Mathematical Model for *In Vitro* Drug Release from Controlled Release Dosage Forms Applied to Propoxyphene Hydrochloride Pellets

FINN NORRING CHRISTENSEN *, FLEMMING YSSING HANSEN ‡, and HELLE BECHGAARD **

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Abstract □ The *in vitro* release of drugs from controlled-release dosage forms has been studied in terms of a diffusion model. The model has been applied to a pellet formulation containing propoxyphene hydrochloride. It is demonstrated that the model may be used to predict the drug release profile adequately, when the pellet size is changed and when the thickness of the coating is varied. The size distribution of pellets in an experiment may be too broad to justify a simulation with just one average pellet size. Therefore, the results for pellets of the same size are generalized to any size distribution of pellets in an experiment. This is only trivial if sink condition exists in the extraction medium, since under that condition, the release from each pellet type is independent of the releases from other pellet types. In that case, the total release may therefore be found as the sum of the individual releases. In the general case considered here, the releases are coupled.

Keyphrases □ Mathematical models—*in vitro* drug release from controlled-release dosage forms, propoxyphene hydrochloride pellets □ Propoxyphene hydrochloride pellets—mathematical model for *in vitro* drug release from controlled-release dosage forms □ Controlled-release dosage forms—mathematical model for *in vitro* drug release, propoxyphene hydrochloride pellets

In a recent paper (1) it was shown that a quasistationary diffusion description of the drug release from controlled release dosage forms formally leads to an expression of the same form as a Rosin-Rammler-Sperling-Weibull distribution when $\beta = 1$, (1–4). The advantage of the diffusion description is that it allows a prediction of the drug release as a function of pellet size and coat thickness once the diffusion coefficient for a given drug in the coat is known. In the present paper, the general solution to the diffusion description without the simplifying assumption about quasistationarity is considered.

THEORETICAL

It is assumed that pellets are spherical and consist of a core containing the drug and a coat which is the rate-limiting element in the release process (5). The radius of the core is b and the radius of the coated pellet is a giving a coat thickness of $(a - b)$.

In practice a dissolution test is done with a large number of pellets. If the pellets have a narrow size distribution, one may use the results for pellets of the given size. In the case of a broad size distribution, it is necessary to take that into account. In the present general solution to the diffusion description, both cases are discussed.

It is evident that the release profile, in general, may not be calculated as a superposition of the profiles from each pellet size since the increase of drug concentration in the extraction medium couples the releases from the pellets. Only in the case of zero concentration in the extraction medium (sink condition) no coupling is present, and a superposition of releases gives the total release.

It is important to note the simplifying assumptions inherent in this description. The initial phase, where dry pellets are introduced into an extraction medium, water penetrates the coat and dissolves the drug in the core, is not included in this description. This model may be applied from the time the drug in the core has been dissolved by the penetrating water. A time lag may be accounted for simply by shifting the zero point on the time axis, corresponding to the duration of the initial phase. Since there are no data available to calculate the initial phase kinetics, it is necessary to rely on experimental evidence for a reasonable assessment of time lag. It is a very important assumption that the pellets do not change dimensions (*e.g.*, due to swelling during the release period). In particular, if the pellet dimensions are determined from dry pellets, it is crucial to check that the dimensions are not changed after introduction into the extraction medium.

Assuming the drug concentration in the extraction medium is uniform at all times, due to effective stirring, the most general boundary condition to be considered is one where the drug concentration in the core gradually decreases as drug is released, while the drug concentration in the extraction medium gradually increases.

In the present paper, modifications of these boundary conditions are also considered. One modification is to assume sink conditions in the extraction medium and another is to assume a constant core concentration. From these examples it will be easy to see how to modify the calculation scheme in order to comply with other boundary conditions.

Pellets of Equal Size—As only radial diffusion is considered, the diffusion equation (6) for the coat is:

$$\frac{\partial[rC(rt)]}{\partial t} = D\frac{\partial^2[rC(rt)]}{\partial r^2} \qquad \text{(Eq. 1)}$$

where D is the diffusion coefficient for the particular drug in the coat, and $C(rt)$ is the drug concentration in the coat at distance r from the center at time t.

Equation 1 is solved with different boundary conditions and with the initial conditions:

$$C_e(t = 0) = 0 \qquad \text{(Eq. 2)}$$

$$C_c(t = 0) = C^0 \qquad \text{(Eq. 3)}$$

$$C(rt = 0) = 0 \qquad b < r < a \qquad \text{(Eq. 4)}$$

$$C(bt = 0) = \frac{C_c(t = 0)}{k_c} = \frac{C^0}{k_c} \text{ [see (Eq. 5)]}$$

where $C_e(t = 0)$ is the initial drug concentration in the extraction medium, and $C_c(t = 0)$ is the initial drug concentration in the core.

Variable Core and Extraction Medium Concentrations—The boundary conditions are sketched in Fig. 1 and may be expressed in the following way:

The Core-Coat Boundary—Assuming local equilibrium at the boundary at any time:

$$C_c(t) = k_c C(bt) \qquad \text{(Eq. 5)}$$

where k_c is the equilibrium constant. The continuity equation at the boundary may be written:

$$4\pi b^2 D\left[\frac{\partial C(rt)}{\partial r}\right]_{r=b} = \frac{4\pi b^3}{3}\frac{\partial C_c(t)}{\partial t} \qquad \text{(Eq. 6)}$$

and with Eq. 5:

$$\left[\frac{\partial C(rt)}{\partial r}\right]_{r=b} = \frac{bk_c}{3D}\frac{\partial C(bt)}{\partial t} \qquad \text{(Eq. 7)}$$

The Coat-Extraction Medium Boundary—The assumption of local equilibrium at the boundary gives:

$$C_e(t) = k_e C(at) \qquad \text{(Eq. 8)}$$

where k_e is the equilibrium constant. If there are n pellets of identical size, the continuity equation at the boundary may be written:

$$-n4\pi a^2 D\left[\frac{\partial C(rt)}{\partial r}\right]_{r=a} = V_e\frac{\partial C_e(t)}{\partial t} \qquad \text{(Eq. 9)}$$

