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MATHEMATICAL SIMULATION OF CONTROLLED DRUG RELEASE FROM CYLINDRICAL MATRIX DEVICES

Kakuji Tojo and Yie W. Chien

Controlled Drug Delivery Research Center, Rutgers,The State University of New Jersey, College of Pharmacy, Piscataway, New Jersey 08854

ABSTRACT

The general mathematical model for controlled drug release from the cylindrical matrix device was developed. The system under consideration is composed of an active agent which is dissolved homogeneously in a cylindrical porous matrix device. The method of lines was employed to solve the partial differential equation in the present study.

The effects of hydrodynamic diffusion layer, the rate of spontaneous decay reaction in the device, the height to radius ratio of the device and the porosity distribution in the device on the rate of drug release were investigated by solving the two dimensional diffusion equation under non-steady state conditions.

The results indicated that the release rate may be significantly underevaluated if the data obtained in the in vitro

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studies under a poor mixing condition are analyzed mistakenly on the assumption of well mixing condition.

The findings in the present analysis are of practical significance to the design and development of matrix-diffusion type controlled release drug products.

INTRODUCTION

The cylindrical matrix device is one of the most popular controlled-release device geometry and has been widely employed for oral, intravaginal, intrauterine and implantable controlled drug delivery(1). The release rate from such a matrix device can be described basically by the Fick's law of diffusion. It is, however, strongly affected by various important parameters: the device geometry(radius to height ratio), internal structure of the device (porosity or pore distribution), physicochemical interactions between the drug molecules and the polymer material, the hydrodynamic condtions of the environment, and so on. The effects of these factors on the rate of drug release should be examined critically for a rational design and formulation of the cylindrical matrix devices as the controlled release drug products. It is especially important for the drug with relatively narrow therapeutic index; in this case, the device should be precisely designed by taking into consideration of the effects of various system parameters.

In this paper, we intend to discuss the effects of device geometry, the porosity and the environmental hydrodynamic

conditions and the spontaneous decay reaction on the rate of drug release by analyzing a mathematical simulation model.

DRUG DEVICE

A cylindrical matrix device is shown in Fig.1. A drug is assumed to be uniformaly dispersed in the porous polymer matrix of the device with a saturation concentration of C_s. Both radial(x) and vertical(y) release are taken into account. H and R are the half height and radius of the device, respectively.

MATHEMATICAL FORMULATION

The system under consideration is composed of an active agent A which is dispersed homogeneously in a cylindrical porous matrix

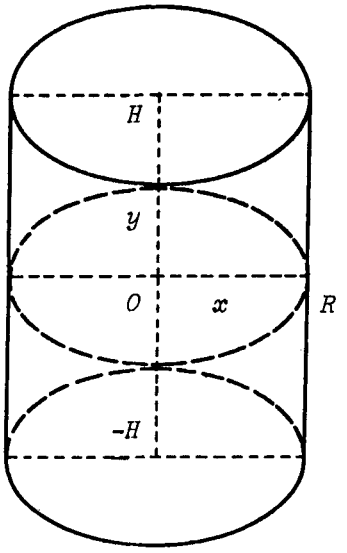


FIGURE 1
Cylindrical matrix device for controlled drug delivery. H is the half height, R is the radius, x is the distance in the radial direction, and y is the distance in the vertical direction.

device shown in Fig.1. The geometry and structure of the device is assumed to be invariant during the process of release. The mass balance of the active agent A over a differential volume element of the drug device yields

$$\frac{\partial(\varepsilon C_A)}{\partial t} = \frac{1}{x}\frac{\partial}{\partial x}\left(D_A \times \frac{\partial C_A}{\partial x}\right) + \frac{\partial}{\partial y}\left(D_A \frac{\partial C_A}{\partial y}\right) - \gamma_A \qquad (1)$$

where ε is the porosity of the device, D_A is the diffusivity, C_A is the concentration of the drug and γ_A is the rate of drug degradation reaction which is assumed to obey the following Michaelis-Menten expression:

$$\gamma_A = \frac{V_{max} C_A}{K_d + C_A} \qquad (2)$$

where V_{max} and K_d are the maximum decay rate and the Michaelis-Menten constant, respectively.

