Diffusion Model for Drug Release from Suspensions I: Theoretical Considerations

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Abstract □ A new mathematical model based on physicochemical principles is presented; it does not require a "diffusion layer" for the release of a suspended drug from a semisolid vehicle. This general model has wide range application to systems where release is controlled by the diffusion rate or dissolution rate of a drug. The appropriate mathematical relationships are derived and evaluated. Theoretical drug concentration distributions in the vehicle and a membrane and the predicted cumulative drug mass uptake by blood under specified conditions are presented. The dissolution rate of solid drug in the vehicle markedly influences predicted drug release using the model presented. It is anticipated that the model will stimulate further research to confirm or reject the assumption that the dissolution rate may be slow enough to be important in the systems studied.

Keyphrases □ Diffusion—suspended drug in semisolid vehicle, mathematical model based on physicochemical principles □ Dissolution—suspended drug in semisolid vehicle, mathematical model based on physicochemical principles □ Pharmacokinetic models—diffusion and dissolution of suspended drug in semisolid vehicle □ Drug release—from suspensions, diffusion model based on physicochemical principles □ Suspensions—drug release, diffusion model based on physicochemical principles

Many physical models for diffusion from solutions were defined and the appropriate mathematical equations were presented in standard texts (1–3). The release of drug from a topically applied ointment was considered (4) when the drug was initially uniformly dissolved in a homogeneous base and the rate-controlling step was in either the applied phase or the skin. The theoretical analysis of drug diffusion through emulsion systems was extensively studied and reported (5–8).

Physical models for diffusion of drug from suspension systems were also reported (4, 5, 9). In one case, the suspension was considered as a potential barrier to drug diffusion (5); in others (4, 9), the suspended drug was considered a source of drug supply.

The most widely accepted theory for dissolution rates was proposed by Noyes and Whitney in 1897 and subsequently modified to include the stagnant or unstirred diffusion layer concept of Nernst and Brunner. These and other theories for dissolution models were reviewed previously (10–12).

The purposes of this study were to describe dissolution and diffusion for a suspended drug in a semisolid vehicle in terms of the molecular rates of escape from, and the return to, a particle surface; to present a mathematical model (a set of nonlinear diffusion equations) for the mass transport of the drug through the suspension and a permeable barrier system to a perfect sink; and to solve the appropriate linearized equations for a general least upper bound case as well as for several specific cases.

Consideration is given to the condition where dissolution is either very slow or very fast with respect to diffusion in the continuous phase of the suspension as well as where dissolution and diffusion occur at about the same rate. Special emphasis is placed on the condition of slow dissolution and fast diffusion, because this case is not treated in the literature and the need for such equations has been stated (13).

MODEL DEVELOPMENT

Suppose that the ointment–skin–blood system can be approximated by the system shown in Fig. 1. The barrier enclosing the ointment on three sides penetrates the skin only as a means of illustrating that the drug is required to move perpendicular to the membrane in this model. Assume that there is a uniformly distributed source (at time $t = 0$) in the region $-L_1 \leq x < 0$ and that this source operates in the following way. In any plane sheet of thickness Δx and cross-section area A (cm^2) in Medium I ($-L_1 \leq x < 0$), the time rate of change of the source mass is equal to the difference between the mass dissolution rate and the crystallization rate. Or:

$$\frac{\partial[\rho_s A\, \Delta x \epsilon(x,t)]}{\partial t} = -K_{dis} A_s(x,t) C_{sol} + K_{cry} A_s(x,t) C_1(x,t) \quad \text{(Eq. 1)}$$

where:

C_{sol} = solvent concentration (grams per milliliter)
ρ_s = crystal or powder density (grams per milliliter)
K_{dis} = dissolution rate constant (centimeters per second)
K_{cry} = crystallization rate constant (centimeters per second)
$A_s(x,t)$ = effective source (crystal) surface area at (x, t) (square centimeters)
$\epsilon(x,t)$ = volume fraction measure of source (milliliters per milliliter)

These relationships between dissolution and crystallization provide a general model and are developed from standard theories of velocity of adsorption and desorption (14) as well as crystallization and dissolution (15). In addition, the coefficients K_{dis} and K_{cry} are assumed to be temperature and activation energy dependent in the sense of their definitions as stated by Szinai and Hunt (16). The volume fraction measure of the source ϵ simply measures how much of the source is left at point (x, t).

Again using the ideas of Rowler (15), let $A_s(x,t) = \kappa A\, \Delta x[\epsilon(x,t)]^{2/3}$, where κ is a surface area to volume constant.

Putting all these hypotheses together yields for the time rate of change of the source mass in the incremental volume $A\, \Delta x$:

$$\frac{\partial \epsilon}{\partial t} = -\frac{K_{dis}\kappa}{\rho_s}\epsilon^{2/3} C_{sol} + \frac{K_{cry}\kappa}{\rho_s}\epsilon^{2/3} C_1 \quad \text{(Eq. 2)}$$

Suppose that at time $t = 0$, $C_1(x,0) = C_s$, the saturation concentration for the free ointment phase drug distribution. Also, let $\epsilon(x,0) = \epsilon_0$, a prescribed positive constant volume fraction. Then, assuming uniform equilibrium conditions between the dissolution and crystallization pro-

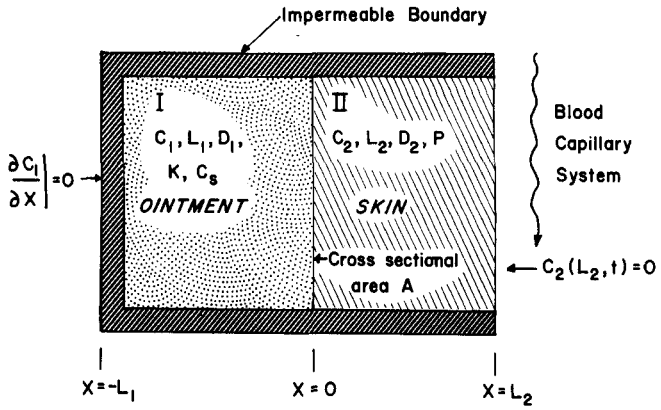

Figure 1—*Model geometry approximating the transport system.*

cesses at time $t = 0$, *i.e.*, $(\partial\epsilon/\partial t)|_{t=0} = 0$, results in:

$$K_{dis}C_{sol} = K_{cry}C_s \qquad \text{(Eq. 3)}$$

and:

$$\frac{\partial \epsilon}{\partial t} = -\frac{\kappa}{\rho_s}\epsilon^{2/3}K_{cry}(C_s - C_1) \qquad \text{(Eq. 4)}$$

This expression may be rewritten as:

$$\frac{\partial(\epsilon^{1/3} - \epsilon_0{}^{1/3})}{\partial t} = -\frac{\kappa}{3\rho_s}K_{cry}(C_s - C_1) \qquad \text{(Eq. 5)}$$

which can be integrated to yield:

$$\epsilon(x, t) = \left\{\epsilon_0{}^{1/3} - \frac{\kappa}{3\rho_s}K_{cry}\int_0^t [C_s - C_1(x, \tau)]d\tau\right\}^3 \qquad \text{(Eq. 6)}$$

The free or solution phase mass balance in the plane sheet then admits the equation[1]:

$$A\,\Delta x\frac{\partial C_1}{\partial t} = -D_1 A\frac{\partial C_1}{\partial x}\bigg|_{x-\Delta x/2} + D_1 A\frac{\partial C_1}{\partial x}\bigg|_{x+\Delta x/2} - \frac{\partial[\rho_s A\,\Delta x\epsilon(x, t)]}{\partial t} \qquad \text{(Eq. 7)}$$

or, in words, the net instantaneous free drug mass gain in the sheet is equal to the mass flux in minus the mass flux out plus the source mass flux into the solution phase from the suspended phase. Substitution for $\rho_s A\,\Delta x[\partial\epsilon(x, t)/\partial t]$ from Eq. 4 into Eq. 7, with subsequent passage to the limit as $\Delta x \to 0$, yields the solution phase concentration distribution rule in Medium I:

$$\frac{\partial C_1}{\partial t} = D_1\frac{\partial^2 C_1}{\partial x^2} + K(C_s - C_1)\left\{1 - \frac{K}{3\rho_s\epsilon_0}\int_0^t [C_s - C_1(x, \tau)]d\tau\right\}^2 \qquad \text{(Eq. 8)}$$

for $t > 0$ and $-L_1 < x < 0$ with K defined as:

$$K = \kappa K_{cry}\epsilon_0{}^{2/3} \qquad \text{(Eq. 9)}$$

Based upon mass balance considerations at time $t = 0$, it is not too difficult to show that:

$$\epsilon_0 = \frac{\frac{M_{DT}}{AL_1} - C_s}{\rho_s - C_s} \qquad \text{(Eq. 10)}$$

for $C_s \leq (M_{DT}/AL_1) \leq \rho_s$, where M_{DT} is equal to the total drug mass in the solution plus suspended phases at time $t = 0$, and AL_1 is the total volume of the ointment slab.

