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Rate of Release of Medicaments from Ointment Bases Containing Drugs in Suspension[1]

Tamotsu Koizumi, Michihiro Ueda, Masawo Kakemi and Haruko Kameda[2]

Faculty of Pharmaceutical Sciences, University of Toyama[2]

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Higuchi's equation that expresses the rate of release of medicaments from ointments containing drugs in suspension has long been used for its surprisingly simple form and convenience. If initial drug concentration is close to the solubility of the drug in the ointment base, however, accuracy of the equation is not always high. In order to improve the accuracy, explicit solution of Fick's laws with the appropriate boundary conditions was attempted.

An equation relating the rate of release of solid drugs suspended in ointment bases into perfect sinks has been derived by Higuchi.[3] The final expression (Eq. 1) is surprisingly simple and convenient:

$$Q = \sqrt{(2C_0 - C_s)C_s Dt} \qquad \text{Eq. 1}$$

where Q=the amount released at time t per unit area of exposure, C_0=the initial concentration of drug expressed in units/cm^3, C_s=the solubility of the drug as units/cm^3 in the ointment base, and D=the diffusion constant of the drug molecule in the base.

Eq. 2, on the other hand, has been deduced for the amount of drug released from (one side of) a layer of ointment in which the drug is uniformly dissolved initially.[4]

$$Q = C_0 h\left[1 - \frac{8}{\pi^2}\sum_{n=0}^{\infty}\frac{1}{(2n+1)^2}\exp\left\{-\frac{D(2n+1)^2\pi^2 t}{4h^2}\right\}\right] \qquad \text{Eq. 2}$$

where h=the thickness of ointment layer, Q, C_0, D, t are the same as in Eq. 1 above. For most practical application, Higuchi[5] has pointed out that a simplified equation (Eq. 3) may be used.

$$Q = 2C_0\sqrt{\frac{Dt}{\pi}} \qquad \text{Eq. 3}$$

Eq. 3 is derived, as the limit when h/t approaches infinity, from Eq. 4 which is an alternate expression of Eq. 2.

$$Q = 2C_0\sqrt{\frac{Dt}{\pi}}\left[1 + 2\sqrt{\pi}\sum_{n=1}^{\infty}(-1)^n \operatorname{ierfc}\left(\frac{nh}{\sqrt{Dt}}\right)\right] \qquad \text{Eq. 4}$$

where *ierfc* represents an integral of error function.

$$\operatorname{ierfc}(x) = \frac{1}{\sqrt{\pi}}\exp(-x^2) - x\operatorname{erfc}(x) \qquad \text{and}$$

$$\operatorname{erfc}(x) = \frac{2}{\sqrt{\pi}}\int_x^{\infty}\exp(-y^2)\mathrm{d}y$$

Consequently, Eq. 3 is an explicit equation for solution type ointments with infinitely large thickness.

1) Partly presented at the 95th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, April 1975.
2) Location: *3190, Gofuku, Toyama, 930, Japan.*
3) T. Higuchi, *J. Pharm. Sci.*, **50**, 874 (1961).
4) T. Higuchi, *J. Soc. Cosm. Chem.*, **11**, 85 (1960).
5) W.I. Higuchi, *J. Pharm. Sci.*, **51**, 802 (1962).

In the extreme when C_o approaches C_s (from higher level), all the solid drugs dissolve into the base and the ointment is just converted from suspension type to solution type. Therefore Q's in Eq. 1 and Eq. 3 should coincide, if $C_o=C_s$. Eq. 1, however, is simplified only to Eq. 5.

$$Q = 2C_o\sqrt{\frac{Dt}{4}} \qquad \text{Eq. 5}$$

Differences (between Eq. 3 and Eq. 5) in D and Q are 27.3% and 12.8%, respectively, because $4/\pi=1.273..$ and $2/\sqrt{\pi}=1.128..$ An assumption adopted on the derivation of Eq. 1 that the concentration gradient is constant in the region where solid drug no more exists might be the cause for the difference.

The purpose of this note is to obtain the explicit equation for the amount of drug released into perfect sinks from ointment base containing drugs in suspension.

Theoretical

Explicit Equation

On the problem just mentioned above, we have a system described as follows: a) the suspended drug is a fine state such that the particles are much smaller in diameter than the thickness of the applied layer; b) the surface to which the drug ointment is applied is immiscible with the ointment and constitutes a perfect sink for the released drug.

