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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* To whom inquiries should be directed.

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

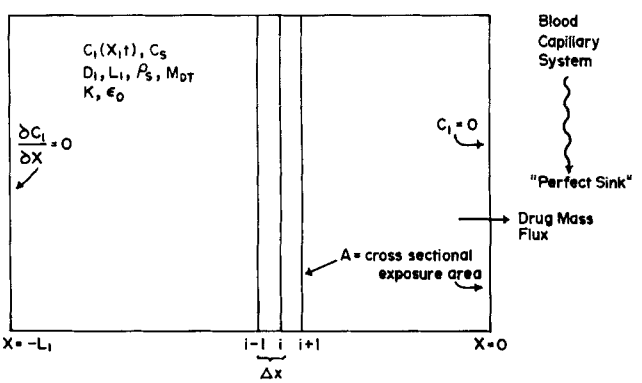

Figure 1—*Schematic of the model system for drug release directly to a perfect sink.*

Table I—Relative Cumulative Mass Release Values for the Distribution $\mu(t)$ as a Function of Time t in Minutes ($\epsilon_0 = 0.025$)[a]

	K, min^{-1}							
Minutes	0.0	0.01	0.1	1.0	10	100	1000	10,000
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
30	0.78	0.79	0.85	1.29	3.02	5.57	6.59	6.73
60	0.96	0.99	1.17	2.33	5.93	11.04	13.16	13.46
120	1.05	1.11	1.63	4.39	11.64	21.63	26.17	26.91
180	1.05	1.17	2.07	6.44	17.20	31.52	38.46	38.94
240	1.05	1.22	2.50	8.49	22.61	40.25	43.29	43.44
300	1.05	1.27	2.93	10.52	27.86	46.76	47.74	47.94
360	1.05	1.32	3.36	12.55	32.95	51.02	52.18	52.43
420	1.05	1.37	3.79	14.56	37.87	55.06	56.61	56.92
480	1.05	1.42	4.22	16.57	42.62	59.03	60.99	61.41
960	1.05	1.82	7.64	32.29	74.34	84.32	85.75	86.09
1440	1.05	2.23	11.04	47.42	96.14	103.63	104.48	104.74

[a] $D = 6 \times 10^{-8}$ cm^2/min, $L = 2 \times 10^{-3}$ cm, $C_s = 100$ μg/cm^3, $\rho_s = 1.0$ g/cm^3, and $\Delta t = 0.5$ min.

would be the application of ointment directly to an exposed capillary bed when the skin has been abraded.

This model also simulates certain laboratory experiments where a drug suspended in a semisolid is in direct contact with a large, well-stirred, uniform temperature receptor phase for a period of time. Drug release from suspension experiments have been carried out in this manner (2–4). This case was solved previously (1) using classical nonnumerical mathematical methods. This paper explores the predicted drug release from such systems obtained by numerical analysis of the system simulated in Fig. 1.

MASS TRANSPORT MODEL

The heart of the mass transport model for drug movement in the solution phase in an ointment base (1) is:

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

where:

C_1 = solution phase drug concentration distribution (grams per cubic centimeter)
D_1 = solution phase drug diffusion coefficient (square centimeters per minute)
C_s = solution phase drug saturation concentration (grams per cubic centimeter)
ρ_s = suspended phase drug density (powder density) (grams per cubic centimeter)
ϵ_0 = initial volume fraction of ointment that is suspended drug (cubic centimeter per cubic centimeter) and equals:

$$\left(\frac{M_{DT}}{AL_1} - C_s\right) \Big/ (\rho_s - C_s) \qquad C_s \leqq \frac{M_{DT}}{AL_1} \leqq \rho_s$$

M_{DT} = total drug mass in ointment sample (free and suspended) (grams)
A = exposure surface area of ointment (square centimeters) (Fig. 1)
L_1 = ointment slab thickness
$K = \kappa K_{cry}$, where K is the overall dissolution rate constant (min^{-1}), the product of the crystal surface area to volume constant and the energy-dependent reverse dissolution rate or crystallization rate constant K_{cry}. A more complete explanation of these terms is found in Ref. 1.

The subscripts (suppressed for the remainder of this paper) simply denote that a particular parameter or dependent variable belongs to the ointment portion of the model (Fig. 1).

The concentration distributions $C(x, t)$ can be obtained by solving the numerical analog of Eq. 1 subject to a no flux–perfect sink set of boundary conditions. The simulated system (Fig. 1) can be described mathematically as:

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

The initial conditions are:

$$C(x, +0) = C_s \qquad -L \leqq x < 0 \quad \text{(Eq. 3)}$$

The boundary conditions are:

$$\left.\frac{\partial C}{\partial x}\right|_{x=-L} = 0 \qquad \text{no flux boundary, } t > 0 \quad \text{(Eq. 4)}$$

$$C(0, t) = 0 \qquad \text{perfect sink, } t > 0 \quad \text{(Eq. 5)}$$

Since the system of mass transport (Eqs. 2–5) is nonlinear and the parameter values (especially K) may be large, the more classical math-

Table II—Relative Cumulative Mass Release Values for the Distribution $\mu(t)$ as a Function of Time t in Minutes ($\epsilon_0 = 0.05$)[a]

