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A mathematical model for drug release from a two-phase system to a perfect sink

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Summary

A mathematical model is presented, which describes drug release from a two-phase system to a perfect sink, taking time-dependent partition within the system as well as outward diffusion into account. An analytical solution to the problem is derived, which may be used for model-bound curve fitting of release data, as well as for predicting release patterns from given starting conditions; in fact, conditions are characterized under which first- or even zero-order release from such systems is expected. Furthermore, the model may serve as a basis for deducing approximations for special cases.

Introduction

Drug delivery systems often comprise more than one phase. This paper primarily deals with biphasic systems in which drugs may be dissolved, partitioned between both phases. Interesting examples are emulsions, micro-emulsions (Hoar and Schulman, 1943), non-ionic ointments (de Vringer et al., 1984), hydrocolloid gels containing liposomes (Mezei and Gulasekharan, 1982) and the stratum corneum insofar as it functions as a drug reservoir.

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In emulsions the drug may partition between the lipophilic and hydrophilic phases; in non-ionic ointments a drug may be distributed among the lipophilic and hydrophilic layers within the gel structure; in gels containing liposomes, drug molecules may be present both in- and outside the liposomes. In the stratum corneum the drug may be distributed between intra- and extracellular space.

Experimental data suggest that the partition of a drug within a biphasic system has consequences for the release of the drug (Ponec and Polano, 1979; Mezei and Gulasekharan, 1982). In existing mathematical models relevant to the problem outlined here, drug partition within the system is either neglected (Higuchi, 1960), or described as an equilibrium (Higuchi and Higuchi, 1960; Hadgraft, 1979), or as diffusion across an interfacial barrier (Yotsuyanagi et al., 1973). In the last mentioned model the interfacial barrier is assumed equally permeable in both directions, and drug partition across it assumed constant; a numerical solution to the problem has been given recently (Yotsuyanagi et al., 1973).

This paper deals with a mathematical model for drug release from a two-phase system, which takes time dependence of drug partition into account by the use of partition rate constants. The model yields a straightforward analytical solution.

Model

Consider a system comprising an internal phase (i) with arbitrary geometry, which is more or less homogeneously dispersed within an external, continuous phase (e). A projection on the x–y plane is shown in Fig. 1a. The system is closed on all sides except at $x = 0$ where the external phase is in direct contact with a perfect sink. We assume that within each element (droplet, cell, layer, etc.) of the internal phase the drug is homogeneously distributed (i.e. each element of the internal phase is a well stirred entity) at all times; within the external phase we assume homogeneous drug distribution (i.e. infinitely fast diffusion) along the y-axis, but allow inhomogeneous drug distribution (slow diffusion) along the x-axis at finite times. This of course implies that concentration differences between elements of the internal phase can be invoked by concentration gradients in the external phase. Concentration gradients across the interfacial barriers between the phases may arise in any direction.

Within these limitations the two-*phase* system is equivalent to a two-*compartment* system extending from $x = -H$ to $x = 0$ and consisting of an 'internal' compartment on top of an 'external' compartment which is in direct contact with a sink (Fig. 1b). The internal compartment has *no* direct contact with the sink. The discontinuity of the internal *phase* is reflected by the absence of diffusion along the x-axis within the internal *compartment*.

Further assumptions are: the drug is the only diffusing compound and does not disintegrate or associate with other compounds; drug partition between the two compartments is a first-order, single-step phenomenon, and drug diffusion through the external compartment obeys Fick's laws, the diffusion coefficient being independent of the drug concentration. Upon these assumptions the mathematical descrip-

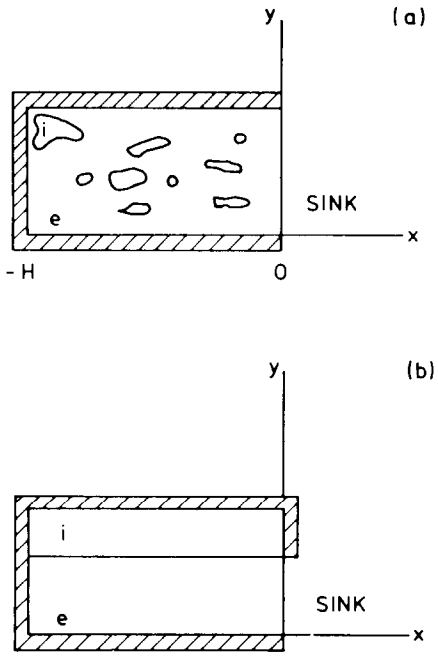

Fig. 1. a: schematic cross-section of a two-phase system in the x–y-plane. i and e denote internal and external phase, resp.; shaded zone is impermeable barrier. b: schematic cross-section of a two-compartment system in x–y-plane. i and e denote internal and external compartment, resp.; shaded zone is impermeable barrier.

tion of the model can now be derived. All symbols used are listed in Table 1.