While Eq. 8 incorporates the realistic ideas of source area changes with time and a decreasing local solvent concentration with an increasing local free phase drug concentration, it is nonlinear and thus out of the realm of classical linear problem solution methods such as integral transforms and eigenfunction expansion.

The analysis presented later in this paper concerns a linear approximation to Eq. 8 valid for small values of time[2].

Since all physical parameters of the dissolution process are positive and $C_s - C_1(x, t) \geq 0$ for all (x, t) such that $-L_1 < x < 0$ and $t > 0$, the source function defined in Eq. 8 is a strictly monotone decreasing function of increasing time t, making the local source term less important; *i.e.*, locally, the source contributes less and less to the overall drug distribution process as time goes on. Hence, setting the source function term equal to 1.0 for all $t > 0$ and $-L_1 < x < 0$, as is done in the remainder of this paper, generates an upper bound on the actual physical process. That is, the assumption is made that the free phase drug concentration distribution in the ointment slab obeys the linearized distribution rule:

$$\frac{\partial C_1}{\partial t} = D_1\frac{\partial^2 C_1}{\partial x^2} + K(C_s - C_1) \qquad -L_1 < x < 0 \qquad t > 0 \qquad \text{(Eq. 11)}$$

By proceeding formally in an analogous manner in Medium II, the solution phase concentration distribution rule can be shown to be:

$$\frac{\partial C_2}{\partial t} = D_2\frac{\partial^2 C_2}{\partial x^2} \qquad t > 0 \qquad 0 < x < L_2 \qquad \text{(Eq. 12)}$$

The following initial conditions are assumed:

$$C_1(x, 0+) = C_s \qquad -L_1 \leq x < 0 \qquad \text{(Eq. 13)}$$

and:

$$C_2(x, 0+) = 0 \qquad 0 < x < L_2 \qquad \text{(Eq. 14)}$$

and the following boundary conditions are assumed:

$$C_1(0, t) = PC_2(0, t) \qquad t > 0 \qquad \text{(Eq. 15)}$$

$$D_1\frac{\partial C_1(0, t)}{\partial x} = D_2\frac{\partial C_2(0, t)}{\partial x} \qquad t > 0 \qquad \text{(Eq. 16)}$$

$$\frac{\partial C_1}{\partial x}\bigg|_{x=-L_1} = 0 \qquad t \geq 0 \qquad \text{(Eq. 17)}$$

and:

$$C_2(L_2, t) = 0 \qquad t \geq 0 \qquad \text{(Eq. 18)}$$

The coefficients D_1 and D_2 are assumed to be constant in this model and are, respectively, the solution phase diffusion coefficients in Media I and II (square centimeters per second), while P is the equilibrium coefficient of partition between solution concentrations in Media I and II. The authors were unable to find this particular mass transport system or its heat conduction analog listed in the literature or in standard references (1, 2, 17, 18). Churchill (19) considered a similar problem and used Laplace transform techniques, which led to a solution of the system by operational methods[3].

A paper (20) important to this discussion reported the conduction of heat in a semi-infinite solid of two different materials.

Laplace transform techniques lead to the following forms for the solution phase drug concentration distributions. In Medium I (ointment):

$$C_1(x, t) = C_s - C_s\frac{\cosh\left[(L_1 + x)\sqrt{\frac{K}{D_1}}\right]}{\cosh\left(L_1\sqrt{\frac{K}{D_1}}\right) + P\sqrt{\frac{KD_1L_2{}^2}{D_2{}^2}}\sinh\left(L_1\sqrt{\frac{K}{D_1}}\right)} + C_s\sum_{n=1}^{\infty}\frac{\sin(2\beta_n)\cosh\left(\frac{L_1 + x}{L_2}\sqrt{\frac{D_2}{D_1}}\sqrt{\frac{K}{D_2}L_2{}^2 - \beta_n{}^2}\right)\exp[-(\beta_n{}^2D_2t/L_2{}^2)]}{\beta_n\Delta_n\cosh\left(\frac{L_1}{L_2}\sqrt{\frac{D_2}{D_1}}\sqrt{\frac{K}{D_2}L_2{}^2 - \beta_n{}^2}\right)} \qquad \text{(Eq. 19)}$$

for $-L_1 \leq x < 0$ and $t > 0$. In Medium II:

$$C_2(x, t) = C_s\frac{\sqrt{\frac{KD_1L_2{}^2}{D_2{}^2}}\left(1 - \frac{x}{L_2}\right)\sinh\left(L_1\sqrt{\frac{K}{D_1}}\right)}{\cosh\left(L_1\sqrt{\frac{K}{D_1}}\right) + P\sqrt{\frac{KD_1L_2{}^2}{D_2{}^2}}\sinh\left(L_1\sqrt{\frac{K}{D_1}}\right)} + \frac{2C_s}{P}\sum_{n=1}^{\infty}\frac{\cos\beta_n\sin\left[\beta_n\left(1 - \frac{x}{L_2}\right)\right]\exp[-(\beta_n{}^2D_2t/L_2{}^2)]}{\beta_n\Delta_n} \qquad \text{(Eq. 20)}$$

where β_n is the nth zero of the transcendental equations:

$$\cot\beta + \frac{P\sqrt{\frac{D_1}{D_2}}\sqrt{\frac{K}{D_2}L_2{}^2 - \beta^2}}{\beta}\tanh\left(\frac{L_1}{L_2}\sqrt{\frac{D_2}{D_1}}\sqrt{\frac{K}{D_2}L_2{}^2 - \beta^2}\right) = 0 \qquad \text{(Eq. 21)}$$

for $0 < \beta \leqq L_2\sqrt{K/D_2}$, and:

$$\cot\beta - \frac{P\sqrt{\frac{D_1}{D_2}}\sqrt{\beta^2 - \frac{K}{D_2}L_2{}^2}}{\beta}\tan\left(\frac{L_1}{L_2}\sqrt{\frac{D_2}{D_1}}\sqrt{\beta^2 - \frac{K}{D_2}L_2{}^2}\right) = 0 \qquad \text{(Eq. 22)}$$

[1] The reviewer correctly pointed out that, as $\epsilon \to 0$, D_1 will be a variable of position and time and Medium I will probably undergo contraction. While these assumptions will be dealt with in future work, they are not included in this first approximation model.

[2] The full numerical analysis will be the subject of a later paper in this series.