	K, min^{-1}							
Minutes	0.0	0.01	0.1	1.0	10	100	1000	10,000
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
30	0.78	0.79	0.88	1.51	3.56	5.94	6.65	6.74
60	0.96	1.00	1.27	2.82	7.04	11.83	13.29	13.48
120	1.05	1.15	1.93	5.43	13.92	23.50	26.56	26.95
180	1.05	1.23	2.56	8.02	20.69	34.96	39.78	40.43
240	1.05	1.31	3.19	10.62	27.34	46.15	52.92	53.89
300	1.05	1.39	3.82	13.20	33.88	56.97	65.89	67.33
360	1.05	1.47	4.45	15.77	40.30	67.26	77.36	77.48
420	1.05	1.55	5.08	18.34	46.60	76.68	81.83	81.98
480	1.05	1.63	5.71	20.89	52.77	84.56	86.31	86.48
960	1.05	2.26	10.72	41.05	97.22	119.08	121.91	122.44
1440	1.05	2.89	15.71	60.67	132.03	146.51	147.42	147.66

[a] $D = 6 \times 10^{-8}$ cm^2/min, $L = 2 \times 10^{-3}$ cm, $C_s = 100$ μg/cm^3, $\rho_s = 1.0$ g/cm^3, and $\Delta t = 0.5$ min.

Table III—Relative Cumulative Mass Release Values for the Distribution $\mu(t)$ as a Function of Time t in Minutes ($\epsilon_0 = 0.1$)[a]

	K, min^{-1}							
Minutes	0.0	0.01	0.1	1.0	10	100	1000	10,000
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
30	0.78	0.80	0.94	1.79	4.13	6.21	6.69	6.74
60	0.96	1.02	1.43	3.42	8.19	12.39	13.37	13.49
120	1.05	1.21	2.33	6.68	16.23	24.72	26.74	26.97
180	1.05	1.34	3.23	9.92	24.29	36.99	40.09	40.46
240	1.05	1.46	4.12	13.16	32.26	49.18	53.44	53.94
300	1.05	1.58	5.01	16.39	40.09	61.29	66.76	67.42
360	1.05	1.71	5.91	19.62	47.87	73.29	80.07	80.91
420	1.05	1.83	6.80	22.83	55.58	85.18	93.36	94.38
480	1.05	1.95	7.69	26.04	63.20	96.92	106.61	107.86
960	1.05	2.94	14.80	51.44	120.96	171.51	172.32	172.51
1440	1.05	3.92	21.89	76.35	172.05	206.02	208.15	208.49

[a] $D = 6 \times 10^{-8}$ cm^2/min, $L = 2 \times 10^{-3}$ cm, $C_S = 100$ μg/cm^3, $\rho_S = 1.0$ g/cm^3, and $\Delta t = 0.5$ min.

ematical methods such as perturbations (regular in this case) are not applicable. Thus, it is necessary to consider numerical methods for obtaining the close approximation concentration distributions. The exact numerical method used is that of backward finite differences, where the global error involved at any point in time and space always remains bounded and goes as $O(\Delta x^2 + \Delta t)$. The details of sectioning the ointment slab up into N discrete, but adjoining, compartments (analogous to N discrete, but intimately connected, well-mixed chemical reactors) are contained in the *Appendix*.

RESULTS AND DISCUSSION

The model drug–vehicle system chosen was cortisone powder suspended in a semisolid vehicle that is not soluble in the receptor sink. Thus, the following parameter data estimates are available (1): $N = 10$ compartments, $\Delta x = L/N$, $D = 6 \times 10^{-8}$ cm^2/min, $L = 2 \times 10^{-3}$ cm, $C_s = 100$ μg/cm^3, $\rho_s = 1.0$ g/cm^3, K is variable, $0 \leqq \kappa < \infty$ min^{-1}, and ϵ_0 is variable ($0 \leqq \epsilon_0 < 1$).

Since the relative cumulative drug mass release (grams) at any time t after the release process has begun is defined as (1):

$$\mu(t) = \frac{\int_0^t \left\{ -AD \left. \frac{\partial C}{\partial x} \right|_{x=0} \right\} d\tau}{M_0} \qquad \text{(Eq. 6)}$$

and $M_0 = ALC_s$, the actual formula used in calculating the relative cumulative drug mass release from the ointment is:

$$\mu(t) = -\frac{D}{L} \int_0^t \left\{ \left. \frac{\partial \eta}{\partial x} \right|_{x=0} \right\} d\tau \qquad \text{(Eq. 7)}$$

where $\eta(x, t) = C(x, t)/C_s$, and the partial derivative in Eq. 7 is replaced by a sufficiently high order (2 or higher) numerical approximation so that $O(\Delta x^2)$ is always retained (see *Appendix* for details).

For the finite sequence $\epsilon_0 = 0.025$, 0.05, 0.1, 0.2, and 0.4, the relative cumulative drug mass release, $\mu(t)$, as a function of time (minutes) over the interval 0–24 hr is summarized in Tables I–V. Note that $\epsilon_0 = 0.025$ is equivalent to a concentration of 2.5% drug in the semisolid and would give a maximum $\mu(t)$ value of 250. In like manner, the other ϵ_0 values follow suit and the maximum $\mu(t)$ for $\epsilon_0 = 0.4$ would be 4000.

Several important effects on the cumulative relative drug mass loss distribution can be observed by study of the distributions in Tables I–V. In the true case of no dissolution of drug in the vehicle ($K = 0$), there is no release of drug since none dissolves. This model assumes a C_s of 100 μg/cm^3; therefore, this total amount is predicted to be released when $K = 0$, since no more drug can dissolve to replace the released drug. Each 100 μg/cm^3 gives a relative release of 1.0; if the numerical approximation is exact, $\mu(t) = 1.00$ for the case $K = 0$ as $t \rightarrow$ large.