The appropriate boundary conditions are

$$x = 0(\text{center}): \quad \frac{\partial C_A}{\partial x} = 0 \qquad (3)$$

$$x = R: \quad -D_A \frac{\partial C_A}{\partial x} = k_m C_A \qquad (4)$$

$$y = 0(\text{center}): \quad \frac{\partial C_A}{\partial y} = 0 \qquad (5)$$

$$y = H: \quad -D_A \frac{\partial C_A}{\partial y} = k_m C_A \qquad (6)$$

and the initial condition is

$$t = 0: \quad C_A = C_{As} \tag{7}$$

In normalized forms, Equations(1), (3) to (7) become, respectively,

$$\frac{\partial(\varepsilon C)}{\partial\theta} = \frac{1}{\xi}\frac{\partial}{\partial\xi}\left(D\xi\frac{\partial C}{\partial\xi}\right) + \frac{\partial}{\partial\zeta}\left(D\frac{\partial C}{\partial\zeta}\right) - \frac{\Phi_v^2 C}{1+kC} \tag{8}$$

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

$$\xi = 1: \quad -D\frac{\partial C}{\partial\xi} = ShC \tag{10}$$

$$\zeta = 0: \quad \partial C/\partial\zeta = 0 \tag{11}$$

$$\zeta = H/R: \quad -D\frac{\partial C}{\partial\zeta} = ShC \tag{12}$$

$$\theta = 0: \quad C = 1 \quad (0 \leq \xi \leq 1 \text{ and } 0 \leq \zeta \leq H/R) \tag{13}$$

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

$$\xi = x/R,\ \zeta = y/R,\ C = C_A/C_{As},\ D = D_A/D_{Ao},$$

$$\theta = t\,D_{Ao}/R^2,\ k = C_{As}/K_d,\ Sh = k_m R/D_{Ao},$$

$$\Phi_v = \sqrt{RV_{max}/K_d \cdot D_{Ao}}$$

The porosity is considered to vary with respect to the spatial coordinates, i.e.,

$$\varepsilon = \text{func}(x,y) \tag{14}$$

The effective diffusivity of drug is assumed to be proportional to the porosity and the drug concentration as (5)

$$D_A \propto \varepsilon/(1 + pC_A) \tag{15}$$

In normalized form,

$$D = \frac{\varepsilon/\varepsilon_0}{1 + pC} \tag{16}$$

Where ε_0 is the porosity in the center of the device.

The cumulative amount of drug released Q is

$$Q = \begin{bmatrix}\text{Amount of drug}\\ \text{initially impregnated}\\ \text{in the device.}\end{bmatrix} - \begin{bmatrix}\text{Amount of drug}\\ \text{remaining in the}\\ \text{device at time t.}\end{bmatrix} \tag{17}$$

The second term of the right hand side of Equation(17) can be evaluated by integrating the concentration profiles(two dimensional) in the device. When the device has a special design: $H/R \gg 1$ or $H/R \ll 1$, $\varepsilon = 1$, $D = 1$ and $\phi_v = 0$, the amount of drug released can be obtained analytically(3):

$$H/R \ll 1;\ \frac{Q}{Q_\infty} = 1 - \sum_{n=1}^{\infty} \frac{2L^2 \exp(-\beta_n{}^2 D_{Ao} + H^2)}{\beta_n{}^2(\beta_n{}^2 + L^2 + L)} \tag{18}$$

where the β_n's are the positive roots of $\tan\beta_n = L/\beta_n (n = 1, 2, \ldots)$ and $L = Hk_m/D_A$.