Drug partition between the two compartments is described by writing the *net*, stationary flux across the interfacial barrier between the two compartments as:

$$\frac{1}{B} \cdot \left(\frac{dM}{dt} \right)_{e \to i} = k_i c_e - k_e c_i \tag{1}$$

or

$$\frac{1}{B} \cdot \left(\frac{dM}{dt} \right)_{i \to e} = k_e c_i - k_i c_e$$

Two different permeabilities (k_i and k_e) are used to account for asymmetry of the interfacial barrier as well as for the time dependence of drug partition between the compartments (see Appendix 1). If diffusion along the x-axis were absent within the external compartment as well, the following mass balance equations would hold:

$$V_i \cdot \frac{dc_i}{dt} = \left(\frac{dM}{dt} \right)_{e \to i} \tag{2}$$

$$V_e \cdot \frac{dc_e}{dt} = \left(\frac{dM}{dt} \right)_{i \to e}$$

TABLE 1

LIST OF SYMBOLS

B	Specific surface area of the interfacial barrier	(m^2)
$c_{i(e)}$	Drug concentration in the internal (external) compartment	($mol \cdot m^{-3}$)
D	Diffusion coefficient in the external compartment	($m^2 \cdot s^{-1}$)
H	Thickness (extension along x-axis) of the system	(m)
$k_{i(e)}$	Permeability of the interfacial barrier from the external to the internal compartment (or vice versa)	($m \cdot s^{-1}$)
$(\frac{dM}{dt})_{(i \rightleftarrows e)}$	Rate of drug transfer from the external to the internal compartment (or vice cersa)	($mol \cdot s^{-1}$)
Q(t)	Cumulative release of drug per unit contact surface area	($mol \cdot m^{-2}$)
$V_{i(e)}$	Internal (external) compartment volume	(m^3)
$\alpha = \frac{Bk_e}{V_i}$, $\gamma = \frac{Bk_e}{V_e}$	Rate constants of 'outward' partition	(s^{-1})
$\beta = \frac{Bk_i}{V_i}$, $\epsilon = \frac{Bk_i}{V_e}$	Rate constants of 'inward' partition	(s^{-1})

Inserting Eqn. 1 into Eqn. 2, we would have:

$$\frac{dc_i}{dt} = \frac{B}{V_i} \cdot [k_i c_e - k_e c_i] \tag{3}$$

and

$$\frac{dc_e}{dt} = \frac{B}{V_e} \cdot [k_e c_i - k_i c_e]$$

For a discussion of the geometry factors B/V_i and B/V_e, see Appendix 2.

By also allowing diffusion through the external compartment along the x-axis into the sink, the following set of differential equations is obtained:

$$\frac{\delta c_i}{\delta t} = -\alpha c_i + \beta c_e \tag{4}$$

and

$$\frac{\delta c_e}{\delta t} = D \cdot \frac{\delta^2 c_e}{\delta x^2} + \gamma c_i - \epsilon c_e \tag{5}$$

where α, β, γ and ϵ are partition rate constants (s^{-1}) (see also Appendix 2).

The boundary conditions imposed are:
homogeneity at zero time:

$$c_i(x, t) = c_i^0; \quad (t = 0) \tag{6}$$

$$c_e(x, t) = c_e^0; \quad (t = 0) \tag{7}$$

partition equilibrium at zero time:

$$\frac{c_i^0}{c_e^0} = \frac{\beta}{\alpha} = \frac{\epsilon}{\gamma} = \frac{k_i}{k_e} \tag{8}$$

perfect sink conditions at all times:

$$c_e(x, t) = 0; \quad (x \geqslant 0) \tag{9}$$

no flux at the impermeable barrier at all times:

$$\frac{\delta c_e}{\delta x} = 0; \quad (x = -H) \tag{10}$$

General solution for $c_e(x, t)$, the drug concentration in the external compartment

Upon Laplace transformation with respect to time of c_i, i.e. $\hat{c}_i(s) = {}_0\int c_i(t)e^{-st}dt$, and similarly for c_e, (Eqns. 4 and 5) yield:

$$\frac{d^2\hat{c}_e}{dt^2} = p\hat{c}_e - q \tag{11}$$

where:

$$p = \frac{1}{D}\left[(s + \epsilon) - \frac{\epsilon\alpha}{s + \alpha}\right] \tag{12}$$

$$q = \frac{1}{D}\left[c_e^0 + \frac{\gamma c_i^0}{s + \alpha}\right] \tag{13}$$

The general solution to Eqn. 11 is:

$$\hat{c}_e = Z_1 e^{-x\sqrt{p}} + Z_2 e^{x\sqrt{p}} + q/p \tag{14}$$

where Z_1 and Z_2 follow from Eqns. 9 and 10:

$$Z_1 = \frac{-q/p}{1 + e^{2H\sqrt{p}}} \text{ and } Z_2 = \frac{-(q/p)\, e^{2H\sqrt{p}}}{1 + e^{2H\sqrt{p}}}$$

Noting from Eqn. 8 that $q/p = c_e^0/s$, we have:

$$\hat{c}_e = \frac{c_e^0}{s}\left[1 - \frac{\cosh\left[(x+H)\sqrt{p}\right]}{\cosh\left[H\sqrt{p}\right]}\right] \tag{15}$$

Inverse transformation of $\hat{c}_e(x, s)$ (see Appendix 3) results in:

$$c_e(x, t) = \frac{c_e \pi}{H^2} \cdot \sum_{n=0}^{\infty} (2n+1) \sin\left[(2n+1)\frac{\pi x}{2H}\right]\left[\frac{e^{s_n^I t}}{s_n^I\left(\frac{dp}{ds}\right)_{s_n^I}} + \frac{e^{s_n^{II} t}}{s_n^{II}\left(\frac{dp}{ds}\right)_{s_n^{II}}}\right] \tag{16}$$

Consistency of this solution with boundary conditions is verified in Appendix 4.