[3] The solution procedure is to be published elsewhere.

for $\beta \geqq L_2\sqrt{K/D_2}$, and where:

$$\Delta_n = 1 + P\frac{L_1}{L_2}\sin^2\beta_n\left[1 - \sqrt{\frac{D_1}{D_2}}\tanh^2\left(\frac{L_1}{L_2}\sqrt{\frac{D_2}{D_1}}\sqrt{\frac{K}{D_2}L_2^2 - \beta_n^2}\right)\right] + P\sqrt{\frac{D_1}{D_2}}\frac{KL_2^2}{\beta_n^2 D_2}\frac{\sin^2\beta_n \tanh\left(\frac{L_1}{L_2}\sqrt{\frac{D_2}{D_1}}\sqrt{\frac{K}{D_2}L_2^2 - \beta_n^2}\right)}{\sqrt{\frac{K}{D_2}L_2^2 - \beta_n^2}} \quad \text{(Eq. 23)}$$

While the concentration distributions (formal solutions) are important for some work, two other important formulas to obtain are the cumulative drug mass taken up by the receptor phase (blood in some cases), $M_{but}(t)$, and the cumulative mass loss from the ointment, $M_1(t)$. These two drug mass distribution functions are defined as:

$$M_{but}(t) = \int_0^t \left(-D_2 A \left.\frac{\partial C_2}{\partial x}\right|_{x=L_2}\right) d\tau \quad \text{(Eq. 24)}$$

and:

$$M_1(t) = \int_0^t \left(-D_1 A \left.\frac{\partial C_1}{\partial x}\right|_{x=0}\right) d\tau \quad \text{(Eq. 25)}$$

Performing the indicated partial differentiations with subsequent evaluations of these results at $x = L_2$ and $x = 0$, respectively, obtains (after some algebra and use of Eqs. 19–22):

$$M_{but}(t) = AC_s\sqrt{KD_1}t\frac{\sinh\left(L_1\sqrt{\frac{K}{D_1}}\right)}{\cosh\left(L_1\sqrt{\frac{K}{D_1}}\right) + P\sqrt{\frac{KD_1L_2^2}{D_2^2}}\sinh\left(L_1\sqrt{\frac{K}{D_1}}\right)} + \frac{2AL_2C_s}{P}\sum_{n=1}^{\infty}\frac{\cos\beta_n\{1 - \exp[-(\beta_n^2 D_2 t/L_2^2)]\}}{\beta_n^2\Delta_n} \quad \text{(Eq. 26)}$$

and:

$$M_1(t) = AC_s\sqrt{KD_1}t\frac{\sinh\left(L_1\sqrt{\frac{K}{D_1}}\right)}{\cosh\left(L_1\sqrt{\frac{K}{D_1}}\right) + P\frac{L_2}{L_1}\sqrt{KD_1}\sinh\left(L_1\sqrt{\frac{K}{D_1}}\right)} + \frac{2AL_2C_s}{P}\sum_{n=1}^{\infty}\frac{\cos^2\beta_n}{\beta_n^2\Delta_n}[1 - \exp(-\beta_n^2 D_2 t/L_2^2)] \quad \text{(Eq. 27)}$$

Uniform convergence of the resulting series is confirmed by an analysis similar to that mentioned by Churchill (19).

Before pursuing an in-depth study of these least upper bounding distributions for published literature values of the transport parameters, a brief discussion is included for the following asymptotic forms to which the relative cumulative receptor phase uptake, $\mu_{but}(t) = M_{but}(t)/M_0$, and/or the cumulative drug mass loss from the ointment, μ_1, converge in the limit of small and large K values.

For finite D_1 and D_2 values, $0 \leq K \leq 0.25\,(D_1/L_1^2)$, $t \geqq (4L_2^2/\beta_1^2 D_2)$, and $M_0 = AL_1C_s$:

$$\mu_{but}(t) \sim \frac{Kt}{1 + KP\frac{L_1L_2}{D_2}} + 2\left(\frac{L_2}{L_1}\right)\frac{\cos\beta_1}{P\beta_1^2\Delta_1} \quad \text{(Eq. 28)}$$

and:

$$\mu_1(t) \sim \frac{Kt}{1 + KP\frac{L_1L_2}{D_2}} + 2\left(\frac{L_2}{L_1}\right)\frac{\cos^2\beta_1}{P\beta_1^2\Delta_1} \quad \text{(Eq. 29)}$$

Again for finite D_1 and D_2 values, $K \geqq 25\,(D_1/L_1^2)$, $t \geqq (4L_2^2/\beta_1^2 D_2)$, and $M_0 = AL_1C_s$:

$$\mu_{but}(t) \sim \frac{\sqrt{KD_1}}{L_1}\frac{t}{1 + P\frac{L_2}{D_2}\sqrt{KD_1}} + 2\frac{L_2}{L_1}\frac{\cos\beta_1}{P\beta_1^2\Delta_1} \quad \text{(Eq. 30)}$$

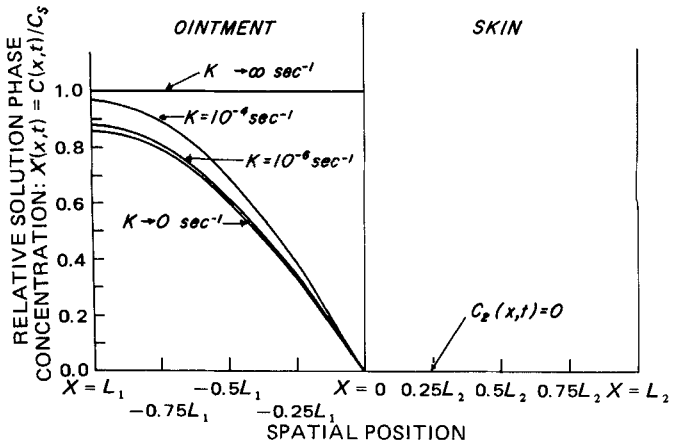

Figure 2—*Plots of relative solution phase drug concentration distribution in the ointment and the skin when* $D_2 \to \infty$ *and time* t = 600 *sec* ($D_1 = 10^{-9}$ *cm²/sec).*

and:

$$\mu_1(t) \sim \frac{\sqrt{KD_1}}{L_1}\frac{t}{1 + P\frac{L_2}{D_2}\sqrt{KD_1}} + 2\frac{L_2}{L_1}\frac{\cos^2\beta_1}{P\beta_1^2\Delta_1} \quad \text{(Eq. 31)}$$

An ointment–drug–stirred water system represents the extreme case of large D_2. Mathematically, if $D_2 \to \infty$, the perfect sink at $x = L_2$ becomes operable throughout the entire skin region; *i.e.*, there is no barrier to overcome. The practical situation might be the topical application of a product containing drug suspended in a vehicle directly to the capillary system exposed due to skin abrasion. Thus, in the limit as $D_2 \to \infty$, $K \geqq 25\,(D_1/L_1^2)$, and $t \geqq 5/[(9\pi^2 D_1/4L_1^2) + K]$, the relative receptor phase uptake of drug mass, μ_{but}, is:

$$\mu_{but} \sim \frac{\sqrt{D_1K}}{L_1}t + \frac{1}{2L_1}\sqrt{\frac{D_1}{K}} \quad \text{(Eq. 32)}$$

RESULTS AND DISCUSSION

Since the main purpose of formulating this mathematical model is to aid in understanding the passive diffusion process (one type of mass transport process) of a drug from a suspension dosage form through the dermal layer to the blood capillary bed, attention is now turned to an evaluation of the equations of the model itself.

The drug cortisone was chosen as an example of a commonly used drug in an ointment form, and a literature search revealed the following estimates for the model parameters. For the partition coefficient and average skin diffusion coefficient:

$$P = \frac{K_{hex}}{K_{skin}} = \frac{0.28}{8.5} = \frac{1}{30} \quad \text{(Eq. 33)}$$

and:

$$D_2 = 10^{-12}\ \text{cm}^2/\text{sec} \quad \text{(Eq. 34)}$$

respectively (21). From a diffusion path length viewpoint, the effective composite layer through which substances must diffuse to enter the bloodstream was estimated to be about 200 μm (21). However, the main skin barrier in most cases of percutaneous absorption is the stratum corneum, reported to be about 10 μm in depth. Since the thickness of the stratum corneum varies with its location on the body, a thickness of 20 μm for L_2 is used in Fig. 2 as a first approximation of the main skin barrier. Variable pathways of diffusion and differing diffusion rates through appendages in the skin (21) are not considered, since Medium II in Fig. 2 is assumed to be homogeneous in the model, although skin is, in reality, a heterogeneous system. This "artificial" membrane, although not an exact equivalent of skin, is used as an approximation in solving the model.

