A Model for Diffusion and Dissolution Controlled Drug Release from Dispersed Polymeric Matrix

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고분자 분산 매트릭스로부터의 약물방출에 관한 확산 및 용출 제어 모델

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A numerical model for diffusion and dissolution controlled transport from dispersed matrix is presented. The rate controlling process for transport is considered to be diffusion of drug through a concentration gradient coupled with time-dependent surface change and/or disappearance of the dispersed drug in response to the dissolution. The transport behavior of drug was explained in terms of ν parameter: ν value means a ratio of diffusion time constant and dissolution time constant. This general model has wide range of application from where release is controlled by the diffusion rate to where release is governed by the dissolution rate. Based on this model, theoretical drug concentration, particle size distributions in the polymer matrix system and the resulting release rate were also investigated.

Keywords—drug release, dispersed matrix, diffusion and dissolution, model.

Modeling of drug delivery system from the polymer matrix has been investigated from 1960's. The mathematical model for the polymer matrix where the drug is loaded above its solubility limit was first proposed by T. Higuchi[1]. Several assumptions were made in this model; the size of drug particles is very small compared to the thickness of the matrix, also a pseudo-steady state and a perfect sink condition exist during the transport process. The Higuchi's model and supplemented by others[5-8].

There have been, however, several cases where the kinetics of drug release from dispersed matrix could not be adequately described by the Higuchi's model. Aryes[9] and Bottari[10] suggested the case where the pseudo-steady state condition between the dissolution and the diffusion did not exist. Several theories have been put forth for dissolution controlled transport mechanisms. Consideration is given to the condition where dissolution is either very slow or fast with repect to the diffusion in the continuous phase of the suspension as well as where dissolution and diffusion occur at about the same rate. Chandrasekaran and Paul[11] proposed the analytical modeling for this case; special emphasis was placed on the condition of slow dissolution and fast diffusion. The numerical modeling was also

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