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Release of medicaments from spherical matrices containing drug in suspension: Theoretical aspects

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Abstract

An equation relating the rate of release of solid drugs suspended in spherical matrices into a perfect sink is derived. The final expression is simple and convenient. Reduction of the matrix size to one half results in a 4-fold greater release rate.

Keywords: Release rate; Spherical matrix; Diffusion in the sphere; Perfect sink; Fick's law of diffusion; Suspension

1. Introduction

An equation relating the amount and rate of release of drugs suspended in an ointment base to time was derived by Higuchi (1961). The final expression (Eq. 1) is surprisingly simple and convenient:

$$Q = \sqrt{(2A - C_s)C_s Dt} \quad (1)$$

where Q is the amount released at time t per unit area of exposure, A denotes the initial concentration of drug expressed in units/cm^3, C_s is the solubility of the drug as units/cm^3 in the ointment base, and D represents the diffusion constant of the drug molecule in the ointment base.

Later, the explicit solution of Fick's law with the appropriate boundary conditions was obtained by Koizumi et al. (1975) and a new equation for Q was derived, trading in the simplicity of Eq. 1 for a little more accuracy.

The above cases are examples of diffusion in a plane sheet. If a similar system is made into a collection of particles and immersed in dissolution medium, it becomes a case of diffusion in a sphere. We would encounter systems of this sort with oral drug delivery devices. Simulations of drug release from spherical droplets have been reported by Takehara and Koike (1977).

The present report is concerned with the theoretical aspects of release of medicaments from spherical devices containing drug in suspension. The system is described as follows: (a) the suspended drug is in a fine state such that the

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particles are much smaller in diameter than the diameter of the matrix, a; (b) the initial amount of drug, A, present per unit volume is substantially greater than C_s, the solubility of the drug per unit volume of the matrix; (c) the matrix is totally immersed in the medium which constitutes a perfect sink for the released drug.

2. Theoretical

Assuming that the diffusion is radial, the diffusion equation for a constant coefficient takes the form of Eq. 2, according to Crank (1975a):

$$\frac{\partial C}{\partial t} = D\left(\frac{\partial^2 C}{\partial r^2} + \frac{2}{r}\frac{\partial C}{\partial r}\right) \tag{2}$$

where r is the distance from the center of the spherical matrix, and C denotes the concentration of the drug dissolved in the matrix at time, t, and at position, r. At steady state the equation is

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(r^2\frac{\mathrm{d}C}{\mathrm{d}r}\right) = 0 \tag{3}$$

of which the general solution is

$$rC = Ur + V \tag{4}$$

where U and V are constants to be determined from the boundary conditions. Since this is the linear equation, we can draw a concentration profile which may exist after the lapse of finite time after application of the matrix (Fig. 1).

The solid line in the diagram would essentially represent the concentration gradient existing after time, t, in the matrix normal to the surface. The total drug concentration, as indicated in the drawing, would be expected to show a more or less sharp discontinuity at distance h from the surface, none of the suspended phase dissolving until the environmental concentration drops below C_s. For the distance, h, from the matrix surface, the gradient of rC would be essentially constant, provided $A \gg C_s$. The linearity of the gradient over this distance follows under these conditions from Eq. 4. The shift in the profile after an additional interval of Δt is shown as a dotted line in the diagram, corresponding to the extension of the zone of partial depletion by the

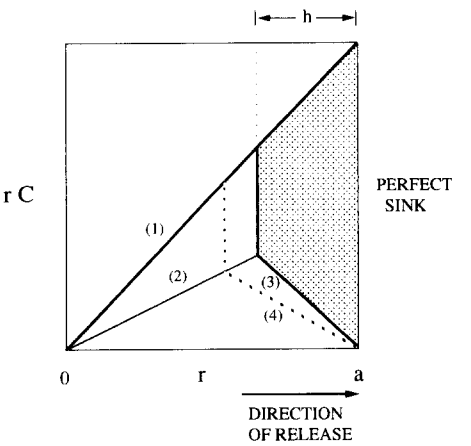

Fig. 1. Theoretical concentration profile existing in a spherical matrix containing suspended drug and in contact with a perfect sink. Equations of lines specified: (1) $rC = rA$, (2) $rC = rC_s$, (3) $rC = (a-h)C_s(a-r)/h$, (4) $rC = (a-h-\mathrm{d}h)C_s(a-r)/(h+\mathrm{d}h)$.

distance, Δh. It is evident, furthermore, that at time, t, the amount of drug released from the matrix corresponds to the shaded region in the diagram.