Let it be assumed that a thinly applied ointment or salve is also around 20 μm in thickness. Thus, $L_1 = 2 \times 10^{-3}$ cm. The authors were unable to find any specific diffusion coefficient data on cortisone in different lipophilic bases. However, the value of $D_1 = 10^{-9}$ cm²/sec was finally chosen, since it is less than the average value for diffusion of steroids in aqueous solution and greater than diffusion through the skin barrier. The knowledge that the vehicle composition can influence the release (22)

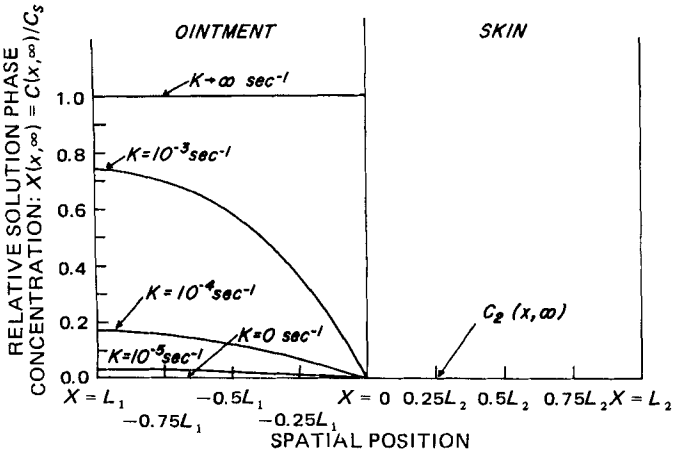

Figure 3—*Plots of relative solution phase drug concentration distribution in the ointment and the skin when* $D_2 \to \infty$ *and time* $t \to \infty$, i.e., *"steady state"* ($D_1 = 10^{-9}$ *cm*^{2}*/sec).*

and physiological response (23) for some steroids makes this value a reasonable estimate.

Finally, the dissolution rate constant K, for which the authors were unable to find any specific values for cortisone in semisolid vehicles, is used as an active parameter. For the remainder of this paper, K is simply assigned order of magnitude values.

Substitution of these parameter values into the appropriate equations, *e.g.*, Eqs. 19, 20, and 26, allows the drug concentration distributions in the solution phases of both media to be estimated at any time after drug application. In addition, the drug mass uptake as a function of time also can be calculated. The discussion of these distributions is carried out starting with the extreme cases ($D_1 \to \infty$, $D_2 \to \infty$, or any subcase thereof) and progressing toward the most general situation, namely, an evaluation of Eqs. 19, 20, and 26.

Extreme Case $D_2 \to \infty$—It is assumed that mass transport through the skin is carried out infinitely fast, as would approximately be the case for some *in vitro* studies or if there is no skin covering the capillary bed and the dosage form is applied directly to the capillary bed. Evaluation of the limiting forms of Eqs. 19, 20, and 26 gives the concentration distributions shown in Figs. 3 and 4 and the relative cumulative drug mass uptake by the blood shown in Fig. 5, respectively. This type of mass transport system may be an example of ointment or salve applied directly to an open wound or abrasion.

Mathematically, the perfect sink boundary condition $C_2(L_2, t) = 0$ is moved left to $C_1(0, t) = 0$ (Fig. 2). Also, as $K \to \infty$, the solution phase concentration phase distribution in Medium I (the ointment) tends to stay at saturation concentrations, C_s, as expected. The distribution curves shown in Fig. 3 are all for one fixed time, $t = 600$ sec, after ointment application. The long time or steady-state concentration distributions to which $C_1(x, t)$ converges for the various K values chosen in this work are shown in Fig. 3.

The cumulative mass of drug taken up by the blood for this special case is shown in Fig. 4. If $K = 0$, then only the finite amount of original solution phase drug in the ointment can be taken up by the blood, because this quantity is the only drug mass available to be taken up. However, if $K > 0$, then the blood uptake of drug distribution over time is seen. The abscissa in all time plots is the square root of time.

This time scale was chosen because it compresses the abscissa, allowing a greater time period to be shown on the graph, and because some models of diffusion[4] have resulted in equations where the total amount of drug transferred from the donor phase is linearly dependent on time$^{1/2}$.

While still operating under the assumption that $D_2 \to \infty$, the asymptotic form (Eq. 32) can be used for the relative cumulative blood uptake of drug mass, μ_{but}. Suppose that $K \geq 25\ (D_1/L_1^2)$ ($= 6.25 \times 10^{-3}$ sec^{-1} based on D_1 and L_1 used for Figs. 2–4) and time t is such that:

$$t \geq t_{min} = 5 \Big/ \left(\frac{9\pi^2 D_1}{4L_1^2} + K\right) \qquad \text{(Eq. 35)}$$

This time would be variable for Figs. 2–4, depending on the value of K. The t_{min} would be 42.3 sec for $K = 10^{-2}$ sec^{-1}. Then the asymptotic form

[4] A comparison among different diffusion models for the predicted release of drug is included in Part II of this series (24).

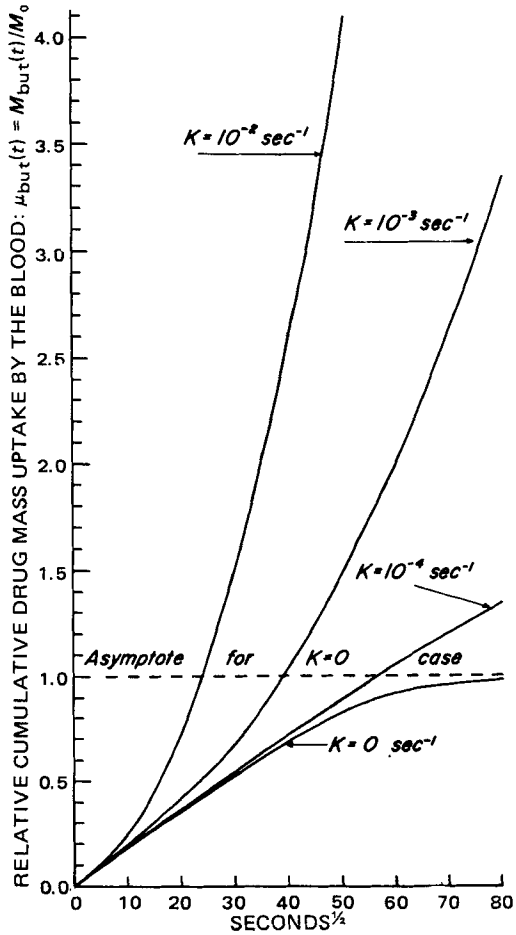

Figure 4—*Plots of relative cumulative drug mass uptake by the blood,* $\mu_{but}(t) = M_{but}(t)/M_0$, $M_0 = AL_1C_s$, *for* $D_2 \to \infty$. *The ordinate is linear while the abscissa is the square root of time with each curve carrying its respective* K *value* ($D_1 = 10^{-9}$ *cm*^{2}*/sec).*

for μ_{but} (Eq. 32) demonstrates directly that under these conditions μ_{but} is proportional to the total drug mass, M_{DT}, to the one-third power, close to agreement with the classical model for drug release from ointments (9). Since:

$$K = \kappa K_{cry} \epsilon_0^{2/3} \qquad \text{(Eq. 36)}$$

and:

$$\epsilon_0 = \left(\frac{M_{DT}}{AL_1} - C_s\right) \Big/ (\rho_s - C_s) \qquad \text{(Eq. 37)}$$

K is directly proportional to $M_{DT}^{2/3}$ and, hence, $\mu_{but} \propto M_{DT}^{1/3}$. Note, however, that the amount of drug taken up by the receptor phase is only predicted to be proportional to the cube root of the total drug mass when the restrictions on K and t are satisfied.

Recasting the classical equation into the notation of the proposed model gives:

$$\mu_H = \frac{\sqrt{D_1 t \left(2\frac{M_{DT}}{M_0} - 1\right)}}{L_1} \qquad \text{(Eq. 38)}$$

where the subscript H stands for the classical model (9).