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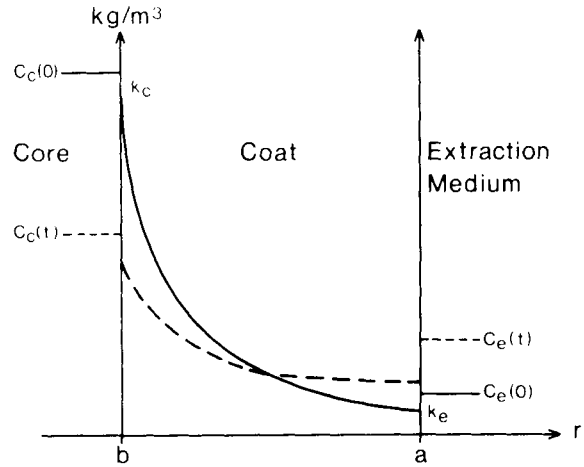

Figure 1—*A sketch of a segment of the core, coat, and extraction medium with boundary conditions corresponding to variable core and extraction medium concentrations. The stationary concentration profiles at time zero and at time* t *are shown. The concentration jumps at the boundaries are governed by the equilibrium constants* k_c *and* k_e.

where V_e is the volume of the extraction medium. Introduction of Eq. 8 into Eq. 9 gives:

$$\left[\frac{\partial C(rt)}{\partial r}\right]_{r=a} = -\frac{V_e k_e}{n4\pi a^2 D}\frac{\partial C(at)}{\partial t} \qquad \text{(Eq. 10)}$$

The time Laplace transform of Eq. 1 with Eq. 4 gives:

$$\frac{\partial^2 \tilde{C}(rs)}{\partial r^2} + \frac{2}{r}\frac{\partial \tilde{C}(rs)}{\partial r} - \frac{s}{D}\tilde{C}(rs) = 0 \qquad \text{(Eq. 11)}$$

where,

$$\tilde{C}(rs) = \int_0^\infty e^{-st} C(rt)\mathrm{d}t \qquad \text{(Eq. 12)}$$

is the Laplace transformed concentration. In the same way Eqs. 7 and 10 are Laplace transformed and give:

$$\left[\frac{\partial \tilde{C}(rs)}{\partial r}\right]_{r=b} = \frac{bk_c}{3D}[s\tilde{C}(bs)] - \frac{b}{3D}C^0 \qquad \text{(Eq. 13)}$$

and;

$$\left[\frac{\partial \tilde{C}(rs)}{\partial r}\right]_{r=a} = -\frac{V_e k_e}{n4\pi a^2 D}s\tilde{C}(as) \qquad \text{(Eq. 14)}$$

Equation 11 is a standard second-order differential equation with the solution

$$\tilde{C}(rs) = \frac{A}{r}\sinh\left(\sqrt{\frac{s}{D}}r\right) + \frac{B}{r}\cosh\left(\sqrt{\frac{s}{D}}r\right) \qquad \text{(Eq. 15)}$$

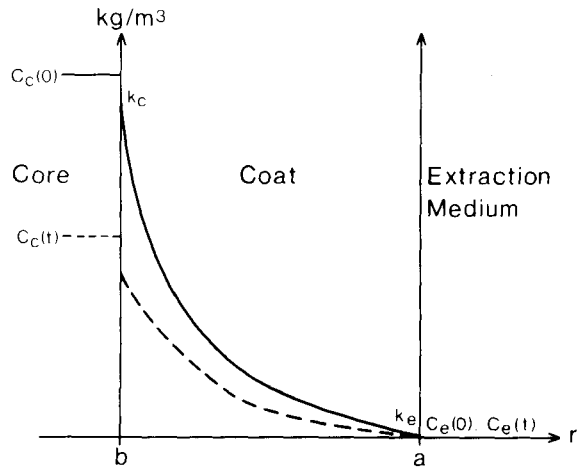

Figure 2—*A sketch of a segment of the core, coat, and extraction medium with boundary conditions corresponding to variable core conditions and sink conditions in the extraction medium. The stationary concentration profiles at time zero and time* t *are shown.*

The integration constants A and B are determined by inserting Eq. 15 into Eqs. 13 and 14. This gives the following system of equations, which in matrix form may be written:

$$\begin{bmatrix}\phi_1 & \phi_2\\ \phi_3 & \phi_4\end{bmatrix}\begin{bmatrix}A\\ B\end{bmatrix} = \begin{bmatrix}-\frac{C^0 b}{3}\\ 0\end{bmatrix} \qquad \text{(Eq. 16)}$$

where:

$$\phi_1 = b\sqrt{sD}\cosh\left(\sqrt{\frac{s}{D}}b\right) - D\sinh\left(\sqrt{\frac{s}{D}}b\right) - \frac{k_c s b^2}{3}\sinh\left(\sqrt{\frac{s}{D}}b\right) \qquad \text{(Eq. 17)}$$

$$\phi_2 = b\sqrt{sD}\sinh\left(\sqrt{\frac{s}{D}}b\right) - D\cosh\left(\sqrt{\frac{s}{D}}b\right) - \frac{k_c s b^2}{3}\cosh\left(\sqrt{\frac{s}{D}}b\right) \qquad \text{(Eq. 18)}$$

$$\phi_3 = a\sqrt{sD}\cosh\left(\sqrt{\frac{s}{D}}a\right) - D\sinh\left(\sqrt{\frac{s}{D}}a\right) + \frac{V_r k_e s a^2}{3}\sinh\left(\sqrt{\frac{s}{D}}a\right) \qquad \text{(Eq. 19)}$$

$$\phi_4 = a\sqrt{sD}\sinh\left(\sqrt{\frac{s}{D}}a\right) - D\cosh\left(\sqrt{\frac{s}{D}}a\right) + \frac{V_r k_e s a^2}{3}\cosh\left(\sqrt{\frac{s}{D}}a\right) \qquad \text{(Eq. 20)}$$

where the relative volume, $V_r = \dfrac{V_e}{\frac{n4\pi a^3}{3}}$

Equation 16 is solved for A and B, and after introduction of A and B in Eq. 15 is found:

$$\tilde{C}(rs) = \frac{-C^0 b^3\phi_4\sinh\left(\sqrt{\frac{s}{D}}r\right) + C^0 b^3\phi_3\cosh\left(\sqrt{\frac{s}{D}}r\right)}{3r(\phi_1\phi_4 - \phi_2\phi_3)} \qquad \text{(Eq. 21)}$$

