Theoretical Comparison of Release Rates of Drugs into Sink and Nonsink Conditions

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Abstract □ Theoretical expressions were derived that show how drug release rates are modified by sink and nonsink conditions. The effect of basic physicochemical parameters and the relevance to *in vitro* testing are discussed.

Keyphrases □ Theoretical release profiles—drug release rates modified by sink and nonsink conditions □ Release rates—theoretical comparison of drug release into sink and nonsink conditions

The release characteristics of formulations are often determined in sink conditions, usually produced either with a continuous supply of fresh receptor solution or by devising an experiment where there is a large receptor volume compared to the donor phase. Mathematical equations were previously derived to describe drug release into sink conditions for certain physical situations (1–6), and experimental confirmation of the results was obtained (7–12). For some cases, the assumption that drug release takes place into sink conditions is an adequate representation of the *in vivo* situation, but nonsink conditions would be more appropriate under certain circumstances. Furthermore, experimental constraints may prevent the attainment of sink conditions *in vitro* and, consequently, a mathematical description of the nonsink situation is necessary.

In this paper, drug release into sink and nonsink conditions is theoretically compared and the manner in which the volume of the receptor phase affects the drug release rate is demonstrated. The relevant diffusion equations are solved for a nonspecific general situation using the method of Laplace transformation. The style of the mathematical approach parallels that of several recent reports (13–17).

THEORETICAL

The Model—The formulation is assumed to release drug at a diffusion-controlled rate into a well-stirred receptor volume. The concentration profile of drug in the formulation and the receptor compartment then have the form shown in Fig. 1.

The cumulative amount of drug that penetrates into the receptor compartment at time t is given by:

$$M_t = D_d A \int_0^t (dc_d/dx)_{x=0}\, dt \qquad \text{(Eq. 1)}$$

where D_d is the diffusion coefficient of the drug in the formulation and A is the surface area across which release takes place.

To simplify solution of the diffusion equations, three normalized variables are defined (18):

$$U = c/c_0 \qquad \text{(Eq. 2)}$$

$$X = x/l \qquad \text{(Eq. 3)}$$

$$T = D_d t/l^2 \qquad \text{(Eq. 4)}$$

where c_0 is the initial drug concentration in the donor phase and l is the thickness of the donor phase. With these variables, it is possible to rewrite Eq. 1 to give:

$$M_t = Alc_0 \int_0^T (\partial U_d/\partial X)_0\, dT \qquad \text{(Eq. 5)}$$

To facilitate solution of the diffusion equations, it is also assumed that diffusion occurs in only one dimension and that the diffusion coefficient is concentration independent.

Diffusion in the donor phase is then described by Fick's second law of diffusion, which, in terms of the normalized variables, is expressed as:

$$\partial U_d/\partial T = \partial^2 U_d/\partial X^2 \qquad \text{(Eq. 6)}$$

This differential equation is solved by using Laplace transforms with boundary conditions appropriate to sink and nonsink conditions.

Sink Conditions—For sink conditions, drug is continuously removed from the surface of the formulation, producing the boundary conditions:

$$T \geq 0 \qquad U_{d,X=0} = 0 \qquad \text{(Eq. 7)}$$

$$T = 0 \qquad U_d = 1 \qquad \text{(Eq. 8)}$$

$$(\partial U_d/\partial X)_1 = 0 \qquad \text{(Eq. 9)}$$

The physical significance of Eqs. 7–9 may be explained as follows. Equation 7 describes the sink condition. For all values of T (the normalized time variable), the concentration at the surface of the formulation ($X = 0, x = 0$) is zero. Equation 8 shows that there is initially a uniform drug concentration in the donor phase (*i.e.*, at $t = 0, c = c_0$ and $U_d = 1$). Finally, Eq. 9 indicates that there is only a finite quantity of drug in the donor phase; *i.e.*, it is not being replenished by any reservoir at $x = l (X = 1)$.

The Laplace transform of Eq. 6:

$$s\bar{U}_d - 1 = \partial^2 \bar{U}_d/\partial X^2 \qquad \text{(Eq. 10)}$$

has the general solution:

$$\bar{U}_d = A \cosh s^{1/2} X + B \sinh s^{1/2} X + s^{-1} \qquad \text{(Eq. 11)}$$

By using boundary conditions Eqs. 7 and 9, the coefficients A and B may be eliminated to give:

$$(\partial \bar{U}_d/\partial X)_0 = s^{-1/2} \tanh s^{1/2} \qquad \text{(Eq. 12)}$$