The major difference between μ_{but} and μ_H is that μ_{but} is proportional to t for large values of time while μ_H is proportional to $t^{1/2}$ for all time values. Furthermore, in the case of small values of time, μ_H is proportional to $t^{1/2}$ while the asymptotic form for μ_{but} for small time can easily be shown to be root t like in this linearized model; that is:

$$\mu_{but} \sim \frac{2\sqrt{D_1 t}}{L_1}\left[1 + \frac{Kt}{3} - O(Kt)^2\right] \qquad \text{(Eq. 39)}$$

where the O notation of Heaviside has been used to collect all higher order terms.

No matter which of these equations is assumed to describe the drug release phenomenon, they are all invalid for values of time $t > t_{C_s}$, the

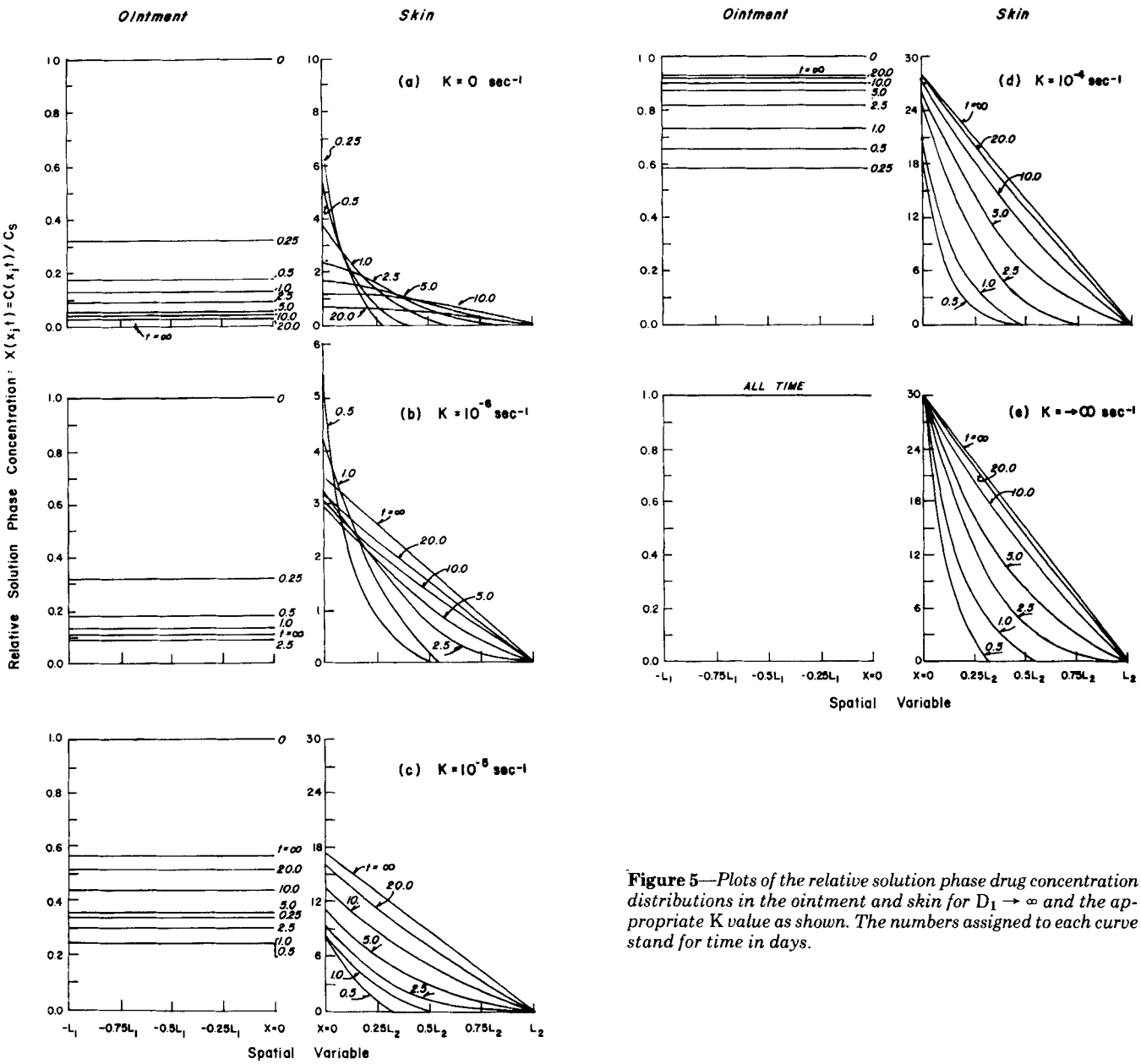

Figure 5—*Plots of the relative solution phase drug concentration distributions in the ointment and skin for* $D_1 \to \infty$ *and the appropriate* K *value as shown. The numbers assigned to each curve stand for time in days.*

exhaustion of source time. The analytical expressions derived here for the cumulative drug mass uptake by the blood are only useful for estimation purposes, since they are actually upper bounding distributions for realistic release situations.

A cursory look at preliminary numerical analysis data for the more realistic model (Eq. 8), *i.e.*, if the source function is *not* constrained at 1.0 but is free to vary in the natural way, shows that, depending upon the magnitude of K, the cumulative relative drug mass uptake by the blood distribution begins to flatten out considerably before t_{C_s} is reached. The preliminary data also show that, for any fixed value of time $t > 0$, μ_{but}, when looked upon as a function of M_{DT}, increases monotonically but nonlinearly toward an asymptotic bounding curve. That is, the release does not continue to be proportional to $(M_{DT})^{1/3}$ at all times, as predicted by Eq. 32, but a maximum release rate is predicted by Eq. 8 with increasing M_{DT}, as reported experimentally (13).

Finally, it should be seen that even in the upper bounding case (Eq. 32), when the crystal or powder density increases, as would be the case in using a finer grind of powder, *i.e.*, a larger surface area to volume ratio, κ increases. Moreover, since μ_{but} is proportional to $\kappa^{1/2}$ (for time t sufficiently large), μ_{but} increases with the increasing surface area of the suspended drug. This increase in the drug release rate with an increasing surface area to volume ratio (smaller suspended particles) has been observed experimentally (13, 24, 25).

For this special case ($D_2 \to \infty$), it can be seen that the relative cumulative blood uptake of drug mass, μ_{but}, is: (*a*) rather linearly dependent upon total drug mass for small time t, (*b*) almost proportional to $t^{1/2}$ for small t, (*c*) linearly dependent upon t for t large, (*d*) proportional to $(M_{DT})^{1/3}$ for large M_{DT} and moderate to large values of time t, and (*e*) increasing accordingly as the surface area to volume ratio of the suspended drug increases for both small and large time values. Another physical factor affecting the release rate is the Arrhenius-type temperature dependence of K_{dis} and K_{cry}; *i.e.*, as T (absolute temperature) goes up, the release rate increases.

Extreme Case $D_1 \to \infty$—This case corresponds to having the transport rate-limiting step occurring in the skin, which is a diffusion barrier-type process. The solution phase concentration distributions are given by limiting forms of Eqs. 19 and 20. The large D_1 limiting form of Eq. 26 is evaluated to demonstrate the cumulative drug mass uptake by the blood. Other special subcases ($K = 0$ and $K \to \infty$) are included here for reference purposes.

Before any actual evaluation of the limiting forms of Eqs. 19, 20, and 26 can be made, the first several zeros, β_n, of the associated transcendental equation (limiting form of Eqs. 21 and 22) must be found for the parameter values of interest. The first 12 zeros for the various values of K and the other designated parameters are listed in Table I.