By a reverse transformation of Eq. 21, $C(rt)$ can be found. This is done by residue calculation (7):

$$C(rt) = \sum_{l=1}^{\infty}\frac{C^0 b^3\left[(\phi_3)_{s_l}\cosh\left(\sqrt{\frac{s_l}{D}}r\right) - (\phi_4)_{s_l}\sinh\left(\sqrt{\frac{s_l}{D}}r\right)\right]e^{s_l t}}{3r\left(\frac{\partial}{\partial s}[\phi_1\phi_4 - \phi_2\phi_3]\right)_{s=s_l}} \qquad \text{(Eq. 22)}$$

Where s_l is the l'th pole of $\tilde{C}(rs)$ in Eq. 21. From Eq. 22 it is clear that $s_l \leq 0$, since $C(rt)$ is final. To find $C_e(t)$, Eq. 8 is used and we obtain from Eq. 22 after lengthy manipulations:

$$C_e(t) = \sum_{l=1}^{\infty}\frac{k_e C^0 b\sqrt{-\frac{s_l}{D}}e^{s_l t}}{N(s_l)} \qquad \text{(Eq. 23)}$$

where:

$$N(s_l) = \left[\sin\left(\sqrt{\frac{s_l}{D}}a\right)\cos\left(\sqrt{-\frac{s_l}{D}}b\right) - \sin\left(\sqrt{-\frac{s_l}{D}}a\right)\times\cos\left(\sqrt{-\frac{s_l}{D}}b\right)\right]\left\{\frac{k_c}{k_e} - \frac{3}{2k_e}\left[1 + \left(\frac{a}{b}\right)^2\right] + V_r\left(\frac{a}{b}\right)^2 - \frac{a^2 s_l}{D}\left[\frac{2}{3}V_r k_c + \frac{k_c}{2k_e}\left(1 - \frac{a}{b}\right) + \frac{V_r}{2}\left(\frac{a}{b} - 1\right)\right]\right\} + \left[\sin\left(\sqrt{-\frac{s_l}{D}}b\right)\sin\left(\sqrt{-\frac{s_l}{D}}a\right) + \cos\left(\sqrt{-\frac{s_l}{D}}a\right)\cos\left(\sqrt{-\frac{s_l}{D}}b\right)\right]a\sqrt{-\frac{s_l}{D}}\left[\frac{k_c}{2k_e}\left(2 + \frac{b}{a}\right) + \frac{V_r}{2}\left(2\frac{a}{b} + \left(\frac{a}{b}\right)^2\right) + \frac{V_r k_c s_l a^2}{6D}\left(1 - \frac{b}{a}\right)\right] \qquad \text{(Eq. 24)}$$

A convenient way of representing the results in Eq. 23 is to plot the release $R(t) = C_e(t)/C_e(t = \infty)$ as a function of time. It is evident that $R(t) \rightarrow 1$ for $t \rightarrow \infty$. The limiting value for $C_e(t)$ is given by the time independent term in Eq. 23, *i.e.*, one of the poles of $\bar{C}(rs)$ in Eq. 21 is zero. Indeed, it is clear from Eqs. 17–20 that $s = 0$ is a pole of $\bar{C}(rs)$. Let $s_1 = 0$, then Eq. 23 may be written:

$$R(t) = 1 + \sum_{l=2}^{\infty} \frac{k_e C^0 b \sqrt{-\frac{s_l}{D}}\, e^{s_l t}}{N(s_l) C_e(t = \infty)} \qquad \text{(Eq. 25a)}$$

where the concentration in the extraction medium at $t = \infty$ is found to be:

$$C_e(t = \infty) = \frac{C^0}{\frac{a^3}{b^3} V_r + \frac{k_c}{k_e} + \frac{1}{k_c}\left(\frac{a^3}{b^3} - 1\right)} \qquad \text{(Eq. 25b)}$$

Sink Condition in Extraction Medium–Variable Core Concentration—With the boundary conditions sketched in Fig. 2, Eq. 8 now changes to:

$$C(at) = 0 \qquad \text{(Eq. 26)}$$

The initial conditions (Eqs. 2–4) and the other boundary conditions (Eqs. 5 and 7) are unchanged. The integration constants A and B in Eq. 15 are now determined by introducing $\bar{C}(rs)$ into Eq. 13 and the Laplace transform of Eq. 26:

$$\bar{C}(as) = 0 \qquad \text{(Eq. 27)}$$

In analogy with Eq. 16, the following system of equations is obtained:

$$\begin{bmatrix} \phi_1 & \phi_2 \\ \phi_3' & \phi_4' \end{bmatrix} \begin{bmatrix} A \\ B \end{bmatrix} = \begin{bmatrix} -\frac{C^0 b^3}{3} \\ 0 \end{bmatrix} \qquad \text{(Eq. 28)}$$

where ϕ_1 and ϕ_2 are given in Eqs. 17 and 18 and

$$\phi_3' = \sinh\left(\sqrt{\frac{s}{D}}\, a\right) \qquad \text{(Eq. 29)}$$

$$\phi_4' = \cosh\left(\sqrt{\frac{s}{D}}\, a\right) \qquad \text{(Eq. 30)}$$

Equation 28 is solved for A and B, and it is found, as previously:

$$\bar{C}(rs) = \frac{-C^0 b^3 \phi_4' \sinh\left(\sqrt{\frac{s}{D}}\, r\right) + C^0 b^3 \phi_3' \cosh\left(\sqrt{\frac{s}{D}}\, r\right)}{3r(\phi_1 \phi_4' - \phi_2 \phi_3')} \qquad \text{(Eq. 31)}$$

where:

$$\phi_1 \phi_4' - \phi_2 \phi_3' =$$
$$\left[b\sqrt{sD} \cosh\left(\sqrt{\frac{s}{D}}\, b\right) - D \sinh\left(\sqrt{\frac{s}{D}}\, b\right) - \frac{k_c s b^2}{3} \sinh\left(\sqrt{\frac{s}{D}}\, b\right)\right] \cosh\left(\sqrt{\frac{s}{D}}\, a\right)$$
$$- \left[b\sqrt{sD} \sinh\left(\sqrt{\frac{s}{D}}\right) - D \cosh\left(\sqrt{\frac{s}{D}}\, b\right) - \frac{k_c s b^2}{3} \cosh\left(\sqrt{\frac{s}{D}}\, b\right)\right] \sinh\left(\sqrt{\frac{s}{D}}\, a\right) \qquad \text{(Eq. 32)}$$