Thus:

$$M_t = Alc_0 \mathcal{L}^{-1} (s^{-3/2} \tanh s^{1/2}) \qquad \text{(Eq. 13)}$$

which is identical to a previous problem (Eq. 15 of Ref. 14) and which has

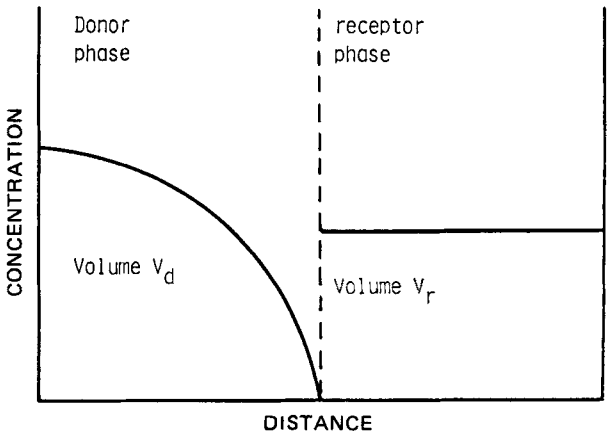

Figure 1—*Concentration profile of drug in the receptor and donor phases at some time t after the start of the experiment.*

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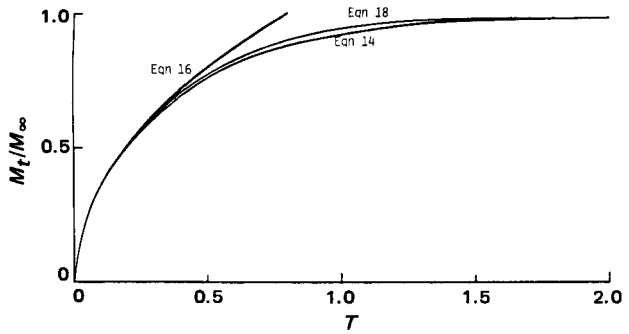

Figure 2—*Release profile generated from Eqs. 14, 16, and 18 for sink conditions.*

a solution:

$$M_t = M_\infty \left[1 - 8/\pi^2 \sum_{n=1}^{\infty} \{(2n-1)^{-2} \exp[-(2n-1)^2\pi^2 T/4]\}\right] \quad \text{(Eq. 14)}$$

where $M_\infty = AlC_0$ and is the initial total amount of drug.

It is also possible to derive simplified expressions by approximating the hyperbolic term in Eq. 13 and then taking the inverse transform.

For short times $T < 1$, $s > 1$, $\tanh s^{1/2} \simeq 1$ (19):

$$M_t \simeq M_\infty \mathcal{L}^{-1}(s^{-3/2}) \quad \text{(Eq. 15)}$$

$$M_t \simeq 2M_\infty T^{1/2}\pi^{-1/2} \quad \text{(Eq. 16)}$$

At long times $T > 1$, $s < 1$, $\coth s^{1/2} \simeq s^{-1/2} + s^{1/2}/3$ (19):

$$M_t \simeq 3M_\infty \mathcal{L}^{-1}[s^{-1}(s+3)^{-1}] \quad \text{(Eq. 17)}$$

$$M_t \simeq M_\infty[1 - \exp(-3T)] \quad \text{(Eq. 18)}$$

Nonsink Conditions—For these release characteristics, the drug concentration is allowed to build up in the receptor phase and the condition described by Eq. 7 is no longer valid. At the interface between the formulation and the receptor compartment, fast interfacial kinetics are assumed, which provide the new boundary condition:

$$K = U_{r,0}/U_{d,0} \quad \text{(Eq. 19)}$$

where K is a partition coefficient.

Solution of the diffusion equation is identical to that previously described. A finite quantity of drug is still present, and the boundary condition Eq. 9 is still valid. The difference arises during the elimination of the coefficients A and B in the general solution, Eq. 11.

The coefficients are eliminated by considering the buildup of concentration in the receptor phase, which is related to the amount diffused at time t by:

$$c_r = M_t/V_r \quad \text{(Eq. 20)}$$

Substitution of Eq. 5 gives:

$$c_r = AlC_0V_r^{-1}\mathcal{L}^{-1}[s^{-1}(\partial\overline{U}_d/\partial X)_0] \quad \text{(Eq. 21)}$$

Thus:

$$\overline{U}_{d,0} = Al(KV_r)^{-1}s^{-1}(\partial\overline{U}_d/\partial X)_0 \quad \text{(Eq. 22)}$$

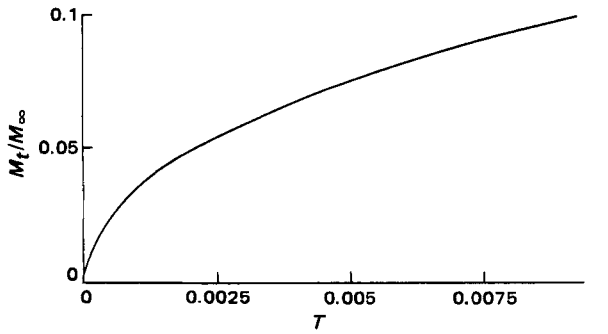

Figure 3—*Release profile given from Eq. 26 with* Q = *1, showing the short time pattern for nonsink conditions.*