For such a system we can draw a concentration profile which may exist after the lapse of finite time after application of the ointment (Fig. 1), and we have the equations

$$\left.\begin{aligned} &\frac{dC}{dt} = D\frac{d^2C}{dx^2} && (0<x<X) && \text{Eq. 6}\\ &C = C_o && (X\leqq x) && \text{Eq. 7}\\ &(C_o-C_s)\frac{dX}{dt} = D\left(\frac{dC}{dx}\right)_{x=X} && t>0 && \text{Eq. 8}\\ &C = C_s && (x=X) && \text{Eq. 9}\\ &C = 0 && (x=0) && \text{Eq. 10}\end{aligned}\right\}$$

$$X = 0 \qquad t=0 \qquad \text{Eq. 11}$$

$$Q = \int_0^t D\left(\frac{dC}{dx}\right)_{x=0} dt \qquad \text{Eq. 12}$$

These equations are solved according to the method of Crank[6] as follows: the solution of Eq. 6 satisfying Eq. 10 is

$$C = A\,\mathrm{erf}\left(\frac{x}{2\sqrt{Dt}}\right) \qquad \text{Eq. 13}$$

were A is a constant. Then Eq. 9 requires

$$C_s = A\,\mathrm{erf}\left(\frac{X}{2\sqrt{Dt}}\right) \qquad \text{Eq. 14}$$

Since Eq. 14 has to be satisfied for all values of t, X must be proportional to $\sqrt{t}$.

$$X = 2p\sqrt{Dt} \qquad \text{Eq. 15}$$

where p is a constant to be determined. Substituting Eq. 13, Eq. 14 and Eq. 15 into Eq. 8 we obtain

$$\frac{1}{\sqrt{\pi}}\frac{C_s}{(C_o-C_s)} = p\exp(p^2)\,\mathrm{erf}(p) \qquad \text{Eq. 16}$$

6) J. Crank, "The Mathematics of Diffusion," Oxford University Press, London, 1957, pp. 99—120.

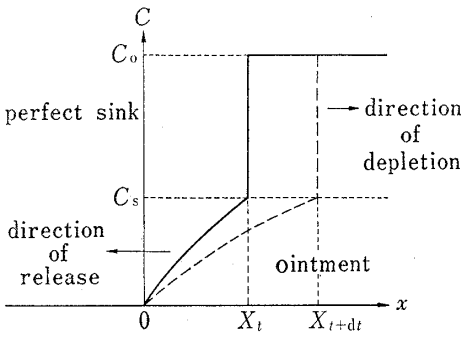

Fig. 1. Theoretical Concentration Profile Existing in An Ointment Containing Suspended Drug and in Contact with A Perfect Sink

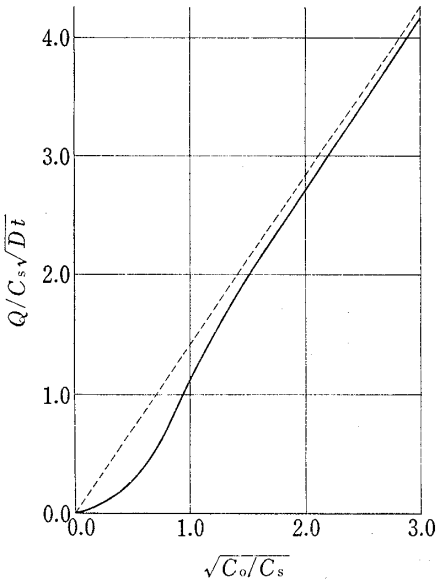

Fig. 2. Theoretical Relation between $Q/C_s\sqrt{Dt}$ and $\sqrt{C_0/C_s}$
Dotted Line indicates The Asymptote

Consequently,

$$A = \sqrt{\pi}(C_0-C_s)p \exp(p^2) = C_s/\mathrm{erf}(p) \qquad \text{Eq. 17}$$

Using Eq. 13, Eq. 14, Eq. 17 in Eq. 12 we obtain

$$Q = 2(C_0-C_s)p \exp(p^2)\sqrt{Dt} \qquad \text{Eq. 18}$$

or

$$Q = \frac{2C_s}{\mathrm{erf}(p)}\sqrt{\frac{Dt}{\pi}} \qquad \text{Eq. 19}$$

where p must satisfy Eq. 16.

It is possible, in principle, to eliminate p from Eq. 16 and Eq. 18. In the present instance, because the situation is algebraically complicated, a single explicit equation for Q is difficult to obtain. However, such a p value that satisfies Eq. 16 is calculated numerically by Newton's method,[7] which permits evaluation of Q at any time t by Eq. 18. If $C_0=C_s$, Eq. 19 and Eq. 1 coincide, since p becomes infinity.

Fig. 2 is a graphical presentation of Eq. 16 and Eq. 18. Eq. 3 was used for the values corresponding to C_0/C_s less than unity.