General solution for Q(t), the cumulative amount of drug released to the sink

Let the interface between the external compartment and the sink be called 'contact surface'. We now define the cumulative release per unit contact surface area as:

$$Q(t) = \int_0^t J_o(\tau)\,d\tau \tag{17}$$

$J_0(\tau) = [-D\frac{\delta c_e}{\delta x}]_{x=0}$ being the drug flux into the sink. Applying Eqn. 17 to Eqn. 16, we obtain:

$$Q(t) = \frac{Dc_e^0 \pi^2}{2H^3} \cdot \sum_{n=0}^{\infty} (2n+1)^2\left[\frac{1 - e^{s_n^I t}}{(s_n^I)^2\left(\frac{dp}{ds}\right)_{s_n^I}} + \frac{1 - e^{s_n^{II} t}}{(s_n^{II})^2\left(\frac{dp}{ds}\right)_{s_n^{II}}}\right] \tag{18}$$

Consistency with boundary conditions is verified in Appendix 5.

Results and Discussion

An essential argument upon which this model is based is that equilibrium parameters such as partition coefficients probably do not apply to the time dependent partition of a drug within a two-phase system during its release. A kinetic description of partition was considered more appropriate. Partition may comprise a number of steps, e.g. desolvation, barrier permeation and resolvation. Any of these steps may give rise to different rate constants depending on the direction of mass movement; such will be the case if for instance the interfacial barrier is asymmetric. For the sake of simplicity, partition in this model is considered a single-step phenomenon.

The formulae deduced above were applied to a number of interesting cases, each characterized by a different set of input parameter values. The purpose of the calculations was to find out how various choices of parameter values would influence concentration profiles and release patterns, and to what extent drug partition between the compartments and diffusion through the external compartment would each contribute to the release processes as a whole. In this way either diffusion or partition control could be predicted. In all cases the initial drug concentration in the external compartment (c_e^0), the thickness of the system (H) and the diffusion coefficient in the external compartment (D) were taken constant; only the partition rate constants (α and ϵ) differed from case to case. To facilitate interpretation of the results of calculations in physical terms, equal compartment volumes were chosen ($V_i = V_e$), so that $\epsilon/\alpha = K$, the partition coefficient (see Appendix 1). To allow direct comparison between partition and diffusion parameters, a characteristic 'diffusion rate constant' was defined as D/H^2. The diffusion rate constant has the dimension of reciprocal time. Thus each case of interest corresponds to a set of values for three parameters of equal dimension: D/H^2, α and ϵ. In total, 7 cases were considered; in each case both the concentration profile in the external compartment ($c_e(x)$ after 500 s) and the cumulative release (Q(t)) were calculated, truncating the summations after 1600 terms. Further extension of the series was considered unnecessary, since the maximal improvement obtained was never more than 0.4%. Input parameter values and results of calculations are listed in Table 2. The results are also plotted in Figs. 2 and 3; only Cases I, VI and VII are shown, since the plots of cases I–V almost coincide.

Case I. Single compartment, diffusion only ($\epsilon = \alpha = 0$)

An important test case for the derived model is the case, where the internal compartment is isolated or taken away, leaving only one single compartment in contact with the sink. Mathematically this means $k_i = k_e = 0$. Application of the model to this case should yield a correct expression for drug release from a single, homogeneous compartment to a perfect sink. Inserting $k_i = k_e = 0$ into Eqns. 12, 13 and 14, we obtain:

$$Q(t) = c_e^0 H \frac{8}{\pi^2} \cdot \sum_{n=0}^{\infty} \frac{1 - e^{-(2n+1)^2 D\pi^2 t/4H^2}}{(2n+1)^2}$$

Indeed, the last expression is equivalent to the one given by Higuchi and Higuchi (1960) for drug release from a homogeneous one-phase system. Since there is only one compartment, drug release is purely diffusion-controlled in this case. The concentration profile and release data pertaining to this case serve as references to the other cases.

Cases II and III. Partition slower than diffusion ($D/H^2 \gg \alpha \gg \epsilon$ or $D/H^2 \gg \epsilon \gg \alpha$)

Not very different from Case I are the cases where partition is much slower than diffusion. This would occur if for instance the interfacial barrier between the

