous work (Albery et al., 1974, 1976) typical values of k_I have been determined, these are of the order of 10^{-5} m s^{-1}. The diffusion coefficient, D, in an organic liquid such as isopropyl myristate is approximately 10^{-10} m^2 s^{-1}. For a κ value of unity this would give ℓ values of 10^{-5} m. The thickness of the organic laminate in the controlled release device would have to be of the order of 10 μm for interfacial kinetics to dominate over diffusion. However some interfacial rate constants are smaller and the diffusion coefficients larger than the typical values quoted above, in these cases the thickness of the organic layer may be larger and the interfacial kinetics still play a dominant role.

For the cases IIIB (long times) and IVL (short times) where the κ terms are, respectively, exponential and squared, the transfer kinetics will exert a larger effect and it would be expected that they will dominate over a wider range of conditions.

In some cases of pharmaceutical importance the release rate/time graphs exhibit a sigmoid profile. This is a result of an initial lag effect followed by a pseudo steady state period. The slowing down at long times is due to depletion when there is only a finite quantity of drug present. It is possible to allow for this effect but the mathematics is complicated and will be considered in a later publication.

The generality of these diffusion equations offers wide applicability. They may be used to interpret the transport of drugs into and out of the skin, which may be regarded as a multiphase laminate. Equally they may be employed in the calculation of gastro-

intestinal absorption rates. In any multiphase system it is important to consider the effects of relatively slow interfacial transfer on total release rates. The barriers should be considered in the design of new drug delivery systems and could be utilized in producing long acting zero order release devices.

APPENDIX

It is interesting to calculate the way in which the concentration varies with time in the sheet. Equations may be easily obtained using those already derived.

The burst effect

(a) No reservoir

Equation 10 shows the way in which the concentration varies with the distance, χ, and the Laplace time variable, s. Substituting the values of A and B

$$\bar{u} = \frac{1}{s} - \frac{\cosh\sqrt{s}\,\chi}{s\cosh\sqrt{s}} \tag{61}$$

This equation is inverted (Spiegel) to give the variation of u with χ and τ,

$$u = \frac{-4}{\pi}\sum_{n=1}^{\infty}\frac{(-1)^n}{(2n-1)}\exp\left(-\frac{(2n-1)^2\pi^2\tau}{4}\right)\cos\left(\frac{(2n-1)\pi\chi}{2}\right) \tag{62}$$

(b) Reservoir present

Using Eqn. 10 with the different boundary condition 23

$$\bar{u} = \frac{1}{s} - \frac{\sinh\sqrt{s}\,\chi}{s\sinh\sqrt{s}} \tag{63}$$

and

$$u = 1 - \chi - \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{(-1)^n}{n}\exp(-n^2\pi^2\tau)\sin(n\pi\chi) \tag{64}$$

The lag effect

The concentration profile for the lag effect is calculated using Eqn. 32 with the coefficients A and B;

$$\bar{u} = \frac{\sinh\sqrt{s}\,(1-\chi)}{s\sinh\sqrt{s}} \tag{65}$$

and

$$u = 1 - \chi + \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{(-1)^n}{n}\exp(-n^2\pi^2\tau)\sin(n(1-\chi)) \tag{66}$$

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