Analysis of Theoretical Behavior of a Proposed Zero-Order Drug Delivery System

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Abstract □ An analysis of the theoretical behavior of a proposed zero-order drug delivery system is presented. Equations describing drug release with time are developed using a physically realistic model. The theory agrees well with experimental data and indicates that drug release from the device is nearly, although not rigorously, zero order.

Keyphrases □ Drug delivery—zero-order system, theoretical behavior, equations developed □ Delivery, drug—zero-order system, theoretical behavior, equations developed

Brooke and Washkuhn (1) presented the design of a drug delivery device, the unique geometry of which would, ideally, lead to zero-order release of its contents *via* dissolution from a solid pellet or diffusion from a suitable matrix. This ideal behavior depends in theory, however, on both the drug molecules and the opening through which they must pass having infinitely small dimensions. In this paper, the theoretical behavior of such a device modeled entirely with finite dimensions will be examined.

Discussion of prior work dealing with geometrical considerations in the determination of drug dissolution and release rates may be found in the previous paper (1).

THEORETICAL

The case to be treated here is that of a device charged with pure solid drug. It is assumed that dissolution takes place isotropically and that diffusion of drug out of the device is the rate-determining process. Similar equations could be derived for the case of drug being released from a polymer or other matrix.

The drug-containing cavity of the device in question (1) is essentially a sector of a right circular cylinder. Its cross section is shown in Fig. 1.

Let the center that defines the arc be outside the device and let the opening of the device be at radius n. The area of arcuate surface at diffusion path length s is then $2\theta L(s + n)$, where L is the length of the drug-filled cavity. The flux, J, at s is, therefore:

$$J = 2\theta LD(s + n)\frac{dC}{ds} \qquad \text{(Eq. 1)}$$

where D is the drug's diffusivity in the dissolution medium. The drug concentration at the dissolving surface is the solubility, C_s. The concentration at the opening is C_b; if sink conditions are assumed, the concentration at distance h into the bulk is zero. At steady state, integration of Eq. 1 from C_b to C_s and from zero to $\lambda - n$ yields:

$$J = \frac{2\theta LD(C_s - C_b)}{\ln\frac{\lambda}{n}} \qquad \text{(Eq. 2)}$$

Diffusion from the opening into the bulk is described by:

$$J = \frac{2\theta LDnC_b}{h} \qquad \text{(Eq. 3)}$$

Equation 3 treats the effective diffusion layer as the typical planar case rather than as radial diffusion from a point source. This treatment is justified if h is much less than the arc length at the opening. In any event, hydrodynamic conditions are important in determining release rate only at very early times when λ is of the order of magnitude of the opening arc length.

By solving for C_b in Eq. 3 in order to eliminate it from Eq. 2, the rate of drug release can be shown to be:

$$J = \frac{2\theta LDC_s}{\frac{h}{n} + \ln\frac{\lambda}{n}} \qquad \text{(Eq. 4)}$$

Given drug of density ρ, the mass dissolved at any time is:

$$M = (\lambda^2 - n^2)L\theta\rho \qquad \text{(Eq. 5)}$$

Integration of Eq. 4 after substituting for λ from Eq. 5 yields a relationship between mass dissolved and time:

$$\frac{\left(\frac{h}{n} - \frac{1}{2}\right)M + \left(\frac{M + L\theta\rho n^2}{2}\right)\ln\left(\frac{M}{L\theta\rho n^2} + 1\right)}{2\theta LDC_s} = t \qquad \text{(Eq. 6)}$$

If it is assumed that the mass in solution in the diffusion layer is negligible compared to the total drug mass, then:

$$M_r = M - M_d \qquad \text{(Eq. 7)}$$

where M_r is the mass released, and M_d is the mass dissolved within the device. At any given time:

$$M_d = \int_0^{\lambda - n} 2\theta L(s + n)C\,ds \qquad \text{(Eq. 8)}$$

where:

$$C = \frac{J}{2D\theta L}\ln\left(\frac{s + n}{\lambda}\right) + C_s \qquad \text{(Eq. 9)}$$

Following integration and the appropriate substitutions, Eq. 7 becomes:

$$M_r = (\lambda^2 - n^2)\left[L\theta\rho - L\theta C_s + \frac{L\theta C_s}{2\left(\frac{h}{n} + \ln\frac{\lambda}{n}\right)}\right] - \frac{L\theta C_s n^2}{\frac{h}{n} + \ln\frac{\lambda}{n}}\ln\frac{\lambda}{n} \qquad \text{(Eq. 10)}$$

and if Eq. 5 is substituted into Eq. 6, the following is obtained:

$$t = \frac{\left(\frac{h}{n} - \frac{1}{2}\right)(\lambda^2 - n^2)\rho + \lambda^2\rho\ln\frac{\lambda}{n}}{2DC_s} \qquad \text{(Eq. 11)}$$

Equations 10 and 11 relate λ to M_r and t, respectively. Thus, values for λ may be selected to generate M_r *versus* t data.