TABLE 2

RESULTS OF CALCULATIONS FOR CASES I–VII

Constants	$c_e^0 = 1\ mol \cdot m^{-3}$ $D = 10^{-11}\ m^2 \cdot s^{-1}$ $D/H^2 = 10^{-5}\ s^{-1}$ $H = 10^{-3}\ m$						
Case	I	II	III	IV	V	VI	VII
$\alpha\ (s^{-1})$	0	10^{-9}	10^{-7}	10^{-5}	10^{-1}	10^{-7}	10^{-3}
$\epsilon\ (s^{-1})$	0	10^{-7}	10^{-9}	10^{-5}	10^{-3}	10^{-3}	10^{-1}
x(mm)	$c_e(mol \cdot m^{-3})$ at t = 5000 s						
0.00000000E+00	0.00000000E+00	0.00000000E+00	0.00000000E+00	0.00000000E+00	0.00000000E+00	0.00000000 +00	0.00000000 +00
−1.00000000E−01	2.48170000E−01	2.48250000E−01	2.48170000E−01	2.56100000E−01	2.49370000E−01	6.32330000E−01	9.9112000 E−01
−2.00000000E−01	4.72910000E−01	4.73010000E−01	4.72910000E−01	4.82670000F−01	4.74970000E−01	8.64760000E−01	9.99820000E−01
−3.00000000E−01	6.57220000E−01	6.57310000E−01	6.57220000E−01	6.65630000E−01	6.59620000E−01	9.50520000E−01	1.00010000E+00
−4.00000000E−01	7.94100000E−01	7.94160000E−01	7.94100000E−01	8.00100000E−01	7.96350000F−01	9.81900000E−01	9.99910000E−01
−5.00000000E−01	8.86150000E−01	8.86190000E−01	8.86150000E−01	8.89870000E−01	8.87940000E−01	9.93520000E−01	1.00010000E+00
−6.00000000E−01	9.42210000F−01	9.42230000E−01	9.42210000E−01	9.44260000E−01	9.43450000E−01	9.97660000E−01	9.99940000E−01
−7.00000000E−01	9.73100000E−01	9.73110000E−01	9.73100000E−01	9.74120000E−01	9.73860000E−01	9.99230000E−01	1.00010000E+00
−8.00000000E−01	9.88440000E−01	9.88440000E−01	9.88440000E−01	9.88900000E−01	9.88850000E−01	9.99710000E−01	9.99940000E−01
−9.00000000E−01	9.95070000E−01	9.95070000E−01	9.95070000E−01	9.95270000E−01	9.95290000E−01	9.99930000E−01	1.00010000E+00
−1.00000000E+00	9.96870000E−01	9.96870000E−01	9.96870000E−01	9.97000000E−01	9.97030000E−01	9.99920000E−01	9.99950000E−01
t(s)	$Q\ (mol \cdot m^{-2})$						
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
500	0.0000798	0.0000796	0.0000797	0.0000798	0.0000801	0.0000923	0.0004456
1000	0.0001128	0.0001127	0.0001127	0.0001131	0.0001133	0.0001469	0.0008005
1500	0.0001382	0.0001381	0.0001381	0.0001388	0.0001388	0.0001984	0.0010948
2000	0.0001596	0.0001595	0.0001595	0.0001605	0.0001602	0.0002490	0.0013453
2500	0.0001784	0.0001784	0.0001783	0.0001798	0.0001792	0.0002993	0.0015637
3000	0.0001954	0.0001955	0.0001953	0.0001972	0.0001963	0.0003493	0.0017579
3500	0.0002111	0.0002112	0.0002110	0.0002134	0.0002120	0.0003993	0.0019335
4000	0.0002257	0.0002258	0.0002255	0.0002285	0.0002267	0.0004493	0.0020945
4500	0.0002394	0.0002396	0.0002392	0.0002427	0.0002404	0.0004992	0.0022439
5000	0.0002523	0.0002526	0.0002522	0.0002563	0.0002534	0.0005492	0.0023837

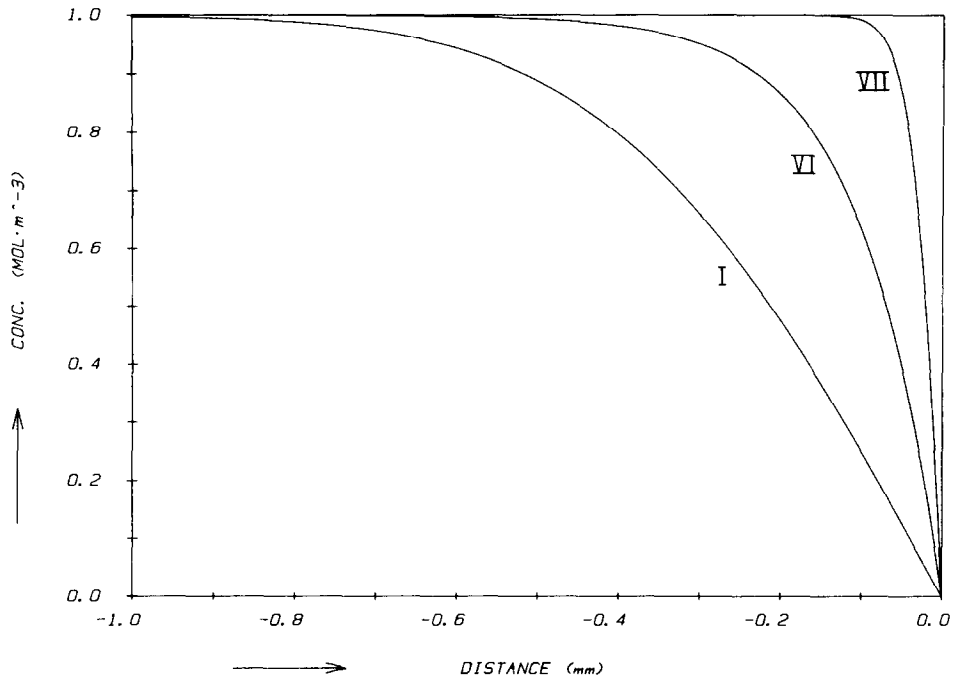

Fig. 2. Calculated concentration profiles in external compartment after 5000 s. Roman numbers refer to Cases I, VI and VII, resp.

compartments (phases) had a poor permeability to the drug, or if (de-)solvation rates were low. The concentration profiles and release plots obtained for these cases hardly differ from the ones corresponding to the single-compartment case (Case I): the system behaves as if consisting of only one compartment. Apparently, under these conditions repartition between the compartments is negligible, and diffusion through the external compartment is the rate determining step.

Case IV. Partition and diffusion equally fast ($D/H^2 = \epsilon = \alpha$)

In this case the rates of partition between the compartments match the rate of diffusion through the external compartment. Consequently, the interfacial barrier between the two compartments vanishes and the system becomes 'transparent': we are in fact dealing with a single compartment which participates in the diffusion process as a whole. Both the release rate and the concentration profile only slightly differ from the single-compartment Case I, the slight difference being entirely due to the larger total drug content in case IV. Again the drug release is diffusion controlled.