When using the β values in Table I, the solution phase concentration phase distributions are obtained by evaluating the appropriate distribution equations. Figure 5 was prepared as an aid in understanding the

Table I—Set of First 12 Zeros of the Transcendental Expression: $\beta \cot \beta - P(L_1/L_2)(\beta^2 - K/D_2 L_2^2) = 0, 0 < \beta < \infty$

Zero (β_i) i	K, sec^{-1}					
	0[a]	10^{-7}	10^{-6}	10^{-5}	10^{-4}	∞
1	1.5202	1.5286	1.6007	2.0880	2.9214	3.1416
2	4.5615	4.5643	4.5891	4.8272	5.8368	6.2832
3	7.6057	7.6073	7.6217	7.7670	8.7435	9.4248
4	10.6544	10.6554	10.6652	10.7648	11.6435	12.5664
5	13.7086	13.7094	13.7164	13.7890	14.5448	15.7080
6	16.7691	16.7697	16.7750	16.8298	17.4585	18.8850
7	19.8362	19.8366	19.8408	19.8831	20.3943	21.9911
8	22.9098	22.9102	22.9134	22.9467	23.3572	25.1327
9	25.9897	25.9900	25.9926	26.0191	26.3473	28.2743
10	29.0754	29.0757	29.0778	29.0992	29.3620	31.4159
11	32.1665	32.1667	32.1684	32.1859	32.3976	34.5575
12	35.2625	35.2627	35.2641	35.2784	35.4502	37.6991

[a]This set of zeros follows from setting $K = 0$, yielding the well-known form $\beta \tan \beta - (L_2/PL_1) = 0$.

effect of varying the dissolution rate coefficient K upon the overall system. The distribution curves in Fig. 5 clearly show that as K sequences in value from $K = 0$ to $K \to \infty$, the solution phase concentration in the skin builds up in time toward the well-known constant negative gradient situation. The magnitude of the slope of the "steady-state" distribution clearly depends upon the value of K. Linear ordinates and abscissa axes are used throughout Fig. 5. The much larger ordinate numbers for Medium II (the skin) are simply a reflection of P being a 30:1 ratio of skin to ointment; *i.e.*, the drug cortisone likes to be in the solution phase in the skin much better than in the ointment vehicle for the conditions described.

Initially (small times, $t < \frac{1}{4}$ day), drug is lost rapidly from the ointment to the surface layers of the skin. Indeed, if $K = 0$ (Fig. 5*a*), then about 87% of the total "available" drug has been lost from the ointment by the end of Day 1 and resides in the outermost region of the skin. Since there is no dissolution from the suspension when $K = 0$, the only available drug is that in the solution phase initially. With the blood capillary system supposedly forming a perfect sink for the drug, both C_1 and $C_2 \to 0$ as time $t \to \infty$.

In cases where $K > 0$, a finite steady state in the skin is easily observable as time $t \to \infty$. At small times, the same apparent rapid loss of drug from the ointment to the skin is seen. However, as time progresses, some drug released by the ointment at previous times is being replaced by the finite dissolution rate process occurring in the suspension (Medium I).

Another interesting phenomenon that occurs as K increases is the generation of a "deficit" zone in the solution phase of the ointment. The drug in the ointment appears to be lost to the skin too rapidly to be replaced by the dissolution from the suspension until a certain solution phase concentration balance between the drug concentration in the solution phase of the ointment and the solution phase in the skin is reached (Figs. 5*b*–5*d*). The time at which this turning point occurs is dependent on K, as expected. The magnitude of the initial drop and the subsequent return to a long time or steady-state level are also dependent on K.

With the cumulative drug mass uptake by the blood distributions (Fig. 6), it is much easier to see why there is little drug mass transmitted to the blood until after time $t = 4$ days. In fact, it is easy to show that if the drug solution phase concentration at the boundary $x = 0$ remains constant at the relative concentration of 1.0 in the ointment (30.0 on the surface of the skin), it takes at least 3.5 days for the concentration at a point 20 μm from this barrier to reach 1% of the surface concentration. A clear indication of the barrier or rate-limiting action of the skin for this particular drug is seen by a careful study of Figs. 5 and 6. The buildup of drug in Medium II (the skin), which is predicted by this model and shown in Fig. 5, is in agreement with the recognized fact that the stratum corneum is a reservoir for drugs (26).

The cumulative drug mass uptake by the blood (Fig. 6) is bounded above for the case $K = 0$ by the asymptote $M_0 = C_s A L_1$. The same reason for this asymptote holds as in the previously discussed limiting case, $D_2 \to \infty$ and D_1 remaining finite. For values of $K > 0$, the drug mass delivered to the blood increases rapidly for values of time t greater than 9 days (77.76×10^4 sec).

Figure 7 demonstrates the relative cumulative drug mass loss from the ointment, $\mu_1(t) = [M_1(t)/M_0]$ (based upon the limiting form of Eq. 27).

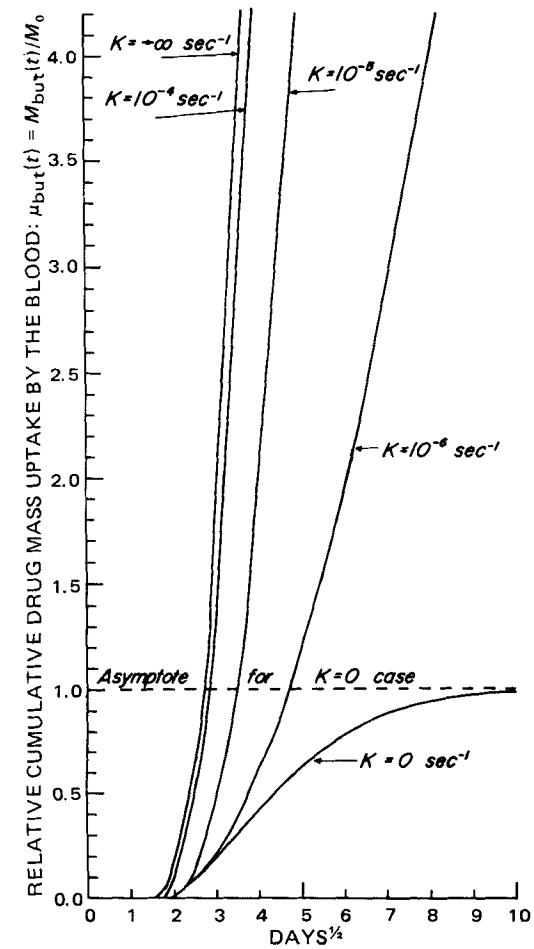

Figure 6—*Plots of the relative cumulative drug mass uptake by the blood, $\mu_{but}(t)$ (see Fig. 4), for $D_1 \to \infty$ and the appropriate K value as shown. The ordinate is linear in drug mass units, M_0, while the abscissa is the square root of time.*

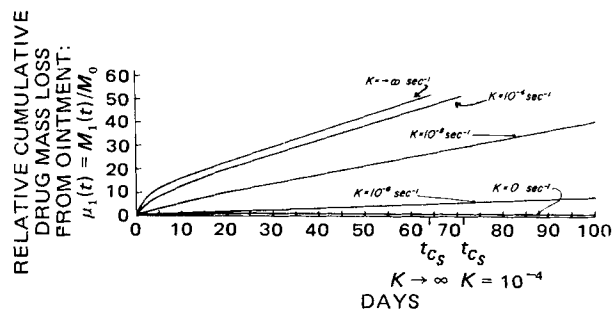

Figure 7—*Plots of the relative cumulative drug mass loss from the ointment under the assumption $D_1 \to \infty$. Both ordinate and abscissa are linear scales. The curves carry their appropriate K values.*