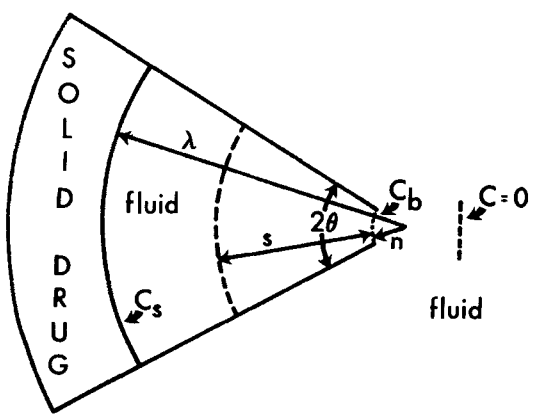

Figure 1—*Cross-sectional view of the device's drug-containing cavity, illustrating the case where the original charge of solid drug is partially dissolved. (See text.)*

RESULTS AND DISCUSSION

Equation 4 differs from the previously derived equation describing the idealized case (1) in that Eq. 4 contains a $\ln \lambda/n$ term. Since λ, the distance from the solid drug surface to the arc center, is time dependent, the flux expression derived here has a time dependence that was previously absent.

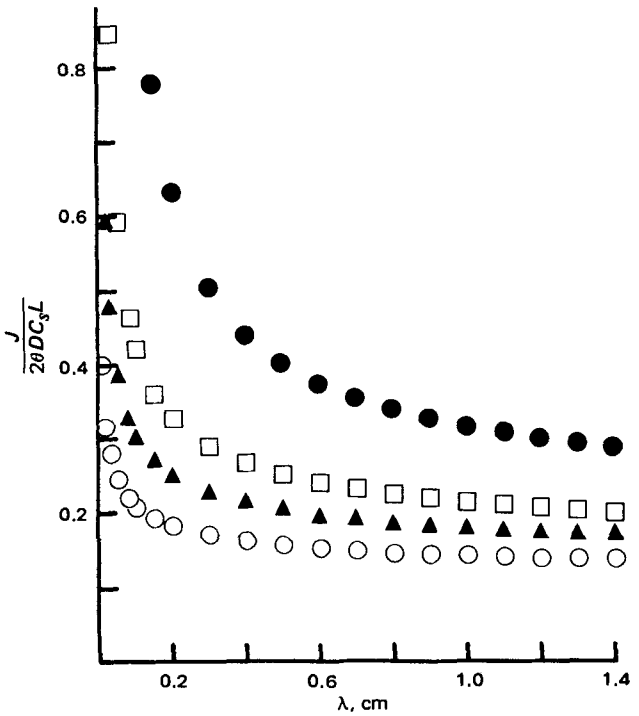

Figure 2—*Flux as a function of* λ *predicted by Eq. 4. The parameters used (in centimeters) are:* n = *0.050 and* h = *0.010* (●), n = *0.025 and* h = *0.025* (□), n = *0.010 and* h = *0.010* (▲), *and* n = *0.010 and* h = *0.025* (○).

Figure 2 shows the behavior of flux as a function of λ as predicted by Eq. 4, using four sets of reasonable parameters. In all cases, flux is initially high but quickly drops to a lower and nearly constant value. Thus, a small portion of the mass within the device would be released quickly, but by far the major portion would be released at a rate *approximating* zero order.

This point is further illustrated in Fig. 3 where the rate of change of flux with respect to λ is shown. The resulting family of curves clearly demonstrates the effect of diffusion layer thickness. For simplicity, λ and h are expressed as multiples of n, and $dJ/d\lambda$ is normalized by dividing by the initial $dJ/d\lambda$, i.e., when $\lambda/n = 1$. The rate of change of flux decreases markedly for $n \leq \lambda \lesssim 2n$; for $\lambda \gtrsim 2n$, the asymptotic approach to zero, *i.e.*, flux constant with λ, is obvious.

