Controlled Release from a Cylindrical Matrix Device

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Kakuji TOJO* and Kei MIYANAMI*

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Controlled drug release from a cylindrical matrix device has been investigated by a mathematical model. A simple cylindrical geometry with a small release hole is proposed as an excellent device for sustaining the drug efficacy. The calculated results have been verified by an experiment of benzoic acid release from a cylindrical agar gel.

Introduction

Monolithic drug devices with a matrix structure in which active agents are uniformly dissolved or dispersed, have been widely employed for controlled release drugs because of its easy fabrication. This type of device has also advantage of less hazardous release even if the device is collapsed accidentally. The release characteristics of an active agent through the monolithic device have been extensively studied by many researchers[1,2,3], and the release mechanism is usually described by Fick's diffusion law. These findings show that the conventional design of the monolithic drug device such a slab, cylinder or sphere, has a difficulty in providing an excellent prolonged release pattern since the path length of the diffusion of the active agent to the drug surface increases with the release period of time. Therefore, it is of great importance to design the drug delivery system to effect the prolonged release of active agent from the simple matrix device.

Brooke and Washkuhn (1977)[4] proposed the special design shown in Fig. 1 to

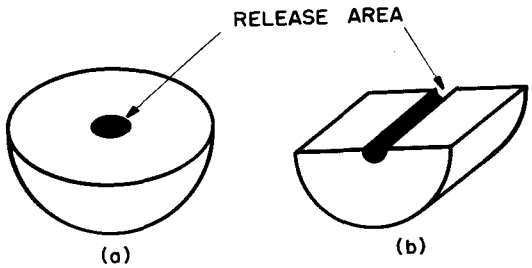


Fig. 1 Matrix devices to achive zero-order drug release

meet this prolonged release problem from the matrix device. Recently Langer *et al.* (1980)[5] have shown a hemispherical device as shown in Fig. 1 to achieve the zero-order drug release. These devices designed specially may provide an excellent sustained release. However, they generally requires a complicated fabrication procedure, and it would be cost much for mass production.

In the present paper, a simpler-designed cylindrical device for prolonged drug release has been proposed on the basis of the mathematical simulation results. The

* Department of Chemical Engineering, College of Engineering

efficacy for the drug release has been verified by an experiment of benzoic acid release from a 1 % agar gel.

Model Formulation

The present study considers the system composed of an active agent A dissolved/dispersed uniformly in an inert substance to form a monolithic device of drug delivery. This matrix device is surrounded by a coating material of a mold through which the active agent can not permeate. The small circular hole for drug release is drilled at the center of the top plane of the device as shown in Fig. 2.

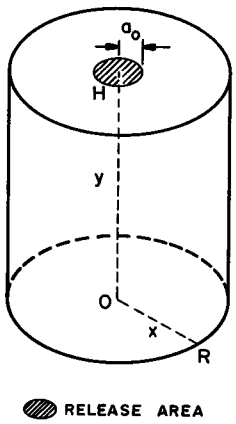


Fig. 2 Simple cylindrical devie for controlled drug release

The mass balance of the active agent A over a differential volume element of the device yields :

$$\frac{\partial C_A}{\partial t} = \frac{1}{x} D_A \frac{\partial}{\partial x}\left(x \frac{\partial C_A}{\partial x}\right) + D_A \frac{\partial}{\partial y}\left(\frac{\partial C_A}{\partial y}\right) \tag{1}$$

The appropriate boundary conditons are

$$x = 0 \ ; \ \partial C_A / \partial x = 0 \tag{2}$$

$$x = R \ ; \ \partial C_A / \partial x = 0 \tag{3}$$

$$y = 0 \ ; \ \partial C_A / \partial y = 0 \tag{4}$$

$$y = H \ ; \ -D_A \frac{\partial C_A}{\partial y} = k_m C_A \ (x \leq a_0)$$

$$\frac{\partial C_A}{\partial y} = 0 \ \ (R \geq x \geq a_0) \tag{5}$$

The initial conditon is;