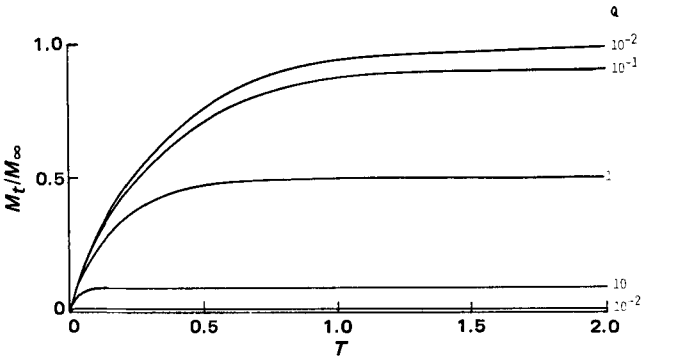

Figure 4—*Release profile from Eq. 28 with various values of* Q, *showing the long time pattern for nonsink conditions.*

Differentiation of Eq. 11 and use of the boundary condition Eq. 9 give:

$$(\partial\overline{U}_d/\partial X)_0 = (\overline{U}_{d,0} - s^{-1})s^{1/2}\tanh s^{1/2} \quad \text{(Eq. 23)}$$

and $(\partial\overline{U}_d/\partial X)_0$ may be eliminated by combination of Eqs. 22 and 23. Hence:

$$c_r = KAlc_0\mathcal{L}^{-1}[s^{-1}(s^{1/2}V_rK\coth s^{1/2} + Al)^{-1}] \quad \text{(Eq. 24)}$$

Simple inversion of this equation is not possible, and approximations are made for long and short time release profiles.

Short Time Approximation—At short times $T < 1$, $s > 1$, the coth function in Eq. 24 may be approximated (19):

$$c_r = Alc_0V_r^{-1}\mathcal{L}^{-1}[s^{-1}(s^{1/2} + Al/V_rK)^{-1}] \quad \text{(Eq. 25)}$$

This function may be most readily inverted by separation into partial fractions followed by inversion of the individual fractions (19):

$$M_t = M_\infty Q^{-1}[1 - \exp(Q^2T)\,\mathrm{erfc}\,(QT^{1/2})] \quad \text{(Eq. 26)}$$

where $Q = Al/V_rK$.

Long Time Approximation—For $T > 1$, $s < 1$, and $\coth s^{1/2} \simeq s^{-1/2} + s^{1/2}/3$, Eq. 24 becomes:

$$c_r = KAlc_0\mathcal{L}^{-1}\{s^{-3/2}[V_rK(s^{1/2} + s^{1/2}/3) + Als^{-1/2}]^{-1}\} \quad \text{(Eq. 27)}$$

which may be inverted:

$$M_t = M_\infty(1+Q)^{-1}\{1 - \exp[-3(1+Q)T]\} \quad \text{(Eq. 28)}$$

Comparison of Sink *versus* Nonsink Conditions—It is now possible to obtain a direct comparison of the two sets of conditions using the approximations at short and long times. At short times, Eqs. 26 and 16 produce:

$$\frac{M_{t,ns}}{M_{t,s}} = \frac{\pi^{1/2}[1 - \exp(Q^2T)\mathrm{erfc}(QT^{1/2})]}{2QT^{1/2}} \quad \text{(Eq. 29)}$$

and this complex expression describes the ratio of the amount released at time t from nonsink compared to sink conditions.

The equivalent ratio for long times is given by combining Eqs. 28 and 18:

$$\frac{M_{t,ns}}{M_{t,s}} = \frac{1 - \exp[-3(1+Q)T]}{(1+Q)[1 - \exp(-3T)]} \quad \text{(Eq. 30)}$$