However, since the numerical simulation is actually formed from a truncated Taylor series, it is not exact but does remain close to the exact value as time $\rightarrow$ large (*i.e.*, the error remains bounded in time). For low overall dissolution rate constants, $0 \leqq K \leqq 0.1$ min^{-1} (the choice of 0.1 is, of course, dependent on D and L), the cumulative drug mass loss is quite slow and becomes linear with time after about 120 min (Tables I–IV, bottom three curves in Fig. 2). The exact value of time where this more or less zero-order type of drug release commences can be seen from the tables to be close to 120 min regardless of the initial total drug mass (ϵ_0). This type of phenomenon is expected for such low values of K, because the rate-limiting step in this region of K values is clearly dissolution. The drug simply cannot go into solution fast enough to replace what has been transported toward the boundary ($x = 0$) by diffusion when $D = 6 \times 10^{-8}$ cm^2/min.

In the highest case of $\epsilon_0 = 0.4$ (40% of the ointment slab consists of suspended drug initially), it can be calculated that as $t \rightarrow \infty$, $\mu(t) \rightarrow 4000$ for the example presented here. At the end of 24 hr, less than 1.0% of the total drug has been released due to the slow dissolution.

For values of K in the range $0.1 \leqq K \leqq 100.0$ min^{-1}, a substantial increase in the cumulative relative drug mass release distribution is seen compared to $K \leqq 0.1$ min^{-1}. This region (again dependent upon D and L) contains those values of K where the dissolution and diffusion processes are somewhat comparable and neither one is clearly the rate-limiting step. In this region of K values (over the first 24 hr anyway), the distributions are somewhat linear (Fig. 2) in time after a similar initial curvilinear buildup, as was observed for K in $0 \leqq K \leqq 0.1$ min^{-1}. The maximum cumulative drug release at 24 hr ($\epsilon_0 = 0.4$) is about 6%.

Table IV—Relative Cumulative Mass Release Values for the Distribution $\mu(t)$ as a Function of Time t in Minutes ($\epsilon_0 = 0.2$)[a]

	K, min^{-1}							
Minutes	0.0	0.01	0.1	1.0	10	100	1000	10,000
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
30	0.78	0.81	1.02	2.14	4.68	6.39	6.71	6.75
60	0.96	1.05	1.65	4.15	9.32	12.77	13.42	13.49
120	1.05	1.30	2.88	8.18	18.57	25.53	26.84	26.98
180	1.05	1.49	4.10	12.19	27.78	38.26	40.25	40.46
240	1.05	1.68	5.32	16.20	36.95	50.97	53.67	53.97
300	1.05	1.87	6.54	20.20	46.08	63.65	67.08	67.46
360	1.05	2.06	7.76	24.19	55.16	76.31	80.48	80.95
420	1.05	2.26	8.99	28.18	64.19	88.94	93.88	94.44
480	1.05	2.45	10.21	32.16	73.18	101.54	107.28	107.93
960	1.05	3.97	19.95	63.77	143.27	200.81	214.22	215.82
1440	1.05	5.50	29.68	94.94	209.69	293.54	308.42	308.55

[a] $D = 6 \times 10^{-3}$ cm^2/min, $L = 2 \times 10^{-3}$ cm, $C_S = 100$ μg/cm^3, $\rho_S = 1.0$ g/cm^3, and $\Delta t = 0.5$ min.

Table V—Relative Cumulative Mass Release Values for the Distribution $\mu(t)$ as a Function of Time t in Minutes ($\epsilon_0 = 0.4$)[a]

	K, min^{-1}							
Minutes	0.0	0.01	0.1	1.0	10	100	1000	10,000
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
30	0.78	0.82	1.13	2.56	5.19	6.52	6.73	6.75
60	0.96	1.10	1.95	5.02	10.35	13.03	13.45	13.50
120	1.05	1.43	3.57	9.94	20.66	26.05	26.90	27.00
180	1.05	1.73	5.19	14.85	30.95	39.07	40.35	40.48
240	1.05	2.02	6.80	19.76	41.21	52.08	53.80	53.98
300	1.05	2.31	8.42	24.66	51.46	65.08	67.24	67.47
360	1.05	2.60	10.04	29.55	61.68	78.07	80.69	80.97
420	1.05	2.89	11.65	34.44	71.87	91.05	94.13	94.46
480	1.05	3.18	13.27	39.32	82.05	104.03	107.58	107.96
960	1.05	5.51	26.18	78.19	162.56	207.51	215.09	215.91
1440	1.05	7.84	39.07	116.68	241.33	310.21	322.50	323.85

[a] $D = 6 \times 10^{-8}$ cm^2/min, $L = 2 \times 10^{-3}$ cm, $C_s = 100$ μg/cm^3, $\rho_s = 1.0$ g/cm^3, and $\Delta t = 0.5$ min.

In the region $100 \leqq K < \infty$ min^{-1} (∞ = 10,000 for Tables I–V), diffusion is the rate-limiting step. When diffusion is the rate-limiting process, the model predicts the following very interesting "moving source" phenomenon, which is in good agreement with literature data for release of medroxyprogesterone acetate from a cylindrical silicone polymer (5). Notice that under the columns labeled K = 10,000 min^{-1}, the relative cumulative drug mass distribution initially has a zero-order (Fig. 3) type of buildup ($0 < t < 60$ min). Then (especially at low ϵ_0 values), the release becomes non-zero order as the suspended drug in the surface layer [first compartment adjacent to the boundary ($x = 0$) in the numerical scheme] becomes exhausted and a type of diffusion layer or ointment boundary is created by the portion of the semisolid vehicle that is now drug free.