By residue calculation (7) Eq. 31 is reversed and it is found that $C(rt)$:

$$C(rt) = \sum_{l=1}^{\infty} \frac{C^0 b^3 \left[(\phi_3')_{s=s_l} \cosh\left(\sqrt{\frac{s_l}{D}}\, r\right) - (\phi_4')_{s=s_l} \sinh\left(\sqrt{\frac{s_l}{D}}\, r\right)\right] e^{s_l t}}{3r\left[\frac{\partial}{\partial s}(\phi_1 \phi_4' - \phi_2 \phi_3')\right]_{s=s_l}} \qquad \text{(Eq. 33)}$$

where s_l is the l'th pole of $\bar{C}(rs)$ in Eq. 31. After lengthy manipulations the following is obtained:

$$C(rt) = \sum_{l=1}^{\infty} \frac{C^0 b}{r N'(s_l)} \left[\sin\left(\sqrt{-\frac{s_l}{D}}\, a\right) \times \cos\left(\sqrt{-\frac{s_l}{D}}\, r\right) - \cos\left(\sqrt{-\frac{s_l}{D}}\, a\right) \sin\left(\sqrt{-\frac{s_l}{D}}\, r\right)\right] e^{s_l t} \qquad \text{(Eq. 34)}$$

where:

$$N'(s_l) = \left[\frac{3}{2}\left(1 - \frac{a}{b}\right) - k_c\right] \left[\sin\left(\sqrt{-\frac{s_l}{D}}\, b\right) \times \cos\left(\sqrt{-\frac{s_l}{D}}\, a\right) - \sin\left(\sqrt{\frac{-s_l}{D}}\, a\right) \cos\left(\sqrt{-\frac{s_l}{D}}\, a\right)\right]$$
$$+ a\sqrt{-\frac{s_l}{D}} \left[\frac{k_c}{2}\left(1 - \frac{b}{a}\right) + \frac{3D}{2 s_l b^2}\right] \left[\sin\left(\sqrt{-\frac{s_l}{D}}\, a\right) \times \sin\left(\sqrt{-\frac{s_l}{D}}\, b\right) + \cos\left(\sqrt{-\frac{s_l}{D}}\, a\right) \cos\left(\sqrt{-\frac{s_l}{D}}\, b\right)\right] \qquad \text{(Eq. 35)}$$

It is clear from Eq. 34 that $C(at) = 0$ at any time t, in accordance with Eq. 26. The flux $dJ(t)/dt$ of drug into the extraction medium is given by:

$$\frac{dJ(t)}{dt} = -4\pi a^2 n D \left(\frac{\partial C(rt)}{\partial r}\right)_{r=a} \qquad \text{(Eq. 36)}$$

and the total amount of drug released at time t is given by:

$$\mathrm{M}(t) = -4\pi a^2 n D \int_0^t \left(\frac{\partial C(rt')}{\partial r}\right)_{r=a} dt' \qquad \text{(Eq. 37)}$$

From Eq. 34 it is found:

$$\left(\frac{\partial C(rt)}{\partial r}\right)_{r=a} = \sum_{l=1}^{\infty} -\frac{C^0 b}{a N'(s_l)} \sqrt{-\frac{s_l}{D}}\, e^{s_l t} \qquad \text{(Eq. 38)}$$

so

$$\mathrm{M}(t) = 4\pi a^2 n D \sum_{l=1}^{\infty} \frac{C^0 b}{a N'(s)} \sqrt{-\frac{1}{s_l D}} (e^{s_l t} - 1) \qquad \text{(Eq. 39)}$$

Divided by the total amount of drug, $M(t = \infty) = 4\pi b^3/3\, NC^0$ (neglecting the capacity of the coat) the release $R'(t)$ is obtained:

$$R'(t) = \frac{\mathrm{M}(t)}{\mathrm{M}(t = \infty)} = \frac{3aD}{b^2} \sum_{l=1}^{\infty} \frac{1}{N'(s_l)\sqrt{-s_l D}} (e^{s_l t} - 1) \qquad \text{(Eq. 40)}$$

Constant Core Concentration–Variable Extraction Medium Concentration—If the solubility of the drug in the core is low, the concentration of dissolved drug remains constant as long as there is undissolved drug in the core. The boundary conditions are sketched in Fig. 3, and Eq. 7 now changes to:

$$C_c(t) = C' = k_c C(bt) \qquad \text{(Eq. 41)}$$

The initial conditions and the other boundary conditions, Eqs. 8 and 10, are unchanged. The integration constants A and B in Eq. 15 are now determined by introducing $\bar{C}(rs)$ into Eq. 14 and the Laplace transform of Eq. 41:

$$\bar{C}(bs) = \frac{C'}{k_c s} \qquad \text{(Eq. 42)}$$

In analogy to Eqs. 16 and 28 the following set of equations is obtained:

$$\begin{bmatrix} \phi_1' & \phi_2' \\ \phi_3 & \phi_4 \end{bmatrix} \begin{bmatrix} A \\ B \end{bmatrix} = \begin{bmatrix} -\frac{C' b}{k_c s} \\ 0 \end{bmatrix} \qquad \text{(Eq. 43)}$$

where:

$$\phi_1' = \sinh\left(\sqrt{\frac{s}{D}}\, b\right) \qquad \text{(Eq. 44)}$$

$$\phi_2' = \cosh\left(\sqrt{\frac{s}{D}}\, b\right) \qquad \text{(Eq. 45)}$$

ϕ_3 and ϕ_4 are given by Eqs. 19 and 20, respectively. In analogy with the previous examples, it is now straightforward to derive an equation for the concentration:

$$C(rt) = \sum_{l=1}^{\infty} \frac{C' b e^{s_l t}}{k_c s r} \frac{\left[(\phi_4)_{s=s_l} \sinh\left(\sqrt{\frac{s_l}{D}}\, r\right) - (\phi_3)_{s=s_l} \cosh\left(\sqrt{\frac{s_l}{D}}\, r\right)\right]}{\left[\frac{\partial}{\partial s}(\phi_1' \phi_4 - \phi_2' \phi_3)\right]_{s=s_l}} \qquad \text{(Eq. 46)}$$

and with Eq. 8:

$$C_e(t) = \sum_{l=1}^{\infty} \frac{k_e C' b e^{s_l t}}{k_c s a} \frac{\left[(\phi_4)_{s=s_l} \sinh\left(\sqrt{\frac{s_l}{D}}\, a\right) - (\phi_3)_{s=s_l} \cosh\left(\sqrt{\frac{s_l}{D}}\, a\right)\right]}{\left[\frac{\partial}{\partial s}(\phi_1' \phi_4 - \phi_2' \phi_3)\right]_{s=s_l}} \qquad \text{(Eq. 47)}$$

At the moment when all undissolved drug has disappeared from the core, the concentration will be given by Eq. 23. Thus, the release profile will be given by two different expressions according to the conditions in the core.

Pellets of Different Size—*Variable Core and Extraction Medium Concentrations*—This is a generalization of the results derived for pellets of equal size to a situation where there is a distribution in the size of pellets used. Assuming that there are N different types of pellets involved, differing in size, coat material, *etc.*, for each of the N types of pellets there is an equation like Eq. 15. For the j'th type:

$$\tilde{C}_j(rs) = \frac{A_j}{r}\sinh\left(\sqrt{\frac{s}{D_j}}r\right) + \frac{B_j}{r}\cosh\left(\sqrt{\frac{s}{D_j}}r\right) \qquad \text{(Eq. 48)}$$

also allowing the diffusion coefficients D_j to be different. If the coating material is the same for all types of pellets $D_j = D$ for all j.

The boundary condition at the core-coat boundary is the same as in Eqs. 5 and 7 for each type of pellet, *i.e.*,

$$\left(\frac{\partial\tilde{C}_j(rs)}{\partial r}\right)_{r=b_j} = \frac{b_j k_{jc}}{3D_j}\left[s\tilde{C}_j(rs)\right] - \frac{b_j C_j^0}{3D_j} \qquad \text{(Eq. 49)}$$

The boundary condition at the coat-extraction medium boundary is:

$$V_e\left(\frac{\partial C_e(t)}{\partial t}\right) = \sum_{j=1}^{N} -4\pi a_j^2 n_j D_j\left(\frac{\partial C_j(rt)}{\partial r}\right)_{r=a_j} \qquad \text{(Eq. 50)}$$

with:

$$C_e(t) = k_{1e}C_1(a_1t) = \ldots = k_{je}C_j(a_jt) = \ldots = k_{Ne}C_N(a_Nt) \qquad \text{(Eq. 51)}$$

Time Laplace transformation of Eqs. 50 and 51 gives:

$$s\tilde{C}_e(s) = \sum_{j=1}^{N} -\frac{3}{a_j V_{rj}} D_j\left(\frac{\partial\tilde{C}_j(rs)}{\partial r}\right)_{r=a_j} \qquad \text{(Eq. 52)}$$

and:

$$\tilde{C}_e(s) = k_{1e}\tilde{C}_1(a_1s) = \ldots = k_{je}\tilde{C}_j(a_js) = \ldots = k_{Ne}\tilde{C}_N(a_Ns) \qquad \text{(Eq. 53)}$$

To determine the $2N$ integration constants, A_j and B_j, it is necessary to have $2N$ equations. The first N equations are obtained from Eq. 49 after introduction of $\tilde{C}_j(rs)$ from Eq. 48. The j'th equation has the form:

$$iA_j\left[\frac{1}{b_j}\sqrt{-\frac{s}{D_j}}\cos\left(\sqrt{-\frac{s}{D_j}}b_j\right) - \frac{1}{b_j^2}\sin\left(\sqrt{-\frac{s}{D_j}}b_j\right) - \frac{sk_{je}}{3D_j}\sin\left(\sqrt{-\frac{s}{D_j}}b_j\right)\right] + B_j\left[\frac{1}{b_j}\sqrt{-\frac{s}{D_j}}\sin\left(\sqrt{-\frac{s}{D_j}}b_j\right) - \frac{1}{b_j^2}\cos\left(\sqrt{-\frac{s}{D_j}}b_j\right) - \frac{sk_{jc}}{3D_j}\cos\left(\sqrt{-\frac{s}{D_j}}b_j\right)\right] = -\frac{b_jC_j^0}{3D_j} \qquad \text{(Eq. 54)}$$

The last N equations are obtained from Eqs. 52 and 53 after introduction of Eq. 48. The j'th equation has the form:

$$\sum_{l=1}^{N}\left\{iA_l\left[\sqrt{-\frac{s}{D_l}}\frac{1}{a_l}\cos\left(\sqrt{-\frac{s}{D_l}}a_l\right) - \frac{1}{a_l^2}\sin\left(\sqrt{-\frac{s}{D_l}}a_l\right) + \delta_{lj}\frac{V_{rj}k_{jl}s}{3D_j}\sin\left(\sqrt{-\frac{s}{D_j}}a_j\right)\right] + B_l\left[-\sqrt{-\frac{s}{D_l}}\frac{1}{a_l}\sin\left(\sqrt{-\frac{s}{D_l}}a_l\right) - \frac{1}{a_l^2}\cos\left(\sqrt{-\frac{s}{D_l}}a_l\right) + \delta_{jl}\frac{V_{rj}k_{jl}s}{3D_j}\cos\left(\sqrt{-\frac{s}{D_j}}a_j\right)\right]\right\} = 0 \qquad \text{(Eq. 55)}$$