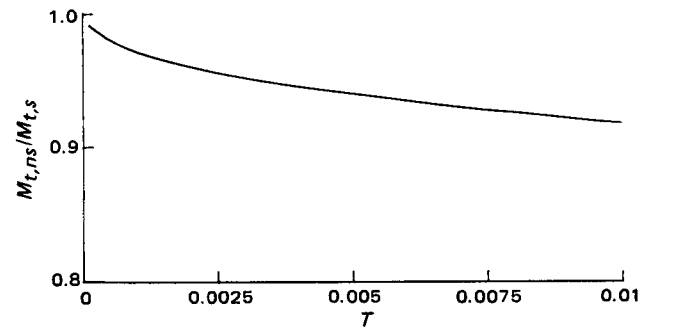

Figure 5—*Comparison of sink* versus *nonsink conditions at short times.*

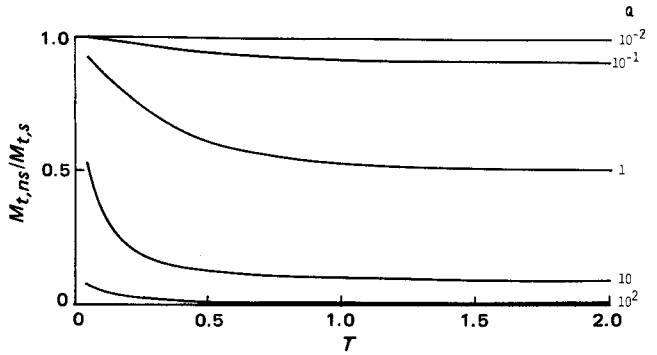

Figure 6—*Comparison of sink* versus *nonsink conditions at long times.*

DISCUSSION

Figure 2 shows the release profile generated using the full solution given by Eq. 14. The figure also shows Eqs. 16 and 18, the two approximations. It is apparent that Eq. 16 is correct up to values of $T \sim 0.5$; from this time onwards, Eq. 18 is applicable.

No unique mathematical expression is obtainable to describe the nonsink conditions. Therefore, concentration is focused on long and short time approximations because it is not possible to predict accurately the release profile for T values approximating to unity. Figure 3 shows the short time approximation given by Eq. 26 for $Q = 1$. The curve generated shows a smooth release pattern not unlike that given by the more simple $t^{1/2}$ approximation applicable to sink conditions. However, there are slight differences as T increases, as shown in Fig. 3. This result would be expected at short periods of time since there is no appreciable concentration buildup in the receptor phase.

The long time approximation, given by Eq. 28, is plotted in Fig. 4. The variation with Q is indicated, and a series of simple first-order curves is obtained. The curves approach the limit, as $T \rightarrow \infty$, of $(1 + Q)^{-1}$, as predicted by Eq. 28. When $Q < 1$, the nonsink limit approaches the long time limit for sink conditions, as expected. This situation corresponds to the experimental conditions of a large receptor volume or large partition coefficient.

Figure 5 compares sink and nonsink conditions at short times for $Q = 1$. At extremely short times, the ratio is unity, as expected. However, as T increases, the deviation from unity becomes more marked and the effect of nonsink conditions becomes apparent. As expected, this general deviation is more pronounced at long times (Fig. 6) and is most noticeable for large values of Q corresponding to small values of the volume of the receptor phase and low partition coefficient.

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Physicochemical and Analytical Characteristics of Itanoxone

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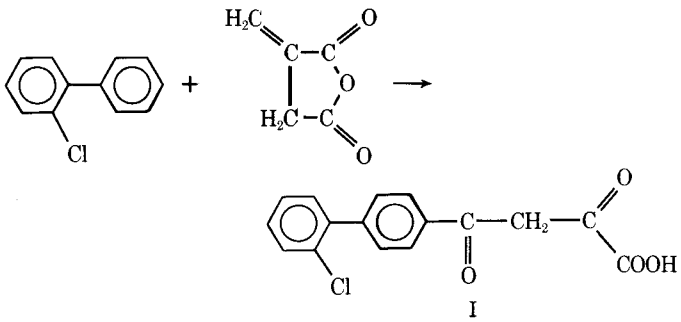
Received March 5, 1980, from the *P. Fabre S.A. Research Center, 17 Avenue Jean Moulin, 81106 Castres, France.* Accepted for publication March 27, 1981.

Abstract □ The analytical and spectroscopic characteristics of itanoxone were determined. These data can be used to identify or assay this new drug.

Keyphrases □ Itanoxone—physicochemical and analytical characteristics of itanoxone □ Spectroscopy—itanoxone, physicochemical and analytical characteristics □ Hyperlipidemic agents—itanoxone, physicochemical and analytical characteristics □ Hyperuricemic agents—itanoxone, physicochemical and analytical characteristics

Itanoxone is the internationally designated name (1) for 4-[4′-(2-chlorophenyl)phenyl]-4-oxo-2-methylenebutanoic acid (I). This compound has pharmacological and clinical properties (2) suitable for the treatment of hyperlipidemia (3–5) and hyperuricemia (6). Theoretical impurities of I (7) and an industrial purification process (8) were studied previously. This paper considers some physical and physicochemical properties of I.



I

Scheme I

EXPERIMENTAL

Synthesis—Itanoxone (I) was synthetized by the Friedel–Crafts reaction between itaconic anhydride and 2-chlorobiphenyl (9, 10) (Scheme I).

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