Approximate Equations

Expansion of Eq. 16 and Eq. 18 by p gives Eq. 20 and Eq. 21.

$$\left\{\frac{Q}{\sqrt{Dt}\,2(C_0-C_s)}\right\}^2 = p^2 + 2p^4 + 2p^6 + \frac{4}{3}p^8 + \cdots \qquad \text{Eq. 20}$$

$$\frac{C_s}{(C_0-C_s)} = 2p^2 + \frac{4}{3}p^4 + \frac{8}{15}p^6 + \frac{16}{105}p^8 + \cdots \qquad \text{Eq. 21}$$

Eliminating p, term by term, we obtain

$$Q = \sqrt{DtC_s\left\{2C_0 - \frac{2}{3}C_s - \frac{1}{45}\frac{C_s^2}{C_0-C_s} + \frac{2}{189}\frac{C_s^3}{(C_0-C_s)^2} - \cdots\right\}} \qquad \text{Eq. 22}$$

Eq. 22 shows that Eq. 23 is better approximation than Eq. 1.

7) P. Henrici, "Elements of Numerical Analysis," John Wiley and Sons, New York, 1964, pp. 77—78.

$$Q=\sqrt{\left(2C_o-\frac{2}{3}C_s\right)C_sDt} \qquad \text{Eq. 23}$$

Much better approximation is obtained as follows: assuming that the series of terms below the third term is represented by a single term, we obtain

$$Q=\sqrt{DtC_s\left(2C_o-\frac{2}{3}C_s+\frac{\beta C_s}{C_o-\alpha C_s}C_s\right)} \qquad \text{Eq. 24}$$

where α and β are constants to be evaluated. By Eq. 3, Eq. 25 and Eq. 26 hold, if $C_o=C_s$.

$$\frac{Q}{C_s\sqrt{Dt}}=\frac{2}{\sqrt{\pi}} \qquad \text{Eq. 25}$$

$$\frac{\mathrm{d}}{\mathrm{d}C_o}\left(\frac{Q}{C_s\sqrt{Dt}}\right)=\frac{2}{\sqrt{\pi}}\left(\frac{1}{C_s}\right) \qquad \text{Eq. 26}$$

Substituting Eq. 24 into Eq. 25 and Eq. 26, we obtain

$$\alpha=-0.8900342\cdots \quad \text{and} \quad \beta=-0.006608263\cdots$$

Rounding these values up to -0.89 and $-2/300$, respectively, we have final equation

$$Q=\sqrt{DtC_s\left\{2C_o-\frac{2}{3}C_s\left(\frac{C_o-0.88C_s}{C_o-0.89C_s}\right)\right\}} \qquad \text{Eq. 27}$$

Discussion

If $C_o=C_s$, Eq. 27 gives

$$Q=2C_o\sqrt{\frac{Dt}{\left(\frac{22}{7}\right)}} \qquad \text{Eq. 28}$$

22/7 is an approximation of π known since the age of Archimedes.[8]

$$22/7\pi=1.0004\cdots \quad \text{and} \quad \sqrt{22/7\pi}=1.0002\cdots$$

Therefore differences are less than 0.05%. $Q/C_s\sqrt{Dt}$ values calculated by approximate equations and by the explicit equation are shown in Table I. It is clear that the approximation by Eq. 27 is excellent. At various values of C_o/C_s, differences between Eq. 18 and Eq. 27 are less than 0.5%.

Table I. Comparison of $Q/C_s\sqrt{Dt}$ Values

C_o/C_s	P	Explicit (Eq. 18)	Approximate (Eq. 27)	Approximate (Eq. 23)	Approximate (Eq. 1)
1.000	∞	1.1284	1.1282	1.1547	1.0000
1.100	1.2570	1.2205	1.2254	1.2383	1.0954
1.500	0.8006	1.5198	1.5239	1.5275	1.4142
2.000	0.6201	1.8216	1.8241	1.8257	1.7321
2.500	0.5257	2.0789	2.0807	2.0817	2.0000
3.000	0.4648	2.3074	2.3087	2.3094	2.2361
3.500	0.4212	2.5151	2.5161	2.5166	2.4495
4.000	0.3881	2.7068	2.7076	2.7080	2.6458
6.000	0.3064	3.3659	3.3663	3.3665	3.3166
8.000	0.2612	3.9154	3.9157	3.9158	3.8730
10.000	0.2315	4.3967	4.3969	4.3970	4.3589
20.000	0.1608	6.2715	6.2716	6.2716	6.2450

8) P. Beckmann, "A History of π," The Golem Press, Boulder, Colorado, 1971, pp. 59—69.

In some of the recent controlled release devices using synthetic membrane, like silicone rubber, the release rate is determined, in general, by the solution to Fick's laws, with the appropriate boundary conditions.[9] Simple relations such as those derived here could be of help for a prediction of the release rate.

9) R.W. Baker and H.K. Lonsdale, "Controlled Release of Biologically Active Agents," ed. by A.C. Tanquary and R.E. Lacey, Plenum Press, New York, 1974, p. 17.