The results in Eqs. 54 and 55 may conveniently be written in matrix form as

$$EF = G \qquad \text{(Eq. 56)}$$

where:

$$E = \begin{bmatrix} g_1 & 0 & 0 & \ldots & 0 \\ 0 & g_2 & 0 & \ldots & 0 \\ 0 & 0 & g_3 & \ldots & 0 \\ \vdots & \vdots & \vdots & & \vdots \\ 0 & 0 & 0 & \ldots & g_N \\ (c_1+l_1) & c_2 & c_3 & \ldots & c_N \\ c_1 & (c_2+l_2) & c_3 & \ldots & c_N \\ c_1 & c_2 & (c_3+l_3) & \ldots & c_N \\ \vdots & \vdots & \vdots & & \vdots \\ c_1 & c_2 & c_3 & \ldots & (c_N+l_N) \end{bmatrix} \begin{bmatrix} h_1 & 0 & 0 & \ldots & 0 \\ 0 & h_2 & 0 & \ldots & 0 \\ 0 & 0 & h_3 & \ldots & 0 \\ \vdots & \vdots & \vdots & & \vdots \\ 0 & 0 & 0 & \ldots & h_N \\ (d_1+f_1) & d_2 & d_3 & \ldots & d_N \\ d_1 & (d_2+f_2) & d_3 & \ldots & d_N \\ d_1 & d_2 & (d_3+f_3) & \ldots & d_N \\ \vdots & \vdots & \vdots & & \vdots \\ d_1 & d_2 & d_3 & \ldots & (d_N+f_N) \end{bmatrix} \qquad \text{(Eq. 57)}$$

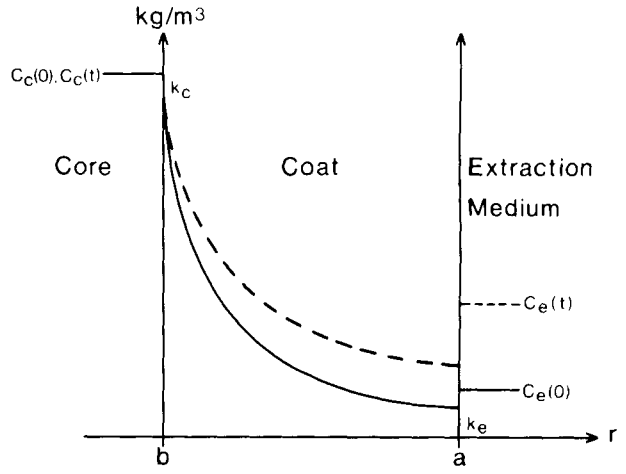

Figure 3—*A sketch of a segment of the core, coat, and extraction medium with boundary conditions corresponding to constant core concentration and variable extraction medium concentration. The stationary concentration profiles at time zero and time t are shown.*

and

$$F = \begin{bmatrix} iA_1 \\ iA_2 \\ \vdots \\ iA_N \\ B_1 \\ B_2 \\ \vdots \\ B_N \end{bmatrix} \quad \text{and} \quad G = \begin{bmatrix} -\frac{b_1C_1^0}{3D_1} \\ \vdots \\ -\frac{b_NC_N^0}{3D_N} \\ 0 \\ \vdots \\ 0 \end{bmatrix} \qquad \text{(Eq. 58)}$$

with:

$$g_i = \sqrt{-\frac{s}{D_i}}\frac{1}{b_i}\cos\left(\sqrt{-\frac{s}{D_i}}b_i\right) - \frac{1}{b_i^2} \times \sin\left(\sqrt{-\frac{s}{D_i}}b_i\right) - \frac{sk_{ic}}{3D_i}\sin\left(\sqrt{-\frac{s}{D_i}}b_i\right) \qquad \text{(Eq. 59)}$$

$$h_i = \sqrt{-\frac{s}{D_i}}\frac{1}{b_i}\sin\left(\sqrt{-\frac{s}{D_i}}b_i\right) - \frac{1}{b_i^2} \times \cos\left(\sqrt{-\frac{s}{D_i}}b_i\right) - \frac{sk_{ic}}{3D_i}\cos\left(\sqrt{-\frac{s}{D_i}}b_i\right) \qquad \text{(Eq. 60)}$$

$$c_i = \sqrt{-\frac{s}{D_i}}\frac{1}{a_i}\cos\left(\sqrt{-\frac{s}{D_i}}a_i\right) - \frac{1}{a_i^2}\sin\left(\sqrt{-\frac{s}{D_i}}a_i\right) \qquad \text{(Eq. 61)}$$

$$d_i = -\sqrt{-\frac{s}{D_i}}\frac{1}{a_i}\sin\left(\sqrt{-\frac{s}{D_i}}a_i\right) - \frac{1}{a_i^2}\cos\left(\sqrt{-\frac{s}{D_i}}a_i\right) \qquad \text{(Eq. 62)}$$

$$l_i = \frac{V_{ri}k_{ie}s}{3D_i}\sin\left(\sqrt{-\frac{s}{D_i}}a_i\right) \qquad \text{(Eq. 63)}$$

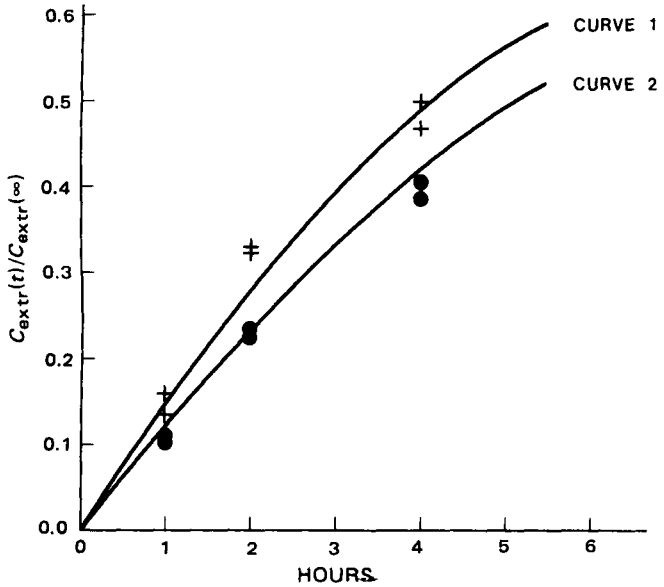

Figure 4—*Curve 1: Release profile calculated from Eq. 25 (or Eq. 56) when* a = *475 μm,* b = *459.2 μm,* V_{ri} = *75,* k_{ic} = k_{ie} = *1 to give the least-squares fit to experimental data. The diffusion coefficient is determined to be* $1.17 \times 10^{-13}\ m^2\ sec^{-1}$. *Curve 2: Predicted release profile of pellets when* a = *478.8 μm,* b = *459.2 μm,* V_{ri} = *75,* k_{ie} = k_{ic} = *1 and* D = $1.17 \times 10^{-9}\ cm^2\ sec^{-1}$.