$$t = 0 \ ; \ C_A = C_{AS} \tag{6}$$

In normalized forms, Eqs. (1) to (6) become, respectively,

$$\frac{\partial C}{\partial \theta} = \frac{1}{\xi}\frac{\partial}{\partial \xi}\left(\xi \frac{\partial C}{\partial \xi}\right) + \frac{\partial}{\partial \zeta}\left(\frac{\partial C}{\partial \zeta}\right) \tag{7}$$

$$\xi = 0 \; ; \quad \partial C / \partial \xi = 0 \tag{8}$$

$$\xi = 1 \; ; \quad \partial C / \partial \xi = 0 \tag{9}$$

$$\zeta = 0 \; ; \quad \partial C / \partial \zeta = 0 \tag{10}$$

$$\zeta = H/R \; ; \quad \frac{\partial C}{\partial \zeta} = -Sh \cdot C \quad (\xi \leq a_0 / R) \tag{11}$$

$$\frac{\partial C}{\partial \zeta} = 0 \quad (a_0 / R \leq \xi \leq 1)$$

$$\theta = 0 \; ; \quad C = 1 \tag{12}$$

The dimensionless groups which appear in the above expressions are defined below :

$$\xi = x/R, \quad \zeta = y/R, \quad C = C_A / C_{AS}, \quad \theta = tD_A / R^2$$

$$Sh = k_m R / D_A$$

The amount of the active agent released to the environment, M , is

$$M = \left[\begin{array}{l}\text{Amount of active agent}\\ \text{initially dissolved in the}\\ \text{device}\end{array}\right] - \left[\begin{array}{l}\text{Amount of active agent}\\ \text{remaining in the device}\\ \text{at time t}\end{array}\right] \tag{13}$$

Generally, the solution to Eq. (7) can be obtained by using a digital computer. If, however, the diameter of the release hole equals to that of the device as a special case, Equation (7) can be solved analytically, and the total amount of the active agent released, M, is expressed by

$$\frac{M}{M_\infty} = 1 - \sum_{n=1}^{\infty} \frac{2L^2 \exp(-\beta_n^2 D_A t/l^2)}{\beta_n^2 (\beta_n^2 + L^2 + L)} \tag{14}$$

where the β_ns are the positive roots of the following equation :

$$\beta_n \tan \beta_n = L \, , \qquad L = lk_m / D_A \tag{15}$$

Method of Solution

Programming the numerical solution of nonlinear partial differential equations is often a highly complicated, tedious, time-consuming and unstable procedure which requires a great many man-hours. However, in light of the recently developed powerful integrators for stiff ordinary differential equations[6], the difficulties involved in the solution of nonlinear partial differential equations which are defined over a two-dimensional region, have largely been eased. This software interface employs the method of lines technique[7] whereby centered differencing with respect to the two spatial variables

results in a system of time-dependent ordinary differential equations. Gear's backward-difference formulas[8] are used for the time integration in the present study. A modified Newton's method with internally generated Jacobian matrix is utilized to solve the non-linear equations. Both of them have been incorporated into the software interface. For each calculation, the integrator adjusts the time step size and/or order of the time integration formula to achieve a specified error level. To test the accuracy of the numerical solution, it is compared with the analytical solution given by Eq. (14) for a special case where slab geometry is assumed. As shown in Fig. 3, the numerical solution of Eq. (7), subject to the initial condition and the boundary conditions for the same set of parameters, agrees well with the analytical solution.

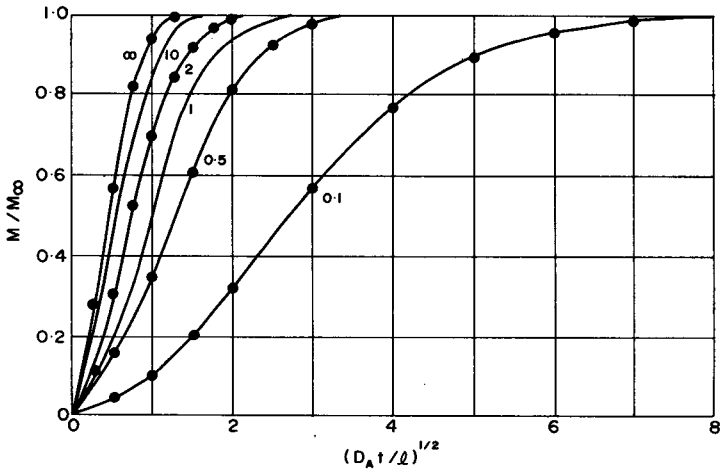


Fig. 3 Comperison of the numerical solution with the analytical solution;
• Numerical solution, — Analytical solution.
Numbers on curves are values of $L = lk_m/D_A$.