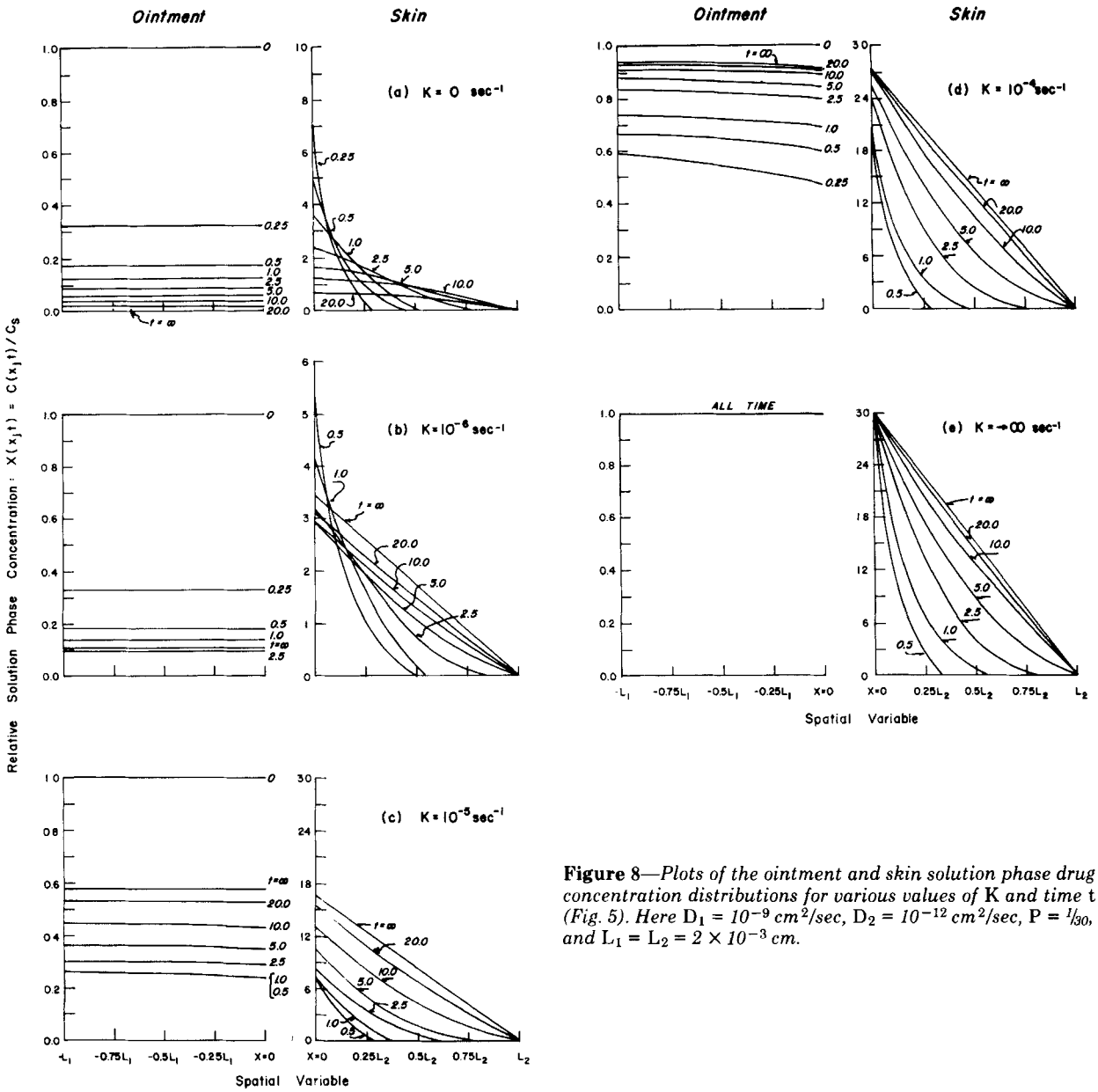

Figure 8—*Plots of the ointment and skin solution phase drug concentration distributions for various values of* K *and time* t *(Fig. 5). Here* $D_1 = 10^{-9}$ *cm²/sec,* $D_2 = 10^{-12}$ *cm²/sec,* P = 1/30, *and* $L_1 = L_2 = 2 \times 10^{-3}$ *cm.*

The scales on this plot are both linear. Suppose, for example, that at time $t = 0$ there exist 50 initial M_0 units of drug in the suspended phase of the ointment and one M_0 unit of drug in the solution phase of the ointment for a total of 51 M_0 units of drug mass. Under the hypothesis of $D_1 \to \infty$, with all other parameters as previously stated, the time t_{C_s} (the time at which 50 M_0 units of drug mass have been lost from the ointment) is easily seen to be 65 days for $K \to \infty$ sec^{-1}, 69 days for $K = 10^{-4}$ sec^{-1}, and > 100 days for $0 < K < 10^{-5}$ sec^{-1}.

If a smaller value of the total initial drug mass is used, then the appropriate values of t_{C_s} can be read off the graphs shown in Fig. 7. The curves in Fig. 7 are peculiar to $D_2 = 10^{-12}$ cm^2/sec. If some other value of D_2 is used, then the relative cumulative mass loss distributions also would be different from those shown in Fig. 7.

General Case D_1 and D_2 Both Finite—As in the special cases, a set of zeros, β_n, associated with the particular transcendental Eqs. 21 and 22 must be obtained. The first 12 zeros of the general case for these transcendental equation(s) for the parameter values $D_1 = 10^{-9}$ cm^2/sec, $D_2 = 10^{-12}$ cm^2/sec, $L_1 = L_2 = 2 \times 10^{-3}$ cm, $P = 1/30$, and several orders of magnitude values of K are listed in Table II.

A careful comparison of the β_n values in Table II with those (for a corresponding K value) in Table I reveals that one should not expect any major differences in the solution phase concentration distributions in either the ointment or the skin (Fig. 2). In fact, an order of magnitude sequence of D_1 values with D_2 fixed at $D_2 = 10^{-12}$ cm^2/sec, *e.g.*, ($D_1 =$: $10^{-9}, 10^{-8}, 10^{-7}, \ldots$), gives essentially no differences between the solution phase concentration distributions for these D_1 values and those obtained under the special case $D_1 \to \infty$. This fact follows from the physical reasoning that, as $D_1 \to \gg D_2$, diffusion across the skin barrier becomes the rate-limiting process. However, if D_2 is about the same order of magnitude as the D_1 value ($D_1 = 10^{-9}$ cm^2/sec), then considerable differences would arise between the general case $D_2 \cong D_1 = 10^{-9}$ cm^2/sec and the special case $D_2 = 10^{-9}$ cm^2/sec and $D_1 \to \infty$.

Figures 8 and 9 summarize the solution phase concentration distributions in the ointment and the skin and the cumulative drug mass blood uptake, respectively. The close similarity of the distributions shown in Figs. 8 and 9 with those in Figs. 5 and 6 is expected as explained. Table III shows some selected values of $\chi_1(x, t)$ and $\chi_1(x, t) = C_1(x, t)/C_s$ and the relative solution phase concentration distribution for several values of (x, t) and K. Note that the slope

$$\left.\frac{\partial \chi_1}{\partial x}\right|_{\substack{-L_1<x<0 \\ t>0}}$$

is almost zero. Only in the case considered, $K = 10^{-4}$ sec^{-1}, does even a shallow gradient exist at small negative x values and small values of time. Somewhere between $K = 10^{-5}$ sec^{-1} and $K \to \infty$ sec^{-1} for small time values, the gradient has a finite maximum value. The spatial position of this maximum gradient lies on the boundary $x = 0$; the exact time at which this maximum occurs is primarily of academic interest and is beyond the scope of this paper.

Table II—Set of First 12 Zeros of the Transcendental Expressions:

$$\beta \cot \beta + P\sqrt{\frac{D_1}{D_2}}\sqrt{\frac{K}{D_2}L_2^2-\beta^2}\tanh\left(\frac{L_1}{L_2}\sqrt{\frac{D_2}{D_1}}\sqrt{\frac{K}{D_2}L_2^2-\beta^2}\right)=0,\ 0<\beta\leqq L_2\sqrt{\frac{K}{D_2}}$$

$$\beta \cot \beta - P\sqrt{\frac{D_1}{D_2}}\sqrt{\beta^2-\frac{K}{D_2}L_2^2}\tan\left(\frac{L_1}{L_2}\sqrt{\frac{D_2}{D_1}}\sqrt{\beta^2-\frac{K}{D_2}L_2^2}\right)=0,\ \beta>L_2\sqrt{\frac{K}{D_2}}$$