$$f_i = \frac{V_{ri}k_{ie}s}{3D_i}\cos\left(\sqrt{-\frac{s}{D_i}}a_i\right) \qquad \text{(Eq. 64)}$$

Equation 56 is solved for iA_j and B_j (j = 1,N) and after introduction of iA_j, B_j into Eq. 49 for the j'th type of pellet, the following expression for $\bar{C}_j(rs)$ is found:

$$\bar{C}_j(rs) = \frac{\chi_j(rs)}{\psi_j(rs)} \qquad \text{(Eq. 65)}$$

where:

$$\chi_j(rs) = |E(j = G)|\sin\left(\sqrt{-\frac{s}{D_j}}r\right) + |E[(N + j) = G]| \times \cos\left(\sqrt{-\frac{s}{D_j}}r\right) \qquad \text{(Eq. 66)}$$

and:

$$\psi_j(rs) = r|E| \qquad \text{(Eq. 67)}$$

$|E|$ is the determinant of the E matrix (Eq. 57) and $|E(j = G)|$ is the determinant of the matrix obtained from E by replacing the j'th column with the vector G. Equation 65 may be reversed in the usual way by residue calculation:

$$C_j(rt) = \sum_{i=1}^{N}\frac{\chi_j(rs_i)e^{s_it}}{\left\{\frac{\partial}{\partial s}[\psi_j(rs)]\right\}_{s=s_i}} \qquad \text{(Eq. 68)}$$

where $\partial\psi/\partial s$ means a differentiation of the determinant $|E|$. This is done by replacing the elements in one row by the same elements differentiated with respect to s. In that way $2N$ new determinants are generated and they are all identical to the original determinant besides one row. Finally the $2N$ determinants are added giving the desired result. Therefore, it is necessary to know:

$$\frac{\partial g_i}{\partial s} = \left(\frac{1}{2D_i} - \frac{k_{ic}}{3D_i}\right)\sin\left(\sqrt{-\frac{s}{D_i}}b_i\right) + \frac{sk_{ic}b_i}{6D_i\sqrt{-sD_i}}\cos\left(\sqrt{-\frac{s}{D_i}}b_i\right) \qquad \text{(Eq. 69)}$$

$$\frac{\partial k_i}{\partial s} = \frac{1}{D_i}\left(\frac{1}{2} - \frac{k_{ic}}{3}\right)\cos\left(\sqrt{-\frac{s}{D_i}}b_i\right) - \frac{sk_{ic}b_i}{6D_i\sqrt{-sD_i}}\sin\left(\sqrt{-\frac{s}{D_i}}b_i\right) \qquad \text{(Eq. 70)}$$

$$\frac{\partial c_i}{\partial s} = \frac{1}{2D_i}\sin\left(\sqrt{-\frac{s}{D_i}}a_i\right) \qquad \text{(Eq. 71)}$$

$$\frac{\partial d_i}{\partial s} = \frac{1}{2D_i}\cos\left(\sqrt{-\frac{s}{D_i}}a_i\right) \qquad \text{(Eq. 72)}$$

$$\frac{\partial l_i}{\partial s} = \frac{V_{ri}k_{ie}}{3D_i}\left[\sin\left(\sqrt{-\frac{s}{D_i}}a_i\right) - \frac{a_i}{2}\sqrt{-\frac{s}{D_i}}\cos\left(\sqrt{-\frac{s}{D_i}}a_i\right)\right] \qquad \text{(Eq. 73)}$$

$$\frac{\partial f_i}{\partial s} = \frac{V_{ri}k_{ie}}{3D_i}\left[\frac{a_i}{2}\sqrt{-\frac{s}{D_i}}\sin\left(\sqrt{-\frac{s}{D_i}}a_i\right) + \cos\left(\sqrt{-\frac{s}{D_i}}a_i\right)\right] \qquad \text{(Eq. 74)}$$

These results can be programmed into a digital computer. The poles of $\bar{C}_j(rs)$ are found as the zero points of the determinant $|E|$, and once they are known, it is straightforward to use Eq. 68 for pellet type j and calculate $C_e(t)$ according to:

$$C_e(t) = k_{ie}C_j(a_jt) \qquad \text{(Eq. 75)}$$

Sink Condition in Extraction Medium–Variable Core Concentration—The boundary condition at the coat-extraction medium is:

$$C_i(a_it) = 0$$

for each type of pellet. That is, there is no coupling between the different types of pellets, which means that the release may be described as a superposition of the release from each type of pellet as given by Eq. 39, for example.

Other Boundary Conditions—It is fairly easy to adapt this calculation scheme to other relevant boundary conditions as discussed under Pellets of Equal Size.

RESULTS AND DISCUSSION

It has been shown that the general solution to the diffusion description of drug release from controlled-release solid dosage forms consisting of either one-size pellets or a broad-size distribution of pellets is straightforward and easy to handle in terms of matrix equations.

The poles s_n of $\bar{C}(rs)$ are found as the zero points of the determinant of the E matrix (Eqs. 56 and 65). The s_n has to be determined numerically, which may be done on computers. Once the poles have been found, either one of the concentrations $C_j(rt)$ and, thus, $C_e(t)$ may be calculated from Eqs. 68 and 75. It is noted that, due to Eq. 51, any one of the concentrations, $C_j(rt)$, may be used to calculate the extraction medium concentration, $C_e(t)$. Finally, it is noted that the one-size pellet case is included as a special case of the general treatment given previously, and in that case, Eq. 56 degenerates to Eq. 16.