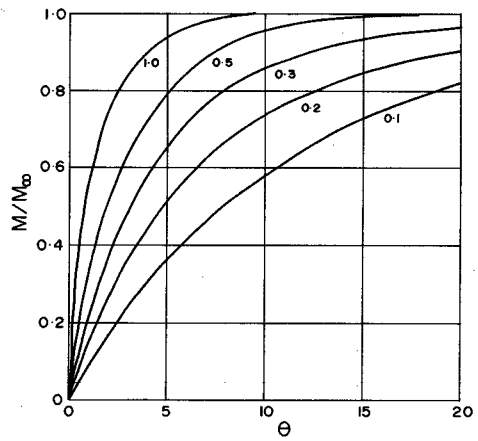
Results and Discussion

Examinations and analyses are made in the present work of the effects of the release hole radius, a_0, radius-to-length ratio of the device, R/H, and the Sherwood number, $Sh = k_m R/D$, on the cumulative amount of the active agent released, M, and the release rate, $d(M/M_\infty)/d\theta$.

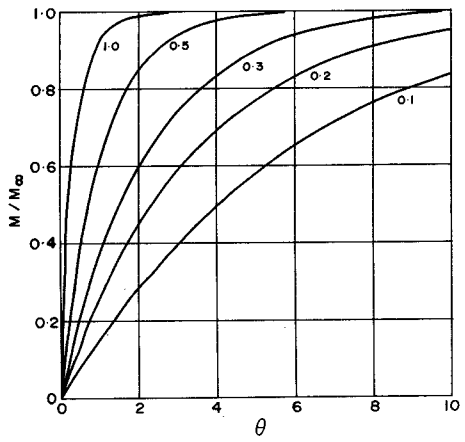
Effect of device geometry

The effect of the release hole radius a_0, on the cumulative release rate, M/M_∞, is shown in Fig. 4. The value of Sherwood number used in this calculation is 100, thereby signifying that the resistance of mass transfer through the environment boundary layer is practically insignificant. As can be seen, the release of active agent is markedly prolonged for the device with the small hole diameter. This chart is useful to design and to formulate the controlled release device for releasing the active agent to meet the environmental constraints.

Figure 5 shows the effect of the release hole radius on the rate of release,



(a)



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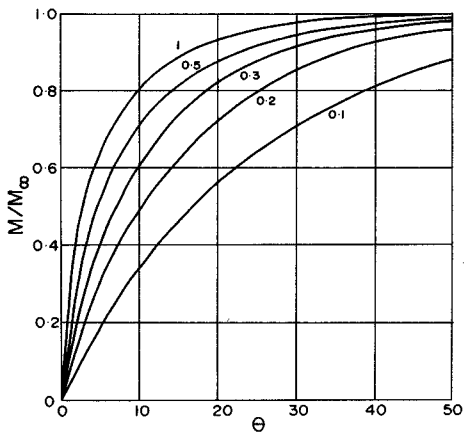
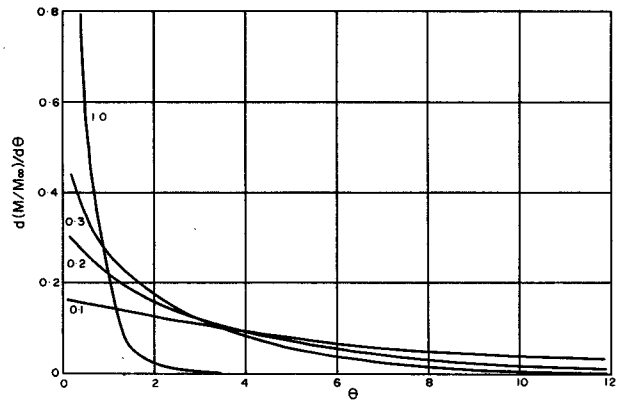
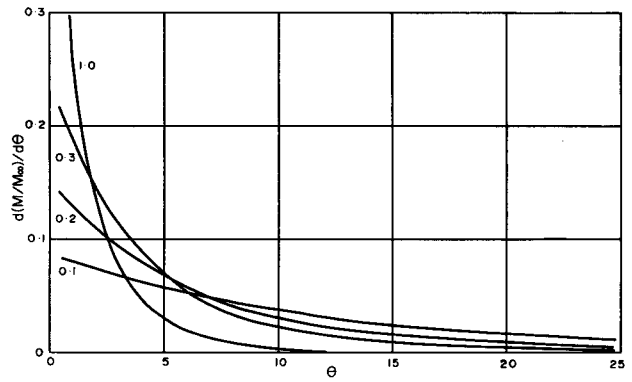