$$H/R >> 1;\ \frac{Q}{Q_\infty} = 1 - \sum_{n=1}^{\infty} \frac{4Sh^2 \exp(-\beta_n{}^2 D_{Ao} t/R^2)}{\beta_n{}^2(\beta_n{}^2 + Sh^2)} \qquad (19)$$

where the β_n's are the roots of $\beta_n J_1(\beta) - Sh\ J_0(\beta) = 0$ and $Sh = k_m R/D_A$. When L in Eq.(18) or Sh in Eq.(19) is so large that the effect of diffusion boundary layer on the rate of drug release is negligible, Eqs.(18) or (19) can be simplified, for early period of release, by the following equations, respectively(3):

$$H/R << 1:\ \frac{Q}{Q_\infty} = 4\sqrt{D_A t/H^2 \pi} \qquad 0 < Q/Q_\infty < 0.6 \qquad (20)$$

$$H/R >> 1:\ \frac{Q}{Q_\infty} = 4\sqrt{D_A t/R^2 \pi} - D_A t/R^2 \qquad 0 < Q/Q_\infty < 0.4 \qquad (21)$$

METHODS OF SOLUTION

The so-called method of lines is employed here to solve the partial differential equation, Equation(8), subject to the boundary and the initial conditions, Equations(9) to (13). This method discretizes all the coordinates but one and converts the partial differential equation into a set of ordinary differential equations. The details of the method of solution was given earlier(5). To test the accuracy, the numerical solutions under the two limiting conditions, H/R << 1 and H/R >> 1, were compared respectively with the analytical solutions, Eqs.(18) and (19). As demonstrated by the results, the numerical solutions showed an excellent agreement

with the analytical solutions and thus the validity of the numerical analysis employed here has been confirmed.

RESULTS AND DISCUSSION

A typical concentration profiles in the matrix device is illustrated in Fig.2. This figure shows how the concentration of drug in the device changes with time.

The cumulative amount of drug, expressed as the fraction of dose, released from a cylindrical matrix device is plotted in Figs.

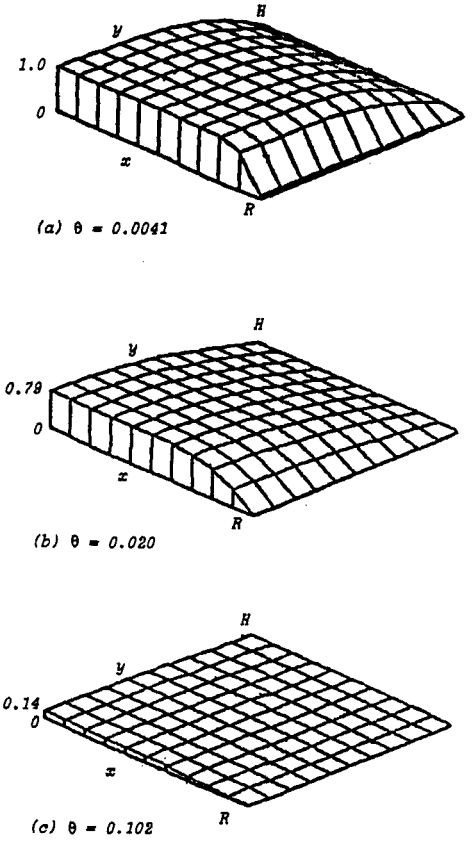


FIGURE 2
Concentration profiles in the matrix device; H/R=0.25(R=0.25 cm), Sh =∞ , D_A=8.1×10^{-6} cm^2/sec, ε=0.99.

3a, b and c for three different Sherwood numbers. The Sherwood number is defined as (device size, R) x (mass transfer coefficient, k_m)/(drug diffusivity in the device, D_{Ao}). From these plots, we can see the effects of hydrodynamic boundary conditions on the drug release through the device environment interface. In Fig.3a when the condition of $Sh \neq \infty$ is maintained in the in vitro studies, the linear relationship between the cumulative amount of drug released and $t^{1/2}$ is obtained for H/R = 0.1 during the initial stage of release as expected by Eq.(20). This relationship has been frequently reported for the matrix-type controlled release drug products(9). However, under nonideal flow conditions, which is characterized by a finite value of Sherwood number, the linear relationship of Q vs. $t^{1/2}$ does not appear(Fig.3b or 3c). These findings clearly indicate that the release pattern is markedly influenced by the environmental flow conditions. In fact, the difference in the release rates between in vitro and in vivo experiments is primarily the result of this hydrodynamic effect.