Initially, under high K values, a large burst of drug is obtained from the surface layer of ointment only. The other deeper regions in the ointment slab have essentially not yet begun to feel any concentration gradient in the local regions and are thus, for all practical purposes, just sitting still in time. However, as time goes on and the surface layer (first compartment) is exhausted of its suspended drug, the second layer (second compartment) begins to contribute drug by diffusion of dissolved drug and by sending suspended drug into solution. But this newly dissolved drug must diffuse through a thin permeable slab of ointment, the empty first compartment which is now devoid of any suspended drug, to the boundary $x = 0$.

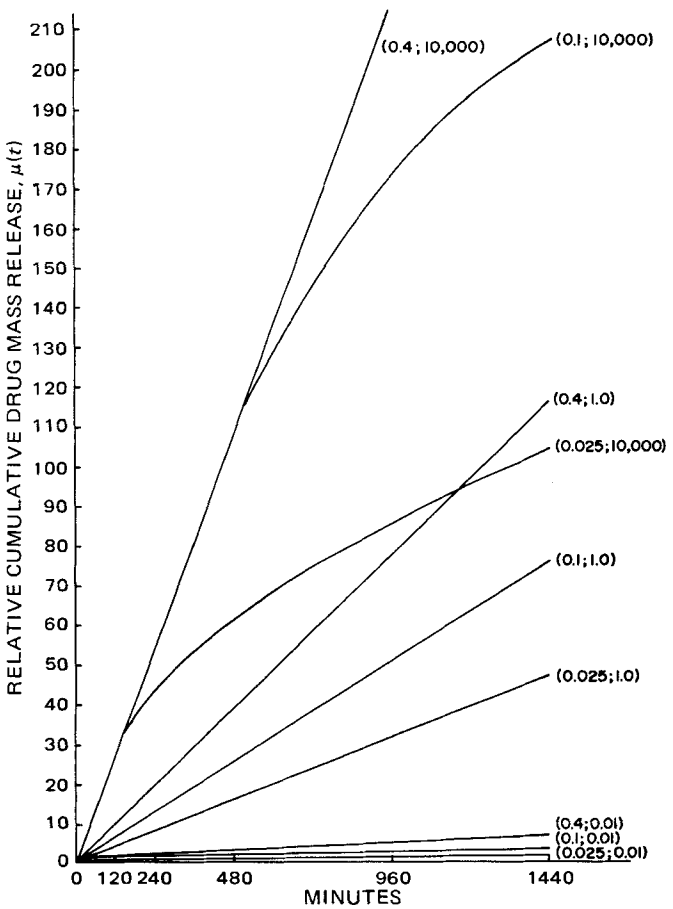

Figure 2—*Relationship between relative cumulative mass loss* μ(t) versus *time* t *in minutes for three different* ϵ_0 *values and three* K *values for each* ϵ_0 *value. The combinations are characterized via the order pair designation* (ϵ_0 = —; K = —).

As time goes on, the second layer is also depleted of its suspended drug and the third compartment begins to contribute. Now drug coming from the third compartment must diffuse through the first two compartments. This sequence is repeated in time until the entire ointment slab is devoid of all suspended and free drug under the hypothesis of this model. The net effect of these large values of K is to produce a moving source of suspended drug, very much like an earlier model (6) in which diffusion is the rate-limiting step.

From Table VI, it can be seen that after 24 hr the first four compartments are nearly exhausted of their initially suspended drug mass (K large) in the case of ϵ_0 being a 2.5% suspension, whereas only the first compartment is extensively depleted when ϵ_0 = 40%. This moving source phenomenon is the reason for the extreme curvilinearity in the case of ϵ_0 small and almost complete linearity for 24 hr for ϵ_0 large (Fig. 3).

Although the current model is in agreement with an earlier model (6) with respect to a moving source when dissolution is very rapid, the models predict different cumulative drug mass release *versus* time curves. The classical model (6) results in Eq. 8 to relate the amount and rate of release of drug suspended in an ointment vehicle to time and variables of the system (when $C_s \ll A$):

$$Q = S\sqrt{2ADC_s t} \qquad \text{(Eq. 8)}$$

where Q = amount of drug released at time t, S = surface area of exposure, A = concentration of drug (units per cubic centimeter), C_s = solubility of drug (units per cubic centimeter) in the vehicle, D = diffusion constant of the drug in the vehicle, and t = time.

Equation 8 predicts that the amount of drug released would be proportional to the square root of the total drug present. The model presented here predicts a limiting or upper bounding distribution (for large K values) as ϵ_0 increases (Fig. 3). Obviously, ϵ_0 cannot be increased beyond 1.0. However, it appears from the tables that ϵ_0 = 40% is probably close to the upper bounding distribution. This upper limit distribution is important and was observed experimentally (7).