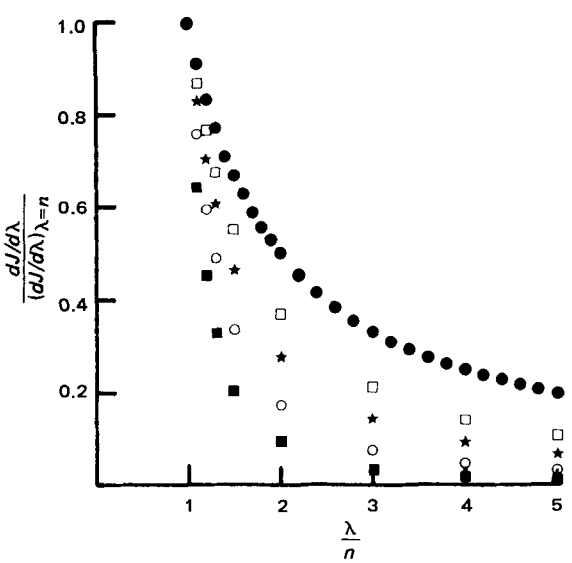

Figure 3—*Relative rate of change of flux with respect to* λ. *For simplicity,* λ *and* h *are expressed as multiples of* n, *such that* h = in *and* λ = jn. *The data shown are for* i = *0.5* (■), *1* (○), *2* (★), *and 4* (□) *and for the limiting right rectangular hyperbola as* i → ∞, i.e., *infinitely thick diffusion layer* (●).

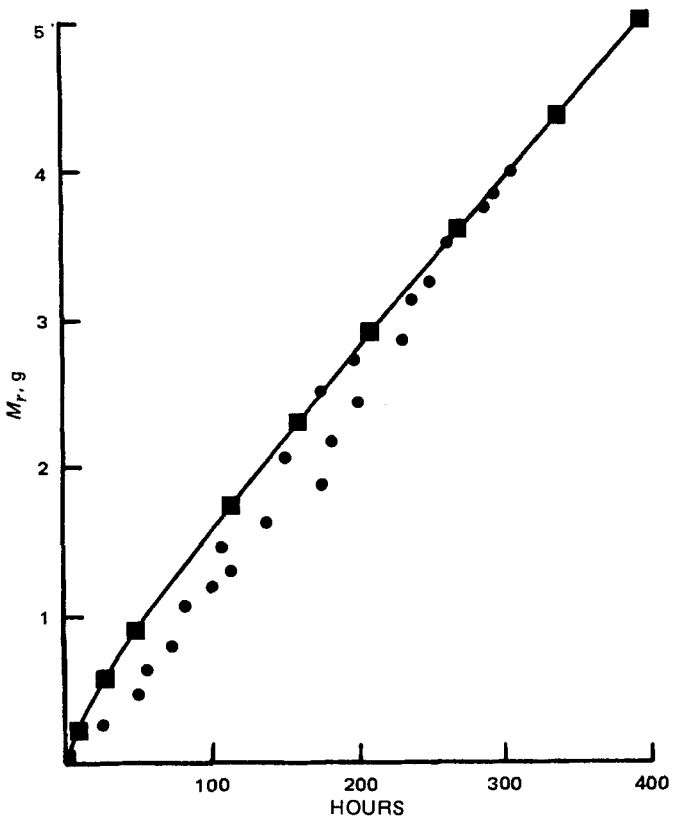

Figure 4—*Mass of stearic acid released with time as predicted by Eqs. 10 and 11* (■). *Experimental data* (●) *are from Ref. 1.*

Mass released *versus* time data were generated from Eqs. 10 and 11 to simulate the case experimentally tested by Brooke and Washkuhn (1), that of stearic acid being released into alcohol USP. The following parameters were used: $h = 100\ \mu m$, $n = 540\ \mu m$, $2\theta = 1.4$ radians, $L = 5.75$ cm, $C_s = 0.048$ g/cm^3 (2), and $\rho = 0.94$ g/cm^3 (3). A value for the only remaining parameter, diffusivity, was generated by forcing Eqs. 10 and 11 to yield the point $M_r = 5.07$ g at $t = 400$ hr from the previous paper's composite regression data (1). This leads to $D = 2.65 \times 10^{-5}$ cm^2/sec, which does not appear to be an unreasonable value (4, 5).

Figure 4 shows the resultant data. Good agreement is seen between the theoretically predicted release profile and the experimental data. Although systematic deviation from true zero order is apparent, the rapid approach to linearity is also evident. Indeed, a linear regression on the data for $t = 100$, 200, 300, and 400 hr gives $r^2 = 0.999$.

Although further experimental testing is certainly in order, it is thus concluded that the device examined here might exhibit release behavior that is nearly zero order and that, as such, it might be useful as a constant-rate drug delivery system.

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