Case V. Partition faster than diffusion; 'outward' partition fastest ($\alpha \gg \epsilon \gg D/H^2$)

Here the rates of partition between the compartments are higher than the diffusion rate, 'outward' partition (i.e. partition towards the external compartment)

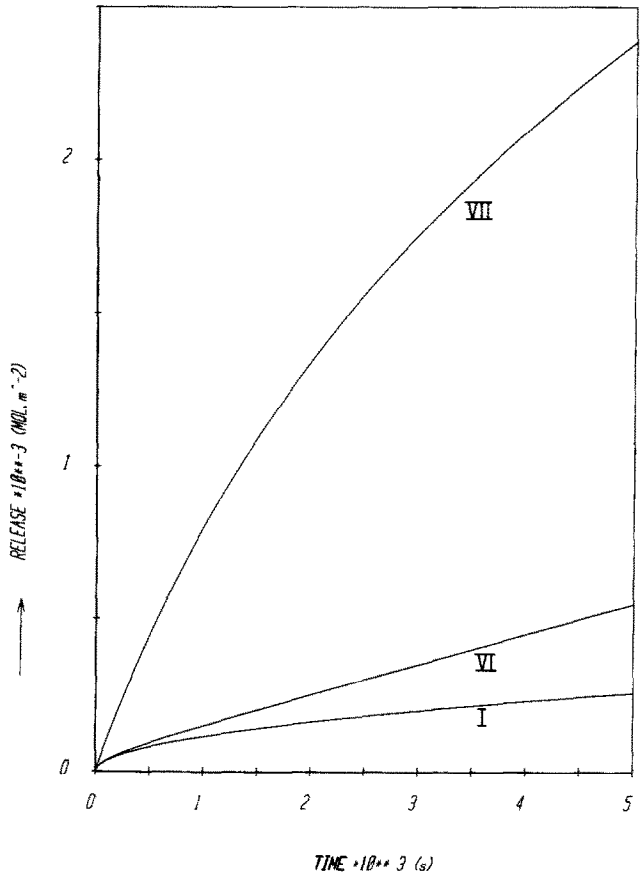

Fig. 3. Calculated cumulative release versus time for Cases I, VI and VII.

being the fastest step. An appreciable increase of release rates with respect to Case I would be expected. However, this only occurs to a very small extent (compare Q(t) values in columns I and V of Table 2). Obviously the internal drug mass is already very small at zero time ($c_i^0 = \frac{\epsilon}{\alpha} c_e^0 \ll c_e^0$) and negligible with respect to the total drug mass. This is inherent to the imposement of partition equilibrium at zero time (Eqn. 8). The drug release is mainly diffusion-controlled in this case.

Case VI. Diffusion slower than 'inward' but faster than 'outward' partition ($\epsilon \gg D/H^2 \gg \alpha$)

An interesting case arises when the diffusion rate is chosen *in between* the rates of partition, 'inward' partition (towards the internal compartment) being the fastest. Here we observe after an initial period roughly a two-fold increase in the steepness of the concentration profile near the sink as well as in the release rate, as compared to Case I (Figs. 2 and 3). Although α is small, 'outward' partition obviously contributes considerably to the release due to the large 'internal' drug mass

($c_i^0/c_e^0 = \epsilon/\alpha = 10^4$) which 'buffers' the 'external' drug mass. This 'buffer' effect is reflected in the high drug content of the external compartment as compared to Case I and in the steep concentration gradient near the sink (Fig. 2, curve VI).

Interestingly after about 1000 s drug release proceeds linearly with time, i.e. we have *zero-order* kinetics (Fig. 3, curve VI). The slope of curve VI (Fig. 3) in the interval 1000 s $\leqslant$ t $\leqslant$ 5000 s was calculated to be:

$$\left(\frac{dQ}{dt}\right)_{lin} = 1.00 \times 10^{-7}\ \text{mol} \cdot \text{m}^{-2} \cdot \text{s}^{-1}$$

with a correlation coefficient larger than 99.999%. Apparently a *steady-state* develops in the external compartment after about 1000 s; the steady-state is maintained as long as partition into the external compartment compensates for outward diffusion, i.e. as long as the 'internal' drug concentration is nearly constant. As soon as the internal compartment becomes substantially depleted, the steady-state breaks down. This obviously occurs at the upper bound of the linear interval, which was in fact calculated to be at $t = 10^7$ s.

It can indeed be shown algebraically that the choice of parameter values made here *inevitably* leads to stationary behaviour; it is even possible to derive an accurate and simple approximation for the stationary release rate; differentiation of Eqn. 8 with respect to time yields:

$$\frac{dQ}{dt} = C_1(R_1 + R_2) \tag{19}$$

with

$$C_1 = \frac{Dc_e^0\pi^2}{2H^3}$$

$$R_1 = \sum_{n=0}^{\infty} (2n+1)^2 \cdot \frac{-e^{s_n^I t}}{s_n^I \left(\frac{dp}{ds}\right)_{s_n^I}}$$

$$R_2 = \sum_{n=0}^{\infty} (2n+1)^2 \cdot \frac{-e^{s_n^{II} t}}{s_n^{II} \left(\frac{dp}{ds}\right)_{s_n^{II}}}$$

$$s_n^{I,II} = (Dp_n - \epsilon - \alpha \mp y)/2$$

$$y = \sqrt{(\epsilon + \alpha - Dp_n)^2 + 4\alpha Dp_n}$$

$$p_n = -\left(\frac{2n+1}{2}\right)^2 \cdot \frac{\pi^2}{H^2}; \quad (n = 0, 1, 2 \ldots.)$$

and

$$\left(\frac{dp}{ds}\right)_{s_n^{I,II}} = \frac{1}{D}\left[1 + \frac{\alpha\epsilon}{\left(S_n^{I,II} + \alpha\right)^2}\right]; \quad (n = 0, 1, 2\ldots.)$$