Other experimental data indicate that the release of drug from a sus-

Table VI—Relative Cumulative Mass Loss Data and Relative Initial Mass Data (K = 10,000 min^{-1})

ϵ_0	Initial Relative Mass in Boundary Compartment	1440-min μ Reading
0.025	25	105
0.05	50	148
0.1	100	208
0.2	200	308
0.4	400	324

Table VII—Comparison of Relative Amounts of Predicted Drug Release Using Two Different Diffusion Models Assuming Rapid Dissolution[a]

	$\epsilon_0 = 0.025$		$\epsilon_0 = 0.10$		$\epsilon_0 = 0.20$		$\epsilon_0 = 0.40$	
Minutes	μ	μ_H	μ	μ_H	μ	μ_H	μ	μ_H
120	26.9	29.98	26.9	59.96	26.9	84.57	26.9	119.22
960	86	84.85	173	169.71	216	239.28	216	338.43
1440	105	103.94	209	207.89	309	337.43	324	413.37

[a] Relative amounts obtained for μ and μ_H using Eq. 7 and converting Eq. 8 to a form (1) that also predicts relative cumulative drug mass release at time t, namely, $\mu_H = \sqrt{2Dt}/L\ \sqrt{\rho\epsilon_0/C_S}$ or $\mu_H = Q/LC_S$.

pension in a semisolid is not always proportional to the square root of drug concentration and the ratio changes with time. Examples are sulfacetamide in hydrogenated cottonseed oil with surfactant and sulfathiazole in hydrogenated cottonseed oil (8). Salicylic acid suspended in several different vehicles was not released as predicted by Eq. 8, possibly due to an inadequate dissolution rate of the suspended particles (9). Release of suspended benzocaine from white petrolatum was not proportional to the square root of concentration for each sample obtained over the time period investigated (10).

Introduction of a membrane between the vehicle and the receptor phase, when the membrane is not rate limiting for release (as occurred in some experiments), would not change the relationship predicted by the model for Eq. 8 between concentration and amount released, although a lag time may be evident. A matrix–boundary diffusion layer model (5, 11, 12) was proposed to explain some cases where the release is not proportional to the square root of concentration. Such models incorporate the realistic assumption of a desorptive phenomenon occurring at the semisolid–receptor phase interface. This assumption is compatible with the model presented here and will be considered in a future publication.

The differences in predicted relative cumulative drug mass release using Eqs. 7 and 8 are shown in Table VII and Fig. 4. In the range of rapid dissolution for increasing drug concentrations, the model presented predicts little effect on the amount of drug released at short times and a limiting upper bound for drug release at longer times. In contrast, the classical model predicts a large effect at short times for increasing drug concentrations. The predicted effect at short times is highly dependent on the parameter constants being used and will vary for each drug–vehicle system. An upper bound, however, is predicted for all systems by the current model and not by the classical model.

The apparent linearity of μ *versus* $\sqrt{t}$ in Fig. 4 is due to computer time limitations. If this numerical simulation were plotted for 10 or 20 days consecutively, a pronounced negative curvature, especially at smaller ϵ_0 values, would clearly be seen at longer times. This negative curvature has no place in the theory of heat and mass transfer when simple $\sqrt{t}$ behavior is assumed. However, the negative curvature is a well-known phenomenon in heat and mass transfer theory when the complete Fourier series representation is given to the drug concentration distribution $C(x, t)$ across the ointment slab, $-L \leqq x < 0$.

The previous discussion was obtained from a rather good (as evidenced by the column labeled $K = 0$) numerical simulation of the transport model under the hypothesis that $D = 6 \times 10^{-8}$ cm^2/min and $L = 20$ μm. When these parameter values are changed for systems other than the one presented here, a new set of drug mass release distribution tables over the same range of K values can be easily obtained[1].

Since this scheme is numerical, it is instructive to consider the effects of changes in the mesh size, Δx, and time step size, Δt, on the distributions, $\mu(t)$. Since it is difficult to generate a large set of tables for the

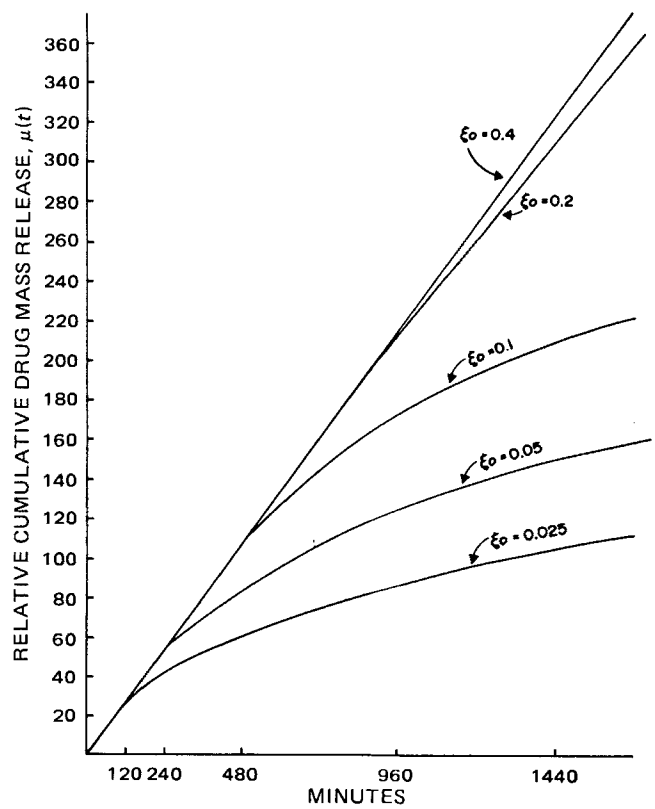

Figure 3—*Relationship of* μ(t) versus t *for* K = *10,000 min*$^{-1}$ *and* ϵ_0 *varying from* ϵ_0 = *0.025 to 0.4. Other parameters used in generating the curves are listed in the text.*