It is interesting to point out the effect of hydrodynamic diffusion layer on the rate of drug release in in vitro studies. Let us consider two types of in vitro controlled release studies; one measures the release rate in the well mixed apparatus and the other uses the mild mixing apparatus. Each experiment will give the release rate as shown in Fig.4, where the broken line and the dotted line are the data under well mixing conditions(Sh = 200) and poor mixing conditions(Sh = 1), respectively. If the data under the poor mixing conditions are mistakenly analyzed on the assumption of well mixing conditions, the release rate may be significantly

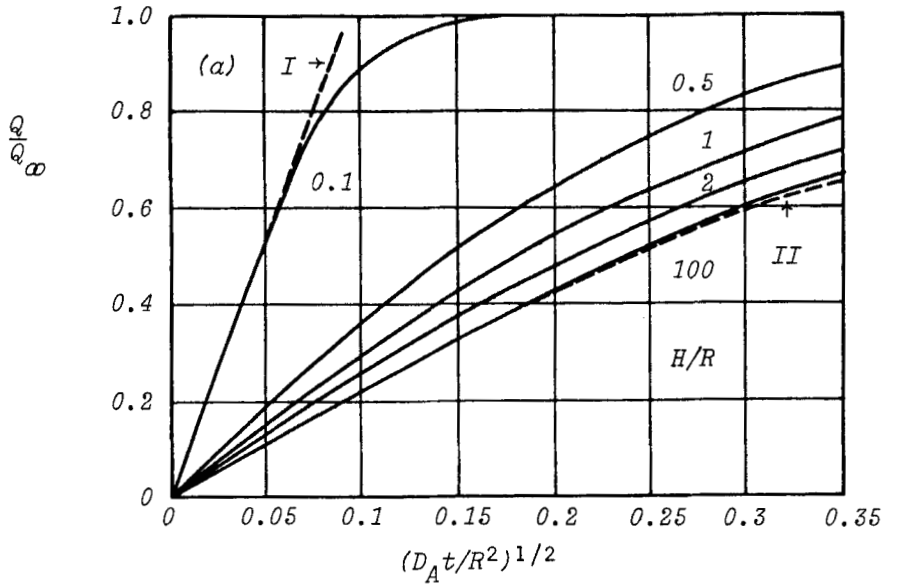
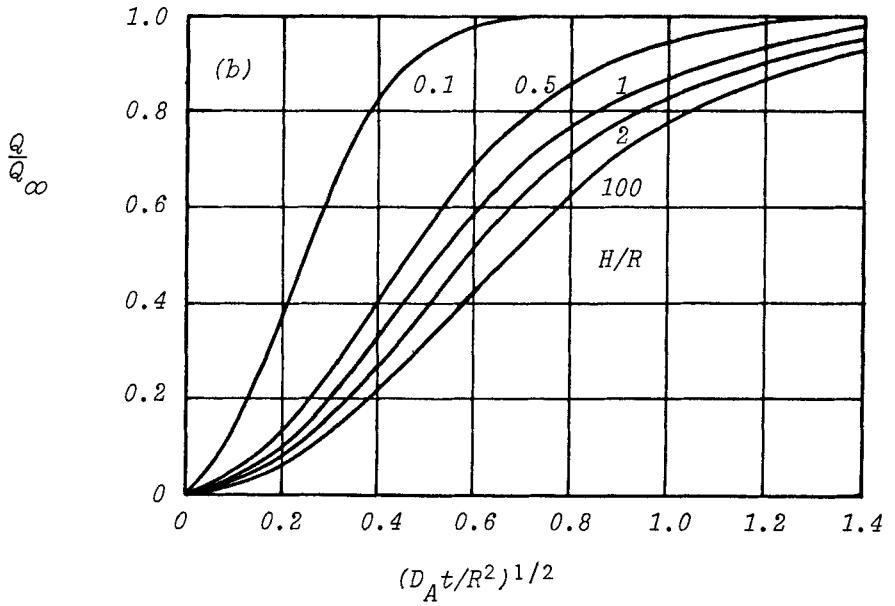