It can be seen, based on the above diagram, that $\mathrm{d}Q$, the amount additionally depleted by further movement of the front by $\mathrm{d}h$, is related to other constants:

$$\mathrm{d}Q = (A - C_s)4\pi(a-h)^2\mathrm{d}h + \int_{a-h}^{a} 4\pi r\left[(a-h)C_s\frac{(a-r)}{h} - (a-h-\mathrm{d}h)C_s\frac{(a-r)}{h+\mathrm{d}h}\right]\mathrm{d}r$$

$$\mathrm{d}Q = (A - C_s)4\pi(a-h)^2\mathrm{d}h + 4\pi C_s\left[\frac{a\,\mathrm{d}h}{h(h+\mathrm{d}h)}\right]\int_{a-h}^{a} r(a-r)\mathrm{d}r$$

where

$$\frac{\mathrm{d}h}{h+\mathrm{d}h} = \left(\frac{\mathrm{d}h}{h}\right) - \left(\frac{\mathrm{d}h}{h}\right)^2 + \left(\frac{\mathrm{d}h}{h}\right)^3 - \cdots$$

Since dh/h is negligibly small compared to unity, the terms higher than second order can be omitted. After integration we obtain Eq. 5:

$$dQ = 4\pi\left[(A - C_s)(a-h)^2 + C_s a\left(\frac{a}{2} - \frac{h}{3}\right)\right]dh \tag{5}$$

However, according to Fick's law

$$dQ = -4\pi a^2\left(\frac{dC}{dr}\right)_{r=a} D dt$$

$$dQ = 4\pi C_s \frac{a(a-h)}{h} D dt \tag{6}$$

or

$$\frac{a(a-h)}{h} C_s D dt = \left[(A - C_s)(a-h)^2 + C_s a\left(\frac{a}{2} - \frac{h}{3}\right)\right]dh \tag{7}$$

Separating the variables and integrating both sides, we obtain

$$\frac{Dt}{a^2} = -\frac{1}{6}X + \frac{1}{2}\left(\frac{A}{C_s} - \frac{2}{3}\right)X^2 - \frac{1}{3}\left(\frac{A}{C_s} - 1\right)X^3 - \frac{1}{6}\log(1-X)$$

where

$$X = \frac{h}{a} \tag{8}$$

Expansion of the logarithm and rearrangement of terms result

$$\frac{Dt}{a^2} = \frac{1}{2}\left(\frac{A}{C_s} - \frac{1}{2}\right)X^2 - \frac{1}{3}\left(\frac{A}{C_s} - \frac{7}{6}\right)X^3 - \frac{1}{6}\sum_{n=4}^{\infty}\frac{X^n}{n} \tag{9}$$

From the diagram it is apparent that the amount of depletion Q (as a function of h), at time, t, is

$$Q = \int_{a-h}^{a} 4\pi r\left[rA - (a-h)C_s\frac{(a-r)}{h}\right]dr$$

$$Q = \frac{4\pi a^3}{3}A\left[3\left(\frac{A}{C_s} - \frac{1}{2}\right)X - 3\left(\frac{A}{C_s} - \frac{5}{6}\right)X^2 + \left(\frac{A}{C_s} - 1\right)X^3\right]\Big/\left(\frac{A}{C_s}\right) \tag{10}$$

Eq. 8 and 10 define parametric expression of the released amount, Q, at time, t. Partially eliminating X, term by term, from Eq. 9 and 10, we obtain

$$Q = 4\pi a^2\left[\sqrt{2(A - C_s)C_s Dt} + \frac{4C_s}{9a}\left\{\frac{C_s}{(2A - C_s)} - 3\right\}Dt\right] \tag{11}$$

The approximate expression (Eq. 11) will be essentially valid for all times less than that corresponding to complete depletion of the suspended phase.

3. Methods

All the computations were carried out on an IBM-compatible personal computer (Mistation 3S, MITAC-Japan, Tokyo) using FORTRAN programs.

3.1. calculation of Q values by finite-difference method (Crank, 1975b)

The following algorithm was used for calculation of Q values, where dt is the time interval, and n the number of equal intervals by which the radius of the spherical matrix is divided (Fig. 2):

[STEP 1] $t = 0, C_i = A(i = 0 \rightarrow n-1)$, $C_n = 0 (t > 0)$

[STEP 2] $CC_i = C_i$, if $CC_i > C_s$ then $CC_i = C_s$

[STEP 3] $t^+ = t + dt$, $C_i^+ = C_i + dC_i\ (i = 0 \rightarrow n-1)$

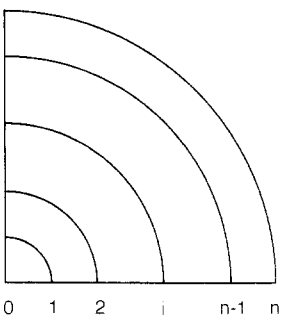

Fig. 2. Schematic illustration of the treatment of radial diffusion in the finite-difference method.