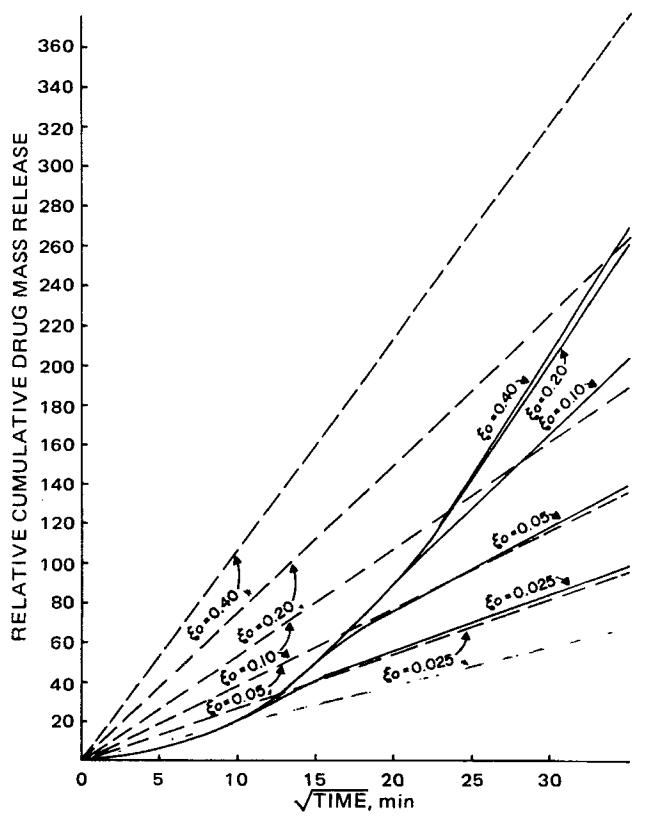

Figure 4—*Relationship of* μ(t) *or* μ_Ht versus $\sqrt{t}$ *for* K = *10,000 min*$^{-1}$ *and* ϵ_0 *varying from* ϵ_0 = *0.025 to 0.4. Other parameters used in generating the curves are listed in the text. Key:* μ(t), ——; *and* μ_H(t), - - -.

[1] This will be discussed in Part III of this series.

Table VIII—Relative Cumulative Mass Release Values for the Distribution $\mu(t)$ as a Function of Time t in Minutes ($\epsilon_0 = 0.1$ and $\Delta t = 0.25$ min)[a]

	K, min^{-1}							
Minutes	0.0	0.01	0.1	1.0	10	100	1000	10,000
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
30	0.76	0.77	0.91	1.77	4.12	6.20	6.69	6.74
60	0.94	0.99	1.41	3.40	8.18	12.39	13.37	13.49
120	1.02	1.18	2.31	6.66	16.27	24.72	26.74	26.97
180	1.03	1.31	3.20	9.90	24.28	36.99	40.09	40.46
240	1.03	1.43	4.10	13.14	32.21	49.18	53.43	53.94
300	1.03	1.56	4.99	16.37	40.07	61.28	66.76	67.42
360	1.03	1.68	5.88	19.60	47.86	73.29	80.07	80.91
420	1.03	1.80	6.77	22.81	55.56	85.17	93.36	94.38
480	1.03	1.93	7.66	26.02	63.18	96.91	106.60	107.86
960	1.03	2.91	14.78	51.42	120.94	171.41	172.15	172.28
1440	1.03	3.90	21.87	76.32	172.03	205.91	207.97	208.26

[a] $D = 6 \times 10^{-6}$ cm^2/min, $L = 2 \times 10^{-3}$ cm, $C_S = 100$ μg/cm^3, and $\rho_S = 1.0$ g/cm^3.

Table IX—Relative Cumulative Mass Release Values for the Distribution $\mu(t)$ as a Function of Time t in Minutes ($\epsilon_0 = 0.1$ and $\Delta t = 1.0$ min)[a]

	K, min^{-1}							
Minutes	0.0	0.01	0.1	1.0	10	100	1000	10,000
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
30	0.83	0.85	0.99	1.83	4.15	6.21	6.69	6.74
60	1.02	1.07	1.48	3.46	8.22	12.40	13.37	13.49
120	1.10	1.26	2.39	6.72	16.30	24.73	26.74	26.97
180	1.11	1.39	3.28	9.97	24.31	37.00	40.09	40.46
240	1.11	1.52	4.17	13.21	32.25	49.19	53.44	53.94
300	1.11	1.64	5.07	16.44	40.11	61.30	66.76	67.43
360	1.11	1.76	5.96	19.66	47.90	73.3	80.07	80.91
420	1.11	1.89	6.85	22.88	55.61	85.19	93.36	94.38
480	1.11	2.01	7.74	26.09	63.23	96.94	106.61	107.86
960	1.11	2.99	14.86	51.48	121.00	171.71	172.67	172.93
1440	1.11	3.98	21.95	76.39	172.11	206.22	208.49	208.91

[a] $D = 6 \times 10^{-6}$ cm^2/min, $L = 2 \times 10^{-3}$ cm, $C_S = 100$ μg/cm^3, and $\rho_S = 1.0$ g/cm^3.

various ϵ_0 *versus* K combinations for selected values of Δx and Δt while still retaining the total ointment thickness, L, and run time $t = 1440$ min, the cases of $\Delta t = 1$ min and $\Delta t = 0.25$ min for $\epsilon_0 = 0.1$ and $N = 10$ were chosen for evaluation. In accordance with theory (13), when N increases and Δx and Δt decrease, the order of the error goes down rapidly. Hence, the approximation becomes better and better.

