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Lag Time involved in the Experiments on Drug Release from Ointments[1]

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Explicit expression was derived for the lag time due to drug accumulation in the diffusion layer of the sink solution, which is encountered at experiments on drug release from ointments.

Higuchi's equation (Eq. 1) that expresses the amount (Q) of drug released from the ointment, in which the initial drug concentration is C_0, into a perfect sink during time t, indicates that the plots of Q against square root of t give a straight line through the origin.

$$Q = 2C_0\sqrt{\frac{Dt}{\pi}} \qquad \text{Eq. 1}$$

In practice, the straight line does not always pass the origin but shows some time lag.[3] One reason for this is explained by the well known lag time of Barrer,[4] which is a measure of the period required for the accumulation of the drug in the membrane, if the membrane is used, (and in the diffusion layer of the sink solution at the neighbor of the ointment). If the drug concentration in the ointment is constant, Barrer's lag time is given by

$$\tau_B = \frac{h^2}{6D} \qquad \text{Eq. 2}$$

were h is the thickness of the membrane and D is diffusion constant. In the case of drug release experiments, however, drug concentration in the ointment is not constant but decreases every minute.

Aim of this note is to express theoretically the lag time observed under such experimental situations.

Theoretical

Let D_1 be the diffusion constant in the diffusion layer, the thickness of which is h, and D_o that in the ointment. Also, let C_1 be the concentration in the diffusion layer and C_o that in the ointment (Fig. 1). Then assume that the diffusion is expressed by the following equations:

$$\text{at } t=0 \quad C_1 = 0 \quad (-h \leq x < 0) \qquad \text{Eq. 3}$$

$$C_o = C_{in} \quad (0 \leq x) \qquad \text{Eq. 4}$$

$$\text{at } t>0 \quad \frac{dC_1}{dt} = D_1\frac{d^2C_1}{dx^2} \quad (-h < x < 0) \qquad \text{Eq. 5}$$

$$\frac{dC_o}{dt} = D_o\frac{d^2C_o}{dx^2} \quad (0 < x) \qquad \text{Eq. 6}$$

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2) Location: *3190, Gofuku, Toyama, 930, Japan.*
3) K. Kakemi, H. Kameda, M. Kakemi, M. Ueda, and T. Koizumi, *Chem. Pharm. Bull.* (Tokyo), 23, 2114 (1975), cf. Fig. 3.
4) R.M. Barrer, "Diffusion in and through Solids," Cambridge University Press, Cambridge, England, 1951, p. 477.

$$D_\text{I}\frac{\mathrm{d}C_\text{I}}{\mathrm{d}x}=D_\text{o}\frac{\mathrm{d}C_\text{o}}{\mathrm{d}x}\quad(x=0)\qquad\text{Eq. 7}$$

$$C_\text{o}=pC_\text{I}\quad(x=0)\qquad\text{Eq. 8}$$

$$C_\text{I}=0\quad(x=-h)\qquad\text{Eq. 9}$$

$$Q=D_\text{I}\int_0^t\left(\frac{\mathrm{d}C_\text{I}}{\mathrm{d}x}\right)_{x=-h}\mathrm{d}t\qquad\text{Eq. 10}$$

where p is the partition coefficient of the drug at the interface ($x=0$).

Solution to these equations with the indicated boundary conditions are obtained by means of the method given by Carslaw and Jaeger.[5] The amount of drug released into sink, Q, is expressed by Eq. 11.

$$Q=\frac{4C_\text{in}}{p+\sqrt{\frac{D_\text{I}}{D_\text{o}}}}\sqrt{\frac{D_\text{I}t}{\pi}}\cdot\sum_{n=0}^{\infty}\left(\frac{p-\sqrt{\frac{D_\text{I}}{D_\text{o}}}}{p+\sqrt{\frac{D_\text{I}}{D_\text{o}}}}\right)^n\exp\left\{\frac{-(2n+1)^2h^2}{4D_\text{I}t}\right\}$$

$$-\frac{2C_\text{in}h}{p+\sqrt{\frac{D_\text{I}}{D_\text{o}}}}\sum_{n=0}^{\infty}\left(\frac{p-\sqrt{\frac{D_\text{I}}{D_\text{o}}}}{p+\sqrt{\frac{D_\text{I}}{D_\text{o}}}}\right)^n(2n+1)\cdot\operatorname{erfc}\left\{\frac{(2n+1)h}{2\sqrt{D_\text{I}t}}\right\}\qquad\text{Eq. 11}$$

For large t, Eq. 11 becomes

$$Q=2C_\text{in}\sqrt{\frac{D_\text{o}t}{\pi}}-\left(\frac{D_\text{o}}{D_\text{I}}\right)pC_\text{in}h\qquad\text{Eq. 12}$$

Therefore the lag time due to drug accumulation in the diffusion layer is given by Eq. 13.

$$\text{Lag time}=\left(\frac{D_\text{o}}{D_\text{I}}\right)^2\frac{p^2h^2\pi}{4D_\text{o}}\qquad\text{Eq. 13}$$

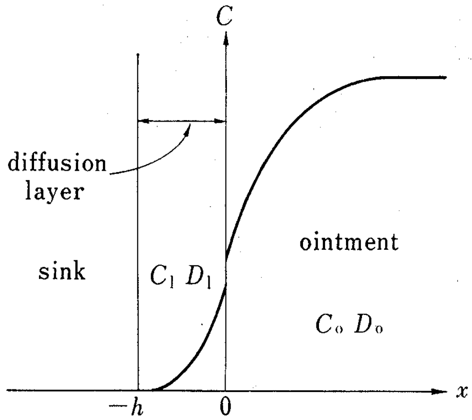

Fig. 1. Concentration Profile Existing in An Ointment, which is in Contact with A Perfect Sink, and in Adjacent Diffusion Layer

Discussion

Lag time calculated in this note is a measure of the period required for building-up of drug concentration in the diffusion layer. Another lag time is present when the diffusion constant of the drug in the membrane is smaller than that in the bulk. Appendix of the previous report[6] deals with such a type of lag time.

5) H.S. Carslaw and J.C. Jaeger, "Conduction of Heat in Solids," Oxford University Press, London, 1959, pp. 319—326.
6) T. Koizumi and W.I. Higuchi, *J. Pharm. Sci.*, **57**, 87 (1968).