As an illustration, the diffusion model has been applied to the prediction of the release profile of pellets with a known diffusion coefficient D and a coat thickness ($a - b$). Two experimental and calculated release profiles of propoxyphene hydrochloride pellets, coated with different amounts of a synthetic coat (5) are shown in Fig. 4. Curve 1 corresponds to pellets with a thin coat (8%) and Curve 2 to pellets with a thick coat (10%). Since the coating material is the same, it is assumed that the diffusion coefficients are identical in both cases which implies that the difference in release profiles is due to a different thickness of the coating. The diffusion model should be able to reproduce this difference if the model reflects essential features of the process. As the pellets had a narrow size distribution, only calculations for pellets of one size were used.

The dimensions of the pellets (a and b) were obtained from microscopy of a series of microtome sections of the pellets. It was found that b = 459.2 μm and a = 475.0 μm and 478.8 μm, respectively. Since there are only one-size pellets in the experiments, the results in Eq. 56 for N = 1 may be used. Adsorption phenomena were considered unimportant, and k_{ic} and k_{ie} were set equal to 1. The relative volume V_{ri} = 75. Equation 56 was then applied to fit data points for pellets with the thin coat (Curve 1) in order to obtain a value for the diffusion coefficient.

The experiments were conducted with the general boundary conditions with varying coat and extraction medium concentrations. It was possible to fit the data points with D = 420 $\mu m^2 h^{-1}$, ~ $1.17 \times 10^{-13}\ m^2\ sec^{-1}$ (Curve 1). Curve 2 was then calculated from Eq. 56 with the relevant b and a, and the predicted release profile is seen to be in good agreement with the experimental data. It is noted that the diffusion coefficient is somewhat different from the one reported earlier (1), where quasistationary conditions were imposed.

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APPENDIX

Variable	Units	
β	—	= parameter in the Rosin-Rammler-Sperling-Weibull distribution (See Ref. 1)
b	m	= radius of core
a	m	= radius of coated pellet
r	m	= radial distance from the center of a sphere
t	sec	= time
s	sec^{-1}	= frequency
s_i	sec^{-1}	= poles in Eq. 22
$C(rt)$	kg/m^3	= concentration of drug in coat at position r and at time t
$C_c(t)$	kg/m^3	= concentration of dissolved drug in the core at time t
$C_e(t)$	kg/m^3	= concentration of drug in extraction medium at time t
C^0	kg/m^3	= initial concentration of drug in core
$\bar{C}(rs)$	kgs/m^3	= time Laplace transform of $C(rt)$ at r
C'	kg/m^3	= constant core concentration in case of a sparingly soluble drug
D	m^2/sec	= diffusion coefficient of drug in coat
k_c	—	= distribution coefficient for drug between core and coat
k_e	—	= distribution coefficient for drug between extraction medium and coat
V_e	m^3	= volume of extraction medium
V_r	—	= the ratio of the volume of extraction medium to total volume of pellets
n	—	= number of pellets of identical size
$N(s_i)$	—	= denominator in Eq. 23 defined in Eq. 24
$M(t)$	kg	= total amount of drug released at time t
N	—	= number of different types of pellets in a sample
$J(t)$	$kg/sec\ m^2$	= flux of drug at time t

Stereoselective Disposition and Glucuronidation of Propranolol in Humans

BERNIE SILBER *[x], NICHOLAS H. G. HOLFORD, and SIDNEY RIEGELMAN [†]

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[†] Deceased. * Present address: Department of Pharmaceutics, BG-20, School of Pharmacy, University of Washington, Seattle WA 98195.

Abstract □ Following oral dosing to steady state, the disposition of $S(-)$- and $R(+)$-propranolol and their corresponding glucuronide conjugates was studied in 4 healthy adults using doses from 40 to 320 mg/day of the racemate. Steady-state plasma concentrations of $S(-)$-propranolol and its corresponding glucuronide conjugate were greater than that for $R(+)$-propranolol and its corresponding conjugate. The average steady-state concentration of both enantiomers increased disproportionately to dose. There was a 52 ± 7 (mean ± *SD*) % decrease in the intrinsic clearance (Cl_{int}) of $S(-)$-propranolol and a 65 ± 22% decrease in the Cl_{int} of $R(+)$-propranolol over the dosing range studied. The terminal elimination half-lives of $S(-)$-propranolol and its glucuronide conjugate were longer than for the $R(+)$-enantiomer at all doses. The formation of glucuronide conjugates of $S(-)$- and $R(+)$-propranolol was best described by a saturable process in all subjects. Within individuals, the ratio of V'_{max}/K_m for the glucuronide conjugate of $S(-)$-propranolol was from 2.1- to 4.9-fold greater than for the conjugate of the $R(+)$-enantiomer. These studies demonstrate for the first time, that propranolol undergoes stereoselective disposition in humans.

Keyphrases □ Propranolol—$S(-)$- and $R(+)$-enantiomers and corresponding glucuronide conjugates, stereoselective disposition, humans □ Stereoselectivity—disposition of $S(-)$- and $R(+)$-propranolol, humans □ Glucuronide—conjugates of $S(-)$- and $R(+)$-propranolol in stereoselectivity disposition studies, humans

Propranolol [1-isopropylamino-3-(1-naphthoxy)-2-propanol] is a nonselective beta adrenergic blocking agent used clinically as a racemic mixture of the $S(-)$- and $R(+)$-enantiomers. Because $S(-)$-propranolol is about 100 times more potent as a beta blocker than the $R(+)$-enantiomer, $S(-)$-propranolol is believed to be largely responsible for the clinical effects of racemic drug (1).

Numerous investigators have described the absorption, distribution, metabolism, and elimination of propranolol in humans and animals. Pharmacokinetic studies in healthy volunteers and in patients have demonstrated up to 20-fold variation between individuals in plasma propranolol concentrations after oral doses (2–8). Age (9, 10); cigarette smoking (9, 11); concomitant drug intake (12);

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