FIGURE 3
Cumulative amount of drug released from cylindrical matrix device. Numbers on curves are values of the height-to-radius ratio of the device. V_{max}=0(no decay reaction); (a) Sh=∞ (>200), *I*:Eq.(20), *II*:Eq.(21), (b) Sh=1.0, (c) Sh=0.1.

underestimated; $Q/\theta^{1/2}$ value on the assumption of well mixing conditions is about one fourth of the correct value in the present typical example. Although the highly mixing condition, under which the effect of diffusion boundary layer on the rate of controlled release can be neglected, is not always necessary for in vitro studies, the flow pattern in the experimental system should be precisely investigated not only to obtain the correct in vitro release data but also to establish a reliable in vitro-in vivo correlation of the controlled drug release rate profiles.

The cumulative amount of drug released under various Sherwood numbers is plotted against that under ideal mixing



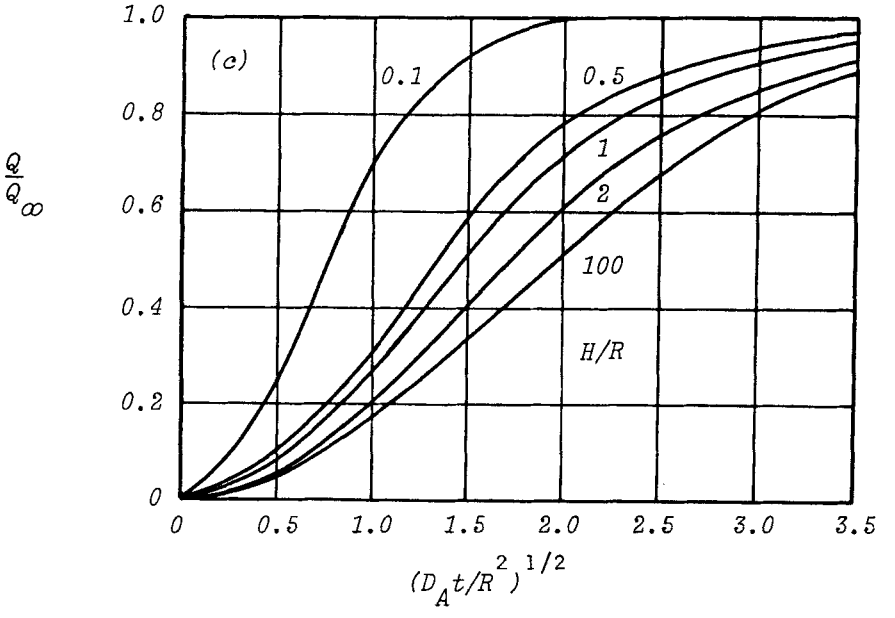


FIGURE 3 (continued)