Rewriting
$y = \sqrt{(\epsilon - \alpha - Dp_n)^2 + 4\alpha\epsilon}$; since $\epsilon \gg D/H^2 \gg \alpha$, we may approximate y by:
$y \approx \epsilon - \alpha - Dp_n + \eta$
with

$$\eta = \frac{2\alpha\epsilon}{\epsilon - \alpha - Dp_n}$$

Hence

$$s_n^I \approx Dp_n - \epsilon$$

$$s_n^{II} \approx -\alpha + \eta/2 \approx \frac{\alpha Dp_n}{\epsilon - Dp_n}$$

$$\left(\frac{dp}{ds}\right)_{s_n^I} \approx \frac{1}{D}$$

and

$$\left(\frac{dp}{ds}\right)_{s_n^{II}} \approx \frac{(\epsilon - Dp_n)^2}{\alpha\epsilon D}$$

We now consider the time interval $1/\epsilon < t < 1/\alpha$ and find that in this interval we have:

$$R_1 \approx 0 \tag{20}$$

and, since $|\alpha Dp_n/(\epsilon - Dp_n)| \leqslant \alpha$:

$$R_2 \approx \frac{16\epsilon H^4}{D\pi^4} \cdot \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2 + \theta} = W \tag{21}$$

with

$$\theta = \frac{4\epsilon H^2}{D\pi^2}$$

The analytical solution (Wheelon, 1968) to W, the righthand side of Eqn. 21, is:

$$W = \frac{2H^3}{\pi^2}\sqrt{\epsilon/D} \cdot \tanh\left(\frac{\pi}{2}\sqrt{\theta}\right) \tag{22}$$

And since $\tanh(\frac{\pi}{2}\sqrt{\theta}) \approx 1$:

$$R_2 \approx \frac{2H^3}{\pi^2}\sqrt{\epsilon/D} \tag{23}$$

Inserting Eqn. 20 and Eqn. 23 into Eqn. 19 we obtain:

$$\left(\frac{dQ}{dt}\right)_{app} \approx c_e^0\sqrt{\epsilon D}\,; \quad \left(\epsilon \gg D/H^2 \gg \alpha \text{ and } \frac{1}{\epsilon} < t < \frac{1}{\alpha}\right) \tag{24}$$

where $(dQ/dt)_{app}$ is the approximate stationary release rate in the given time interval.
Taking $c_e^0 = 1\ \text{mol} \cdot \text{m}^{-3}$, $\epsilon = 10^{-3}\ \text{s}^{-1}$ and $D = 10^{-11}\ \text{m}^2 \cdot \text{s}^{-1}$ we find:
$(dQ/dt)_{app} = 10^{-7}\ \text{mol} \cdot \text{m}^2 \cdot \text{s}^{-1}$, which is in excellent agreement with $(dQ/dt)_{lin}$ found from the numerical calculations.

Note that the *duration* of the steady-state is determined by ϵ and α: the further they are apart, the longer the steady-state lasts. This can be explained with reference to the physical significance of the terms R_1 and R_2 in Eqn. 19. The term R_1 describes the partial contribution to the drug release of the external compartment alone. The more complicated term R_2 describes the mutual competition between partition and diffusion. Initially at times smaller than $1/\epsilon$, the term R_1 is the largest of the two and the external compartment controls the release of the drug. As drug release proceeds beyond $t = 1/\epsilon$ the term R_1 vanishes and the external compartment no longer partially acts as a source of drug, but only as a medium of transport. By that time the *net* 'outward' partition has become fast enough to keep up with diffusion into the sink. Hence $t = 1/\epsilon$ marks the starting point of the steady-state.

The steady-state is characterized by the term R_2, which as shown earlier is approximately constant within the time interval $1/\epsilon < t < 1/\alpha$. The parameter $1/\alpha$ is a timescale characterizing depletion of the internal compartment; it indicates the moment when the term R_2 tends to decrease, meaning that 'outward' partition can no longer keep up with diffusion into the sink. Therefore $t = 1/\alpha$ marks the breakdown of the steady-state. An interesting question is whether partition rate constants exist, which fall into the range of magnitudes indicated. Data from the literature show that this is indeed the case. Partition rate constants across octanol–water interfaces have been determined for various drugs (Lippold and Schneider, 1976; Van de Waterbeemd et al., 1980), and in many cases found to be three decades or more apart and within the range of values used in this study ($\sim 10^{-1}$–$10^{-7}\ \text{s}^{-1}$).

These data suggest that zero-order release from two-phase systems is a distinct

possibility, given the proper conditions concerning e.g. drug lipophilicity, permeability of the barrier between the phases and diffusivity of the external phase.

Case VII. Partition faster than diffusion; 'inward' partition fastest ($\epsilon \gg \alpha \gg D/H^2$)

In this case we have a large supply of drug from the internal compartment ($\epsilon/\alpha \gg 1$) as well as fast 'outward' partition ($\alpha \gg D/H^2$) compared with diffusion. As a consequence, the release rate increases more than 10-fold with respect to Case I (Fig. 3); however, the *net* loss of drug from the external compartment is very small (Fig. 2). Apparently drug release from the external compartment is almost entirely compensated by fast uptake from the internal compartment, so that a steep concentration gradient is maintained near the sink. This implies that the major part of the released drug is supplied by direct delivery from the internal compartment; the latter process therefore controls the overall rate of release.