(c)

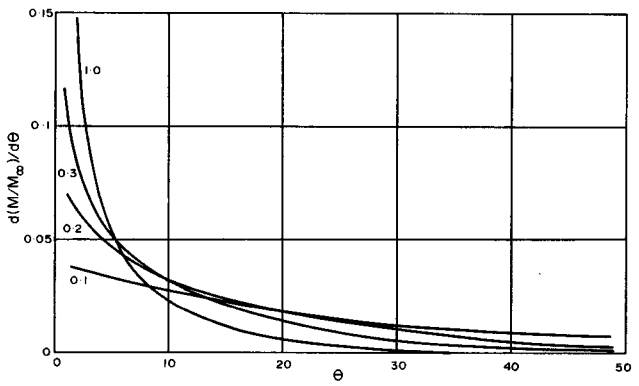
Fig. 4 Effect of release hole radius a_0 on cumulative release rate. Numbers on curves are values of a_0/R; $Sh = 100$. (a) $H/R = 1.0$, (b) $H/R = 2.0$, (c) $H/R = 4.0$



(a)



(b)



(c)

Fig. 5 Effect of release hole radius on release rate of active agent. Numbers on curves are values of a_0/R. $Sh = 100$.
(a) $H/R = 1.0$, (b) $H/R = 2.0$, (c) $H/R = 4.0$

$d\,(M/M_\infty)\,/\,d\theta$. The release rate is increasingly prolonged as the release hole diameter becomes smaller. Although the perfect zero-order release is never attained with this matrix device, an excellent sustained release can be obtained if the device is formulated by the optimum design. This figure also shows easiness in the device fabrication; the optimum design can be easily obtained by making a suitable set of design parameters to meet the problem with the help of this chart of release pattern.

Effect of Sherwood Number

The effect of Sherwood number on the cumulative release rate is shown in Fig. 6, where the Sherwood number means a dimensionless parameter characterizing the resistance of mass transfer in the environment boundary layer. Because a controlled

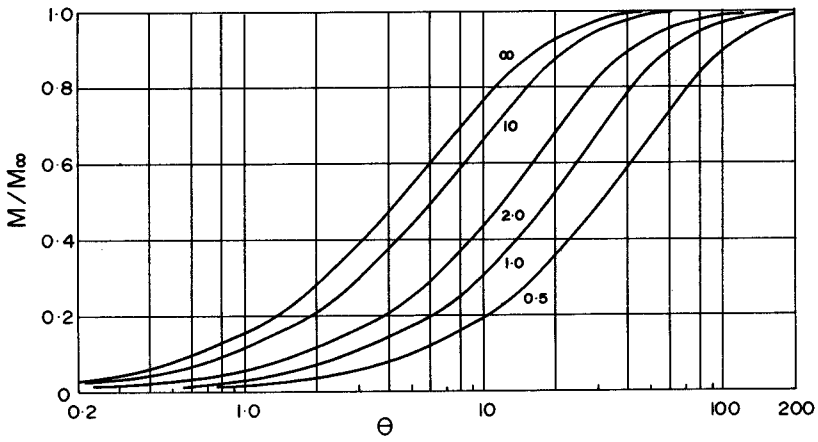


Fig. 6 Effect of Sherwood number on cumulative release rate.
Numbers on curves are values of *Sh*. H/R = 2.0, a_0/R = 0.20.

release product is usually administered in a field or body where the fluid mixing is relatively strong and then the effect of Sherwood number may be insignificant. However, if the drug is implanted near the target tissue, or if the agricultural chemicals, pesticides or fertilizers, are applied in a poor mixing zone, the effect of Sherwood number must be carefully examined. Otherwise, the precious active agent of the drug may be wasted at an ineffective release level.