Although this paper does not attempt to give an exact error analysis for the model presented, Tables III, VIII, and IX illustrate the accuracy and error stability of the numerical simulator used to approximate the solution to the complete nonlinear mass transport system. Tables VIII, III, and IX reflect the values $\Delta t = 0.25$, 0.5, and 1.0 min, respectively. All have the common parameter values used earlier. Examination of the tables shows that not only does the error remain bounded in all cases, as theory says it should (13), but also that the percentage difference between values for corresponding K values decreases with increasing time when Tables III and VIII are compared and when Tables VIII and IX are compared. The worst error occurs at early times and small K values ($0 \leqq K \leqq 0.1$). This finding is justified, however, by the error analysis (13) for parabolic-type partial differentio-integral equations of the type adapted for the transport model.

The value of Δt throughout this paper is 0.5 min. This value is the geometric mean of the two values 1.0 and 0.25, although the main reason for choosing 0.5 min is simply that it gives reasonably accurate μ values coupled with ease of computation.

SUMMARY

A numerical method was used to solve the equations associated with a new model for the release of suspended drug from a semisolid vehicle to an infinite sink. Evaluation of the method through the consideration of increasing t values shows the mathematics to be stable and bounded in the scheme presented. The model predicts a curvilinear relationship between the amount of drug released and the amount of drug present and the time elapsed other than time$^{1/2}$.

The release pattern may or may not appear linear with time or time$^{1/2}$ if release is evaluated over short time intervals. Use of such linear relationships to project drug release at earlier or later times than those actually evaluated may introduce considerable error with respect to the actual amount released.

APPENDIX

Consider the following nonlinear parabolic integro-differential problem for mass transport of drug in an ointment–perfect sink system:

$$\frac{\partial \eta}{\partial t} = D\frac{\partial^2 \eta}{\partial x^2} + K(1-\eta)\left(\epsilon_0^{1/3} - \frac{KC_s}{3\rho_s}\int_0^t [1-\eta(x,\tau)]\,d\tau\right)^2 \quad \text{(Eq. A1)}$$

for all (x, t) in $\{(-L_1 < x < 0) \times (t > 0)\}$ subject to the initial conditions:

$$\eta(x, +0) = 1.0 \qquad -L_1 \leqslant x > 0 \quad \text{(Eq. A2)}$$

and boundary conditions:

$$\left.\frac{\partial \eta}{\partial x}\right|_{x=-L_1} = 0 \qquad t > 0 \quad \text{(Eq. A3}a\text{)}$$

and:

$$\eta(0, t) = 0 \qquad t > 0 \quad \text{(Eq. A3}b\text{)}$$

and $\eta(x, t) = C(x, t)/C_s$. Note that D, K, ϵ_0, ρ_s, C_s, and L_1 are all positive parameters.

By using a reported scheme (13), the time derivative $\partial\eta/\partial t$ can be replaced by a backward in time difference quotient:

$$\left.\frac{\partial \eta}{\partial t}\right|_{t_{n+1}} \doteq \frac{\eta^{(n+1)} - \eta^{(n)}}{\Delta t} \quad \text{(Eq. A4)}$$

while the space derivative is approximated by a space-centered difference quotient:

$$\frac{\partial^2 \eta}{\partial x^2} \doteq \frac{1}{\Delta x^2}(\eta_{i-1} - 2\eta_i + \eta_{i+1}) \quad \text{(Eq. A5)}$$

and the integral term is evaluated backward in time by the trapezoidal rule. Note that $\Delta x = L_1/N$ and Δt is chosen arbitrarily small but positive. The $\eta_i^{(n)}$ notation used for the remainder of the paper means simply this:

$$\eta_i^{(n)} = \eta(x_i, t_n) = \eta(i\Delta x, n\Delta t)$$
$$i = 0, 1, 2, \ldots, N \qquad n = 0, 1, 2, \ldots \qquad \text{(Eq. A6)}$$

The space, time, and integral operators have been approximated in such a way that an implicit, irreducible, diagonal dominant linear system must be solved at each time step. The resulting iterative scheme is not only unconditionally stable but has been shown (13) to produce an approximating solution which converges uniformly to the true solution as Δx and $\Delta t \to 0$.

Define:

$$I_i^{(n)} = \left(\epsilon_0^{1/3} - \frac{KC_s}{3\rho_s}\int_0^{t_n}[1 - \eta_i(\tau)]\,d\tau\right)^2 \qquad \text{(Eq. A7)}$$

For computer computation, define:

$$J_i^{(n)} = \int_0^{t_n}[1 - \eta_i(\tau)]\,d\tau \qquad \text{(Eq. A8)}$$

By using the trapezoid rule, which retains $O(\Delta t)^2$ globally:

$$J_i^{(n)} = J_i^{(n-1)} + \frac{\Delta t}{2}\{2 - [\eta_i^{(n)} + \eta_i^{(n-1)}]\} \qquad \text{(Eq. A9)}$$

with $J_i^{(0)} = 0$ and $i = 0, 1, 2, \ldots, N$. Hence:

$$I_i^{(n)} = \left[\epsilon_0^{1/3} - \frac{KC_s}{3\rho_s}J_i^{(n)}\right]^2 \qquad \text{(Eq. A10)}$$