An important result of the calculations concerns the *rate-determining process*. In the model system described above, two main processes take place: (1) 'net outward partition' (i.e. net drug transfer from the internal to the external compartment); and (2) 'diffusion' (i.e. diffusion of the drug through the external compartment into the sink). In the present model they are in principle *parallel* processes. They do not take place *consecutively* (except initially when diffusion necessarily preceeds 'outward' partition, starting from equilibrium), but there is always a '*choice*' between the two: if diffusion through the external compartment is fast, most of the released drug will be supplied from the external compartment alone, and partition will only play a minor role; if, on the other hand, the net 'outward' partition outweighs the diffusion through the external compartment, then the released drug will be supplied directly from the internal compartment and diffusion through the external compartment plays a secondary role because it only takes place over a very small distance. Under such conditions the *fastest* process normally determines the overall rate of mass transfer. This is reflected in all cases but V and VI. In Case V the *slowest* process (diffusion) dominates simply because of early depletion of the internal compartment, and in case VI both processes contribute to the release.

We may conclude that the model presented here allows us to predict drug release from a two-phase system on the basis of its structure and composition, taking both partition and diffusion phenomena into account. From the analytical solution given here, approximations for special cases can be deduced. Furthermore, the model may serve as a basis to analyze release data obtained from a variety of two-phase systems in order to elucidate release mechanisms. Currently the model is being put to test in release experiments, the results of which are to be published elsewhere (Boddé and Junginger, in preparation)

Appendices

(1) Permeabilities and partition parameters

If we would assume the interfacial barrier to be symmetric and allow partition

equilibrium across it, the stationary flux would be:

$$\frac{1}{B}\left(\frac{dM}{dt}\right)_{i\to e} = P(c_i - Kc_e)$$

where P = permeability coefficient across the barrier in either direction ($m \cdot s^{-1}$); K = internal–external partition coefficient. For the sake of general applicability, these assumptions are not included in the model presented here, and P and $P \cdot K$ are replaced by two permeabilities, namely k_i and k_e. Both permeabilities have the same dimensions as P ($m \cdot s^{-1}$).

α, β, γ and ϵ have the dimension of partition rate constants (s^{-1}) and may therefore be compared with the ones given in the literature (Lippold and Schneider, 1976; van de Waterbeemd et al., 1980). Defining the partition coefficient between the compartments as $K = \tilde{c}_i/\tilde{c}_e$ where the superscript $\sim$ denotes equilibrium, we have:

$$K = \frac{\beta}{\alpha} = \frac{\epsilon}{\gamma} = \frac{k_i}{k_e}$$

If $V_i = V_e$, then $\beta = \epsilon$ and $\alpha = \gamma$, hence $K = \epsilon/\alpha$.

(2) Geometry factors

If a relationship between the geometry of a two-phase system and drug release from it is to be established, the geometry factors B/V_i and B/V_e should be known.

In systems where the internal phase consists of spherical drops we have:

$$B/V_i = 3/R_i \text{ and } B/V_e = (3/r_i)(f_i/(1 - f_i))$$

where r_i = drop radius; and f_i = volume fraction of the internal phase. In lamellar surfactant–water systems, assuming water is the external phase and the lipid bilayers constitute the internal phase, we would have:

$$B/V_i = 1/d_0 \text{ and } B/V_e = 1/d_w$$

where d_0 and d_w are the thicknesses of the lipid bilayers and water layers, respectively. Such parameters can in principle be determined independently by X-ray diffraction (de Vringer et al., 1984).

(3) Inverse transformation of $\hat{c}_e(x, s)$

Inverse transformation of $\hat{c}_e(x, s)$ with respect to the Laplace variable s yields $c_e(x, 't)$:

$$c_e(x, t) = \frac{1}{2\pi i}\int_{s_0-i\infty}^{s_0+i\infty} \hat{c}_e(x, s)\, e^{st} ds$$

$\hat{c}_e(x, s) \cdot e^{st}$ has poles at: $s = 0$ (A1)

and

$$\sqrt{p_n} = \pm i\left(\frac{2n+1}{2}\right)\frac{\pi}{H}; \quad (n = 0, 1, 2\ldots) \tag{A2}$$

with

$$s_n^{I,II} = Dp_n - \epsilon - \alpha \mp \sqrt{(-Dp_n + \epsilon + \alpha)^2 + 4Dp_n\alpha} \tag{A3}$$

Using the theorem of residues (Doetsch, 1943) and denoting the residues in the various poles by $(Res)_0$, $(Res)_{s_n^I}$ and $(Res)_{s_n^{II}}$, we obtain:

$$(Res)_0 = 0 \tag{A4}$$

$$(Res)_{s_n^I} = \left[\frac{h(s)}{g'(s)}\right]_{s_n^I}; \quad (n = 0, 1, 2\ldots) \tag{A5}$$

$$(Res)_{s_n^{II}} = \left[\frac{h(s)}{g'(s)}\right]_{s_n^{II}}; \quad (n = 0, 1, 2\ldots) \tag{A6}$$

with

$$h(s) = -c_e^0 e^{st}\left[\cosh\left(x\sqrt{p}\right)\cdot\cosh\left(H\sqrt{p}\right) + \sinh\left(x\sqrt{p}\right)\cdot\sinh\left(H\sqrt{p}\right)\right]$$

$$g'(s) = \cosh\left(H\sqrt{p}\right) + s\frac{dp}{ds}\frac{H}{2\sqrt{p}}\sinh\left(H\sqrt{p}\right)$$

and

$$\frac{dp}{ds} = \frac{1}{D}\left[1 + \frac{\alpha\epsilon}{(s+\alpha)^2}\right] \tag{A7}$$

In the poles given by (Eq. A2) we have:

$$\cosh\left(H\sqrt{p_n}\right) = 0$$

$$\sinh\left(H\sqrt{p_n}\right) = \pm i(-1)^n; \quad (n = 0, 1, 2\ldots)$$

$$\cosh\left(x\sqrt{p_n}\right) = \cos\left[(2n+1)\frac{\pi x}{2H}\right]; \quad (n = 0, 1, 2\ldots)$$

$$\sinh\left(x\sqrt{p_n}\right) = \pm i\sin\left[(2n+1)\frac{\pi x}{2H}\right]; \quad (n = 0, 1, 2\ldots)$$