Comparison with experimental results

The cylindrical molds as shown in Fig. 2 made of PMMA are used as drug containers. Agar sol. of 1 % by weight, in which the benzoic acid is saturated, is filled in the cylindrical device to form the drug dissolved matrix device. The dimensions of the devices were 0.8 cm in diameter by 1.6 cm in height. The radius of the release hole, a_0, was varied from 0.1 cm to 0.4 cm. Benzoic acid release studies from the devices were conducted at room temperature in a 300 ml beaker containing 200 - 300 ml of deionized water. To reduce boundary layer effects, the aqueous phase was stirred continuously. The medium was replaced with fresh deionized water every 24 hours. Under these

conditions, the concentration of benzoic acid in the aqueous phase was far below saturation so that sink conditions were maintained. The amount of benzoic acid released was determined continuously by an electric conductivity meter.

Experimental data are plotted in Fig. 7 to compare with the calculated ones; the lines on this figure were the calculated by the present model. As can be seen, the calculated results well agree with the experimental data, and this verifies the validity of the theoretical calculation of the present work.

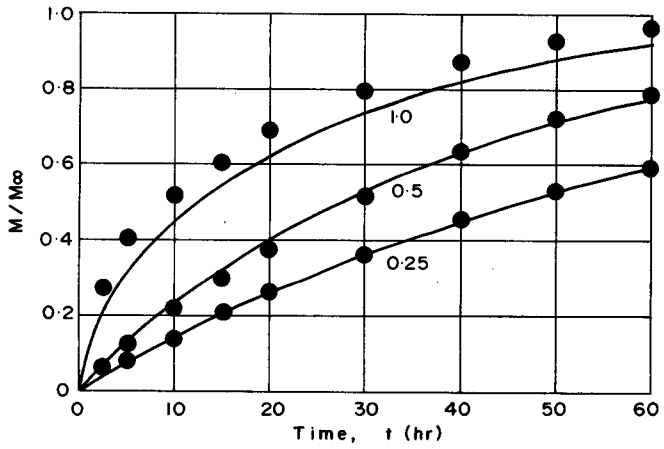


Fig. 7 Comparison of calculated cumulative release rate with the experimental release rate; – Calculated, • Experimental, R = 0.4 cm, H = 1.6 cm, $D_A = 8.1 \times 10^{-6}$ cm^2/sec, k_m = 0.005 cm/sec. Numbers on curves are values of a_0/R.

Concluding Remarks

The controlled drug release from a specially designed matrix device has been investigated both theoretically and experimentally. The simple cylindrical device with a small release hole proposed in the present work for sustaining the drug efficacy, is quite useful to prolong and control the release rate of the active agent. The durg device examined here can be applied widely in pharmaceutical, agricultural, food and household products.

Nomenclature

a_0	radius of the release hole, m
C_A	concentration of active agent, mol/m^3
C_{AS}	saturated concentration of active agent, mol/m^3
C	$= C_A/C_{AS}$
D_A	diffusivity of the molecule of active agent, m^2/sec
H	height of the cylindrical drug device, m
k_m	mass transfer coefficient, m/sec

L	Modified Sherwood number defined by lk_m/D_A
l	thickness of the slab device, m
M	amount of active agent released to the environment, mol
M_∞	total amount of active agent released, mol
Sh	Sherwood number defined by k_mR/D_A
t	time, sec
x	radial distance from the center of the device, m
y	horizontal distance from the bottom of the device, m
θ	dimensionless time, tD_A/R^2
ξ	$=x/R$
ζ	$=y/R$

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