where

$$dC_i = \frac{Dn^2 dt}{a^2 i}[(i-1)C_{i-1} - 2iC_i + (i+1)(C_{i+1})](i = 1 \rightarrow n-1)$$

$$dC_0 = \frac{6Dn^2 dt}{a^2}[C_1 - C_0]$$

[STEP 4] $t = t^+, C_i = C_i^+ (i = 0 \rightarrow n-1)$

[STEP 5] go to [STEP 2]

At any time, t,

$$Q = \frac{\pi a^3}{3n^3}\sum_{i=0}^{n-1}(6i^2 + 4i + 1)C_i + (6i^2 + 8i + 3)C_{i+1}$$

3.2. Calculation of Q values using parametric equations (Eq. 8 and 10)

The value of h, satisfying Eq. 8 for a given value of t, is obtained using the Newton-Raphson

Table 1
Comparison of Q values calculated from the parametric equations (Eq. 8 and 10), Q_{PE}, the simplified equation (Eq. 11), Q_{SE}, and the finite-difference method, Q_{FD}

$(Dt)/(a^2)$	h/a	$(Q_{PE})/(Q_\infty)$	$(Q_{SE})/(Q_\infty)$	$(Q_{FD})/(Q_\infty)$ [a]
$A/C_s = 2.0$				
0.001	0.0368	0.0804	0.0804	0.0996
0.002	0.0521	0.1126	0.1126	0.1267
0.003	0.0640	0.1370	0.1370	0.1528
0.004	0.0740	0.1572	0.1572	0.1725
0.005	0.0829	0.1748	0.1748	0.1884
0.010	0.1180	0.2420	0.2420	0.2544
0.020	0.1685	0.3318	0.3319	0.3447
0.030	0.2078	0.3965	0.3967	0.4104
0.040	0.2415	0.4483	0.4485	0.4638
0.050	0.2715	0.4918	0.4921	0.5085
0.100	0.3921	0.6433	0.6438	0.6650
0.150	0.4875	0.7389	0.7396	0.7641
0.200	0.5692	0.8059	0.8063	0.8332
0.250	0.6410	0.8549	0.8546	0.8830
0.300	0.7044	0.8913	0.8897	0.9192
0.400	0.8082	0.9393	0.9321	0.9645
0.500	0.8825	0.9664	0.9482	0.9851
$A/C_s = 10.0$				
0.005	0.0328	0.0905	0.0905	0.0996
0.010	0.0466	0.1268	0.1268	0.1267
0.020	0.0663	0.1770	0.1771	0.1809
0.030	0.0816	0.2146	0.2147	0.2174
0.040	0.0946	0.2457	0.2458	0.2430
0.050	0.1061	0.2726	0.2728	0.2686
0.100	0.1525	0.3738	0.3742	0.3680
0.200	0.2208	0.5049	0.5062	0.4982
0.300	0.2759	0.5958	0.5983	0.5883
0.400	0.3244	0.6659	0.6698	0.6572
0.500	0.3690	0.7224	0.7282	0.7131
1.000	0.5676	0.8963	0.9147	0.8881
1.500	0.7643	0.9737	1.0121	0.9693
2.000	0.9549	0.9976	1.0634	0.9980

[a] $n = 20$, $dt = 0.0001$.

method (Press et al., 1992). The h value is then substituted into Eq. 10 to determine the value of Q that corresponds to time, t.

4. Results and discussion

The cumulative amounts of medicaments released from spherical matrices containing drugs in suspension were estimated from parametric equations (Eq. 8 and 10) and from Eq. 11. Since these values are approximations, they were compared in Table 1 with those obtained by the finite-difference method, which is similar to the procedure used by Takehara and Koike (1977) for the simulation of drug release from droplets.

When the amount of drug, A, present per unit volume is substantially greater than C_s, the solubility of the drug per unit volume of the matrix ($A/C_s = 10$), the Q values from the parametric equations (Eq. 8 and 10) and those from the finite-difference method are almost identical, whereas in the case of $A/C_s = 2$, the differences are small but notable.

Eq. 11, an approximated form of the parametric equations (Eq. 9 and 10), retains some vestige of Higuchi's equation (Eq. 1) and is handy to use for the evaluation of Q.

It is apparent from Eq. 11 that a reduction of the size of the matrix to one half leads to a 4-fold increase in the rate of release of the drug. According to Hixson and Crowell's 'Cubic Root Law' for dissolution (Abdou, 1989), a reduction of particle size to one half results in only a 2-time increase in the dissolution rate. It is noteworthy that the effect of size reduction is different in the dissolution of solid drugs and in the release of a drug from a spherical matrix containing solid drug in suspension.

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