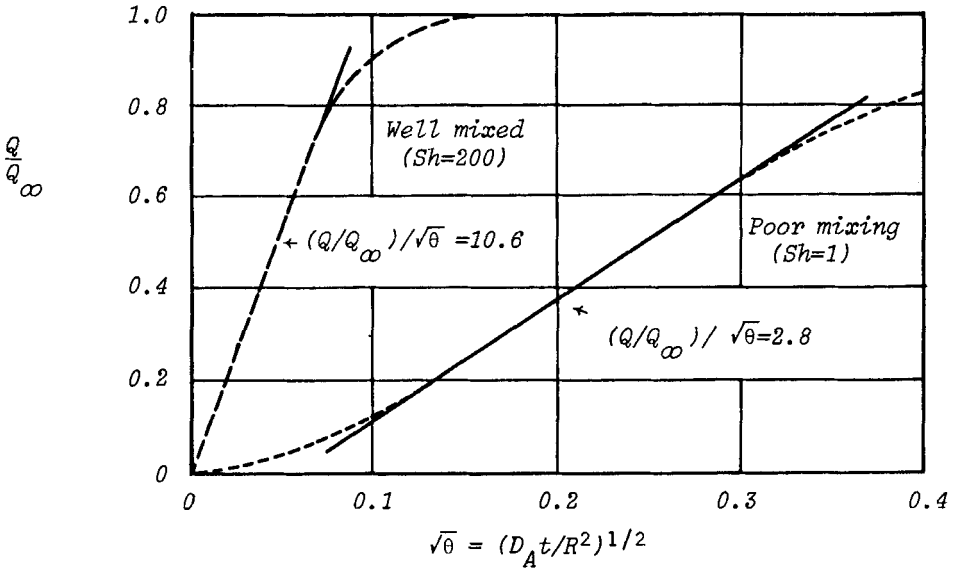


FIGURE 4
Effect of hydrodynamic diffusion boundary layer($Sh \propto \delta^{-1}$: δ is the thickness of diffusion boundary layer) on the rate of controlled drug release. H/R=0.1.

condition(Sh = ∞) as a function of the Sherwood number in Fig.5. This figure suggests a certain relationship between the release rate under nonideal hydrodynamic conditions surrounding the device and the release rate under an ideal condition. It is interesting to observe that an approximately linear relationship exists between Q/Q_∞ and Q/Q_∞(Sh = ∞) during the initial period of drug release; the release rate under Sh = 10 is about 75% of that under Sh = ∞ when the amount of drug released is less than 40%.

Figure 6 shows the effects of spontaneous decay reaction in the device on the cumulative amount of drug released. If the active agent in the device is significantly deactivated during the long period of controlled release administration, the effective period and the amount of drug loaded should be carefully determined.

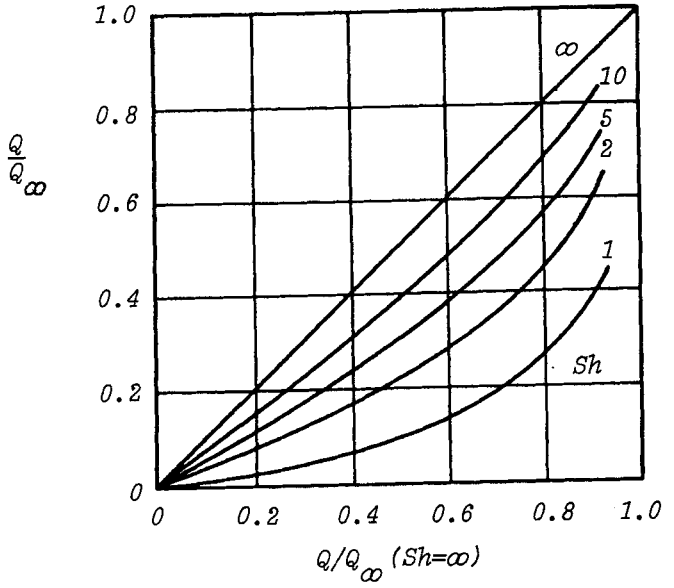


FIGURE 5
Correlation of cumulative drug release under ideal mixing condition($Sh=\infty$) and nonideal mixing conditions($Sh<\infty$). $H/R>0.5$.