	K, sec^{-1}					
Zero (β_i)	0[a]	10^{-7}	10^{-6}	10^{-5}	10^{-4}	∞
1	1.5201	1.5286	1.6007	2.0840	2.8965	3.1416
2	4.5605	4.5633	4.5884	4.8266	5.7950	6.2832
3	7.6012	7.6028	7.6177	7.7664	8.6977	9.4248
4	10.6423	10.6435	10.6539	10.7593	11.6069	12.5664
5	13.6841	13.6850	13.6928	13.7727	14.5249	15.7080
6	16.7266	16.7273	16.7335	16.7966	17.4535	18.8850
7	19.7700	19.7706	19.7756	19.8266	20.3942	21.9911
8	22.8143	22.8148	22.8189	22.8609	23.3475	25.1327
9	25.8596	25.8600	25.8634	25.8989	26.3134	28.2743
10	28.9058	28.9061	28.9090	28.9385	29.2912	31.4159
11	31.9529	31.9532	31.9556	31.9805	32.2799	31.9529
12	35.0008	35.0010	35.0031	35.0243	35.2785	37.6991

[a] This set of zeros follows from setting $K = 0$, yielding the transcendental equation:

$$\cot \beta - P\sqrt{\frac{D_1}{D_2}}\tan\left(\frac{L_1}{L_2}\sqrt{\frac{D_2}{D_1}}\beta\right)=0$$

The model developed in this report is based on parameters known or anticipated to affect drug release. Therefore, for semisolids containing suspensions for topical application, the following are predicted to affect drug release and uptake: (*a*) powder density or particle size, (*b*) partition coefficient between the vehicle and the receptor phase, (*c*) solubility of the drug in the vehicle, (*d*) area of application, (*e*) viscosity of the vehicle (affects the diffusion coefficient), (*f*) temperature (affects release and would be different for semisolids applied rectally compared to semisolids applied to the forearm), and, (*g*) total time the material remains in contact with the receptor phase.

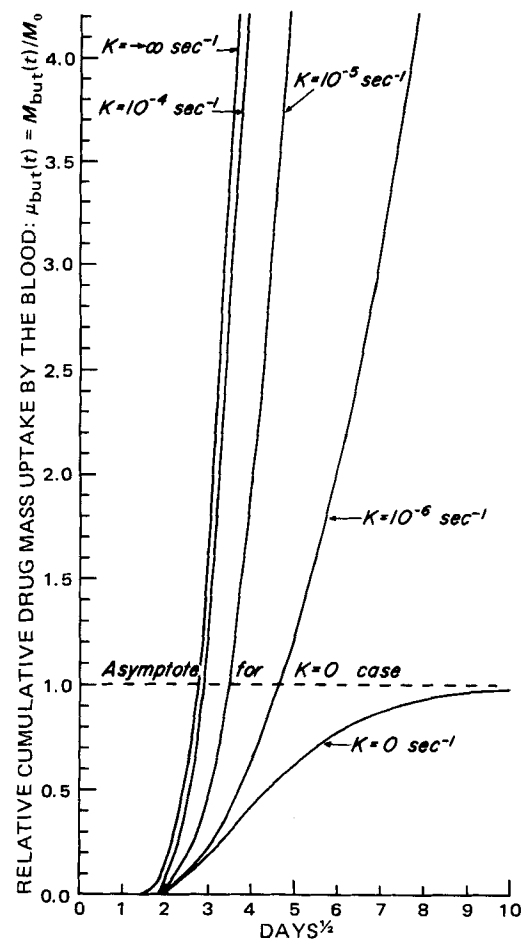

Figure 9—*Plots of the relative drug mass uptake by the blood, $\mu_{but}(t)$, versus the square root of time for the general case (Fig. 8).*

CONCLUSIONS

A general model system for the mass transport of drug in a suspension through the suspension and a permeable barrier to a perfect sink was presented. The appropriate equations for a general case and several specific cases were solved and evaluated. Drug distribution in a vehicle and a membrane and the cumulative drug mass uptake by a receptor phase were all related to the dissolution rate of the drug in the vehicle and diffusion through the vehicle and membrane for specified model conditions. If dissolution is essentially nonexistent during the time considered, then a suspension system behaves as a solution with respect to drug release. Where dissolution of the suspended drug into a semisolid vehicle is slower than diffusion, the rate of dissolution markedly influences the rate of drug release from the vehicle.

The classical model (9) for drug release from suspensions is simple to apply and describes drug release in many systems. It should certainly be used where the model requirements are satisfied. The system presented

Table III—Typical Example Values for the First Few Values of the Relative Solution Phase Concentration Distribution for Finite D_1; $D_1 = 10^{-9}$ cm^2/sec

	$\chi_1(x, t) = C_1(x, t)/C_S$			
Days	$x = -0.75L_1$	$x = -0.5L_1$	$x = -0.25L_1$	$x = 0L_1$
		$K = 0$ sec^{-1}		
0.5	0.1717	0.1711	0.1699	0.1684
1.0	0.1245	0.1242	0.1238	0.1232
2.5	0.0800	0.0800	0.798	0.0797
5.0	0.0569	0.0569	0.0568	0.0568
10.0	0.0398	0.0398	0.0397	0.0397
		$K = 10^{-6}$ sec^{-1}		
0.5	0.1823	0.1814	0.1799	0.1777
1.0	0.1408	0.1402	0.1393	0.1381
2.5	0.1081	0.1077	0.1071	0.1062
5.0	0.0984	0.0981	0.0975	0.0967
10.0	0.0999	0.0996	0.0994	0.0987
		$K = 10^{-4}$ sec^{-1}		
0.5	0.6649	0.6534	0.6339	0.6059
1.0	0.7446	0.7356	0.7202	0.6981
2.5	0.8316	0.8254	0.8149	0.8000
5.0	0.8794	0.8749	0.8673	0.8565
10.0	0.9134	0.9102	0.9047	0.8969

here is more complex and results in equations that are not simple and do not predict a simple relationship between drug release and time, particle size, or drug concentration. This model should be considered if its assumptions appear to be met and if experimental data are not described by the classical model.

The model presented here probably will provide some insight into the formulation of suspensions for application to the skin or mucous membranes. The equations presented are only valid for systems that satisfy the requirements of the model. Parameters other than dissolution rate that can affect drug release and parameter interrelationships will be investigated and discussed in a subsequent publication based on the model presented here.

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Diffusion Model for Drug Release from Suspensions II: Release to a Perfect Sink

F. TOM LINDSTROM *x and JAMES W. AYRES ‡

Abstract □ Numerical mathematical methods are applied to a diffusion model based on physicochemical principles to predict drug release from suspensions of drug in semisolid vehicles. The predicted mass of drug released *versus* time curves using this model are in agreement with some reported experimental data but differ from predictions using the classical model for semisolid suspensions. The differences are discussed in relation to the drug dissolution rate and diffusion rate in the vehicle.

Keyphrases □ Diffusion—suspended drug in semisolid vehicle, mathematical model based on physicochemical principles □ Dissolution—suspended drug in semisolid vehicle, mathematical model based on physicochemical principles □ Pharmacokinetic models—diffusion and dissolution of suspended drug in semisolid vehicle □ Drug release—from suspensions, diffusion model based on physicochemical principles □ Suspensions—drug release, diffusion model based on physicochemical principles

Previously (1), the complete theoretical development of a general nonlinear mass transport model was presented. Thus, this paper simply gives the nonlinear mass transport equations that incorporate local drug dissolution mechanics as already reported. The case under consideration is the mass transfer of drug out of an ointment vehicle containing dissolved and suspended drug when the semisolid is in immediate contact with a perfect sink (Fig. 1). A typical "real world" case where these conditions can exist

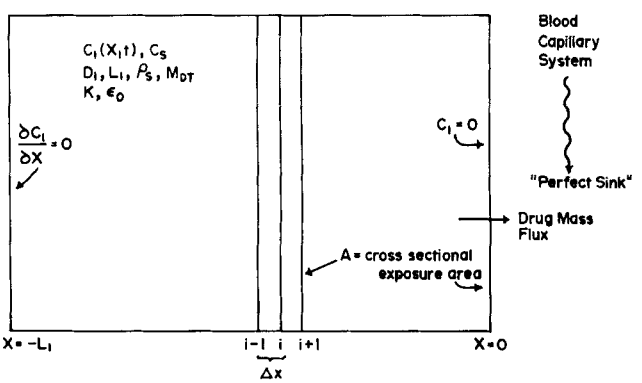

Figure 1—*Schematic of the model system for drug release directly to a perfect sink.*