Putting all parts together gives the numerical scheme (tridiagonal system):

$$\frac{\eta_i^{(n+1)} - \eta_i^{(n)}}{\Delta t} = \frac{D}{\Delta x^2}\left[\eta_{i-1}^{(n+1)} - 2\eta_i^{(n+1)} + \eta_{i+1}^{(n+1)}\right] + K[1 - \eta_i^{(n+1)}]I_i^{(n)} \qquad \text{(Eq. A11)}$$

where $i = 1, 2, 3, \ldots, N-1$. The boundary conditions (no flux boundary) at $x = -L_1$, which corresponds to $i = 0$ in the "bookkeeping" of this numerical scheme, is approximated as:

$$\left.\frac{\partial\eta^{(n+1)}}{\partial x}\right|_{x=-L_1} \doteq \frac{1}{2\Delta x}[-3\eta_0^{(n+1)} + 4\eta_1^{(n+1)} - \eta_2^{(n+1)}] \qquad \text{(Eq. A12)}$$

where the $O(\Delta x^2)$ accuracy is preserved *via* this approximation. Since the boundary condition requires $(\partial\eta/\partial x)|_{x=-L_1} = 0$ for all $t \geq 0$, then:

$$\eta_0^{(n+1)} = \frac{4}{3}\eta_1^{(n+1)} - \frac{1}{3}\eta_2^{(n+1)} \qquad \text{(Eq. A13)}$$

This equation, together with the boundary condition at $i = N$ ($x = 0$), $\eta_N^{(n+1)} = 0$, and $n = 0, 1, 2, \ldots$, and Eq. A11 give, after some algebra, the tridiagonal system (interative):

$$\begin{aligned}
a_{11}\eta_1^{(n+1)} + a_{12}\eta_2^{(n+1)} + 0\eta_3^{(n+1)} + \ldots + 0\eta_{N-1}^{(n+1)} &= \eta_1^{(n)} + K\Delta t I_i^{(n)} \\
a_{21}\eta_1^{(n+1)} + a_{22}\eta_2^{(n+1)} + a_{21}\eta_3^{(n+1)} + 0\eta_4^{(n+1)} + \ldots + 0\eta_{N-1}^{(n+1)} &= \eta_2^{(n)} + K\Delta t I_2^{(n)} \\
&\vdots \quad \vdots \quad \vdots \\
0\eta_1^{(n+1)} + \ldots + a_{21}\eta_{N-2}^{(n+1)} + a_{N-1,N-1}\eta_{N-1}^{(n+1)} &= \eta_{N-1}^{(n)} + K\Delta t I_{N-1}^{(n)}
\end{aligned} \qquad \text{(Eq. A14)}$$

where:

$$a_{11} = 1 + \frac{2}{3}\frac{D\Delta t}{\Delta x^2} + K\Delta t I_1^{(n)}$$
$$a_{12} = -\frac{2}{3}\frac{D\Delta t}{\Delta x^2}$$
$$a_{21} = -\frac{D\Delta t}{\Delta x^2}$$
$$a_{ii} = 1 + \frac{D\Delta t}{\Delta x^2} + K\Delta t I_i^{(n)},\ i = 2, 3, 4, \ldots, N-1$$

Hence, by iteration with the matrix system:

$$A^{(n)}\eta^{(n+1)} = \eta^{(n)} + K\Delta t\,\mathbf{I}^{(n)} \qquad \text{(Eq. A15)}$$

the relative concentration distribution $\eta^{(n+1)} = [\eta_0^{(n+1)}, \eta_1^{(n+1)}, \eta_2^{(n+1)} \ldots \eta_N^{(n+1)}]^1$, is obtained in terms of the previous time level relative concentration distribution and any new drug which has come into solution in the intervening time.

It remains now to calculate $\mu_1(t)$, the relative cumulative drug mass loss from the ointment system. Since $\mu_1(t)$ is defined as:

$$\mu_1(t) = \frac{\int_0^t\left\{-DA\left.\frac{\partial C}{\partial x}\right|_{x=0}\right\}}{AL_1C_s}d\tau = -\frac{D}{L_1}\int_0^t\left.\frac{\partial\eta}{\partial x}\right|_{x=0}d\tau \qquad \text{(Eq. A16)}$$

the space derivative at the right-hand boundary $x = 0$ is replaced by the numerical approximation which preserves the $O(\Delta x^2)$ accuracy locally and globally in time:

$$\left.\frac{\partial\eta}{\partial x}\right|_{x=0} \doteq \frac{1}{2\Delta x}[\eta_{N-2} - 4\eta_{N-1} + 3\eta_N] \qquad \text{(Eq. A17)}$$

Under the assumption that there is a perfect sink condition operating at all times at the ointment–sink boundary, $x = 0$, $\eta_N^{(n)} = 0$, and $n = 1, 2, \ldots$. Hence, substituting for this space derivative approximation and again using the trapezoid rule for numerical quadrature in time yield:

$$\mu^{(n+1)} = \frac{D}{2\Delta x L_1}I_2^{(n+1)} \qquad \text{(Eq. A18)}$$

where:

$$I_2^{(n+1)} = I_2^{(n)} + \frac{\Delta t}{2}\{4[\eta_{N-1}^{(n+1)} + \eta_{N-1}^{(n)}] - [\eta_{N-2}^{(n+1)} + \eta_{N-2}^{(n)}]\} \qquad \text{(Eq. A19)}$$

with $I_2^{(0)} = 0$.

Equations A9, A10, A13, and A14 constitute the numerical simulation for the relative solution phase drug concentration at any point in time, while Eqs. A18 and A19 are used to obtain the relative cumulative drug mass release from the ointment slab at time $t \geq 0$.

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ˣ To whom inquiries should be directed.