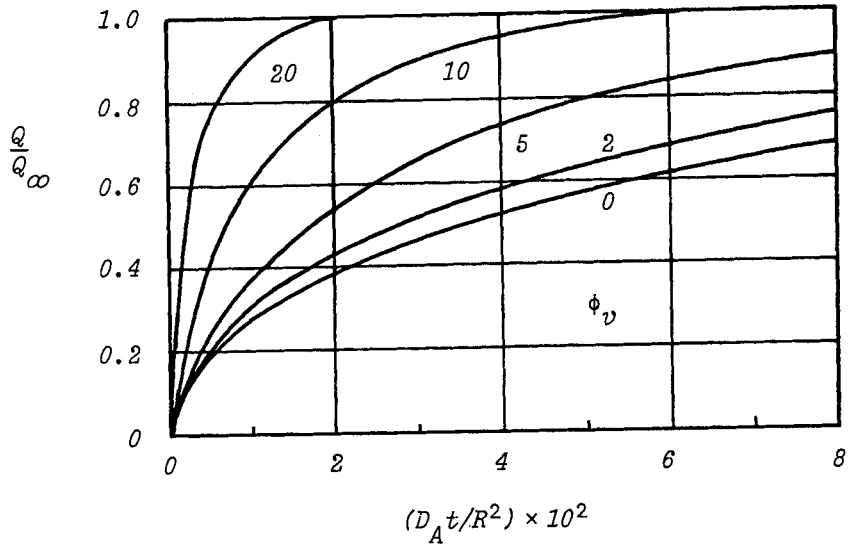


FIGURE 6
Effect of spontaneous decay reaction rate ϕ_v on the cumulative amount of drug released; $Sh=\infty$, $H/R=1.0$.

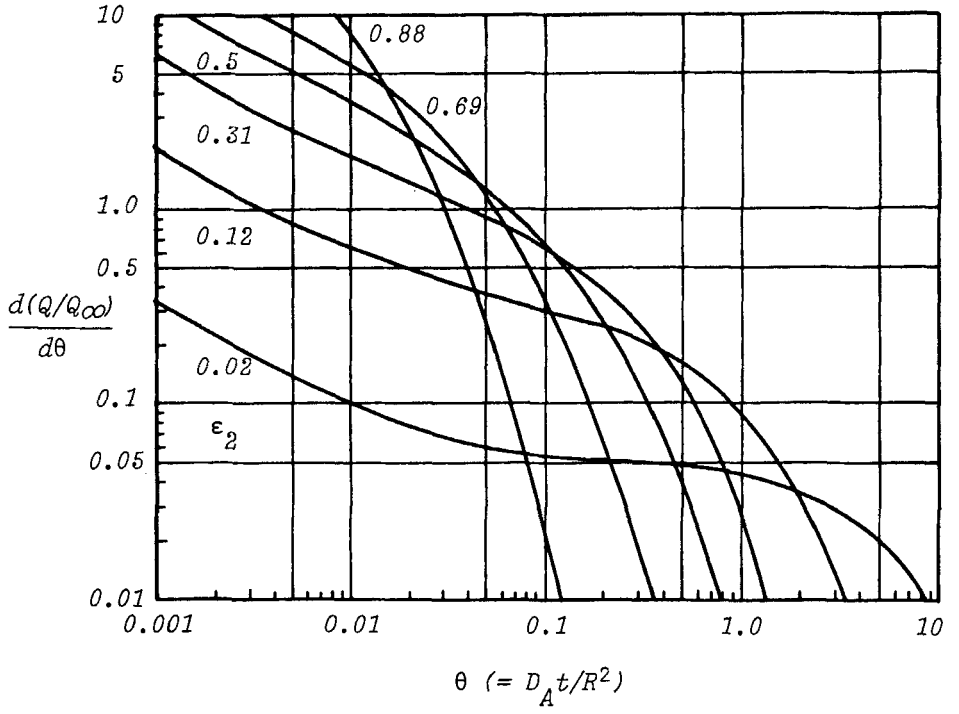


FIGURE 7
Effect of the porosity in the area near the device surface ε_2 on the rate of drug release. ε_2 is the porosity in the surface area($d_m < x < R$), average porosity=0.5, d_m/R=0.7.