Hence:

$$\left[\frac{h(s)}{g'(s)}\right]_{s_n^{I,II}} = \frac{c_e^0(2n+1)\pi \sin\left[(2n+1)\frac{\pi x}{2H}\right] e^{s_n^{I,II}t}}{H^2 s_n^{I,II}\left(\frac{dp}{ds}\right)_{s_n^{I,II}}}; \quad (n = 0, 1, 2\ldots) \tag{A8}$$

We finally obtain

$$c_e(x, t) = (Res)_0 + \sum_{n=0}^{\infty} (Res)_{s_n^I} + \sum_{n=0}^{\infty} (Res)_{s_n^{II}}$$

yielding Eqn. 16.

(4) Consistency of $c_e(x, t)$ with the boundary conditions
Homogeneity at zero time (Eqn. 7):
inserting $t = 0$ into Eqn. 16 we get:

$$c_e(x, o) = \frac{c_e^0 \pi}{H^2} \cdot \sum_{n=0}^{\infty} (2n+1) \sin\left[(2n+1)\frac{\pi x}{2H}\right] T_n \tag{A9}$$

with

$$T_n = \frac{1}{s_n^I\left(\frac{dp}{ds}\right)_{s_n^I}} + \frac{1}{s_n^{II}\left(\frac{dp}{ds}\right)_{s_n^{II}}} \tag{A10}$$

noting that

$$s_n^{I,II}\left(\frac{dp}{ds}\right)_{s_n^{I,II}} = \pm \frac{s_n^{I,II}}{D} \cdot \frac{y}{s_n^{I,II} + \alpha} \tag{A11}$$

we find

$$T_n = 1/p_n \tag{A12}$$

Inserting Eqn. A12 into Eqn. A9 and recalling that $-H < x < 0$:

$$c_e(x, 0) = -\frac{4}{\pi} c_e^0\left(\frac{-\pi}{4}\right) = c_e^0,$$

which is in agreement with Eqn. 7.
Sink conditions:
the only space-dependent term in $c_e(x, t)$, $\sin[(2n+1)\frac{\pi x}{2H}]$, vanishes for $x = 0$;

hence:

$c_e(x, t) = 0$ for $x = 0$.

No flux at the impermeable barrier:
absence of flux at $x = -H$ can be verified at once by differentiating the space dependent term in $c_e(x, t)$ with respect to x:

$$\left[\frac{\delta}{\delta x}\sin\left[(2n+1)\frac{\pi x}{2H}\right]\right]_{x=-H} = (2n+1)\frac{\pi}{2H}\cos\left[\frac{2n+1}{2}\pi\right] = 0$$

Total depletion at infinite time:
in principle, the set of boundary conditions imposed allows total depletion of the system at infinite time. This can be verified by taking $\lim_{t\to\infty} c_e(x, t)$. This limit will be zero only if both s_n^I and s_n^{II} are negative for all values of n (see Eqn. 16). From Eqn. A3 we recall:

$$2\, s_n^{I,II} = Dp_n - \epsilon - \alpha \mp y$$

where

$$y = \sqrt{(\epsilon + \alpha - Dp_n)^2 + 4\alpha Dp_n}$$

Since $(\epsilon + \alpha) > \alpha > 0$ and $4\, D\alpha p_n < 0$, we have $y < |\epsilon + \alpha - Dp_n|$ for all n;
Furthermore: $(Dp_n - \epsilon - \alpha) < 0$ for all n.
Hence both s_n^I and s_n^{II} are negative for all n. At infinite time we therefore have total depletion of the external compartment and, due to chemical considerations, of the internal compartment as well.

(5) Consistency of Q(t) with the boundary conditions
All drug in the system at zero time:
inserting $t = 0$ into Eqn. 18 we find: $Q(0) = 0$.
Total depletion of the system at infinite time:
from Eqn. 18 we obtain:

$$\lim_{t\to\infty} Q(t) = Q_{max} = \frac{DC_e^0\pi^2}{2H^3} \cdot \sum_{n=0}^{\infty} (2n+1)^2 U_n; \quad (n = 0, 1, 2\ldots)$$

with

$$U_n = \frac{1}{(s_n^I)^2\left(\frac{dp}{ds}\right)_{s_n^I}} + \frac{1}{(s_n^{II})^2\left(\frac{dp}{ds}\right)_{s_n^{II}}} \qquad \text{(A13)}$$

Inserting Eqn. A11 into Eqn. A13 we have:

$$U_n = \frac{D}{y}\left[\frac{\left[s_n^I s_n^{II} + \alpha\left(s_n^I + s_n^{II}\right)\right]\left(s_n^I - s_n^{II}\right)}{\left(s_n^I s_n^{II}\right)^2}\right]$$

$$= \frac{16(\epsilon + \alpha)H^4}{D\alpha(2n+1)^4\pi^4}$$

Hence $Q_{max} = c_e^0 H(1 + \epsilon/\alpha)$

$$= c_e^0 H\left(1 + \frac{c_i^0 V_i}{c_e^0 V_e}\right) \tag{A14}$$

Denoting the contact surface area between external compartment and sink by A, and noting that $HA = V_e$, we obtain:

$$AQ_{max} = c_e^0 v_e + c_i^0 V_i$$

which corresponds to total depletion of the system at infinite time. Consequently, Q(t) behaves asymptotically at large times.

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