Figure 7 shows the effect of pore distribution of matrix device on the dimensionless rate of drug release. Here the porosity in the area near the surface of the device(ε_2) is assumed to be different from that in the center core(ε_1) although the average value of porosity is a constant of 0.50. As can be seen from Figure 7, the release rate is markedly prolonged with decreasing the porosity in the area near the surface of the device. In the present mathematical simulation, we assume the pore structure is capillary pore where the effective diffusivity is directly proportional to the porosity(6). If the pore structure is

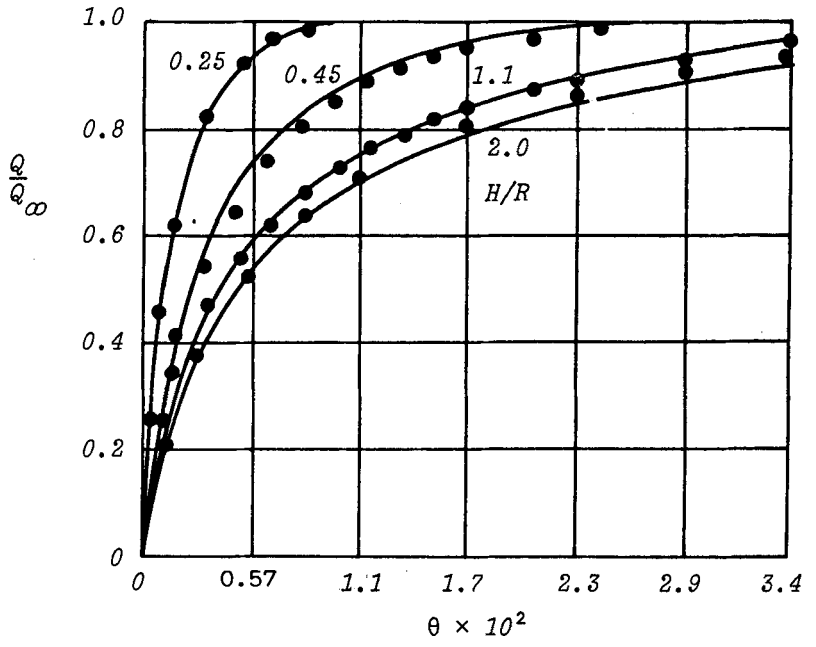


FIGURE 8
Effect of height-to-radius ratio, H/R, of cylindrical matrix device(Fig.1) on cumulative drug release; —— calculated by the present model(ε=0.99, ϕ_v=0, Sh=179), ● experimental(Device: R=0.29cm, k_m=0.005cm/sec, D_A=8.1×10^{-6}cm/sec).

micropore-macropore bimodal structure, more significant effect will be appeared because the relationship of $D_A \propto \varepsilon^2$(7).

The calculated values of the cumulative amounts of drug released are compared with the experimental data in Fig.8. The experiments were carried out by using four sizes of cylindrical devices fabricated from 1% agar gel in which benzoic acid is entrapped at a saturated concentration. The release rate from the devices in the distilled water was continuously measured in the stirring container with an electro-conductivity meter. Since the mass transfer coefficient k_m in benzoic acid-water system is in the range of 0.01 to 0.001 cm/sec under the present in vitro

flow conditions(8), the value of Sherwood number is much larger than 100. Therefore, the diffusion of the active agent through the matrix structure of the device is the rate-limiting step in this in vitro experiment. The experimental data agreed fairly well with the calculated results. This finding indicates that we can identify the optimum design for a cylindrical matrix, controlled release drug delivery device to meet the therapeutic needs using the general mathematical simulation method.

CONCLUSION

The mathematical simulation model for the controlled drug release from the cylindrical matrix devices was presented. The effects of the device geometry(radius to height ratio), diffusion boundary layer surrounding the device, spontaneous decay reaction of the drug in the device and the porosity distribution of the device on the rate of controlled drug release were explained numerically by the present model. The findings in the present analysis are of practical significance for the design and development of matrix-type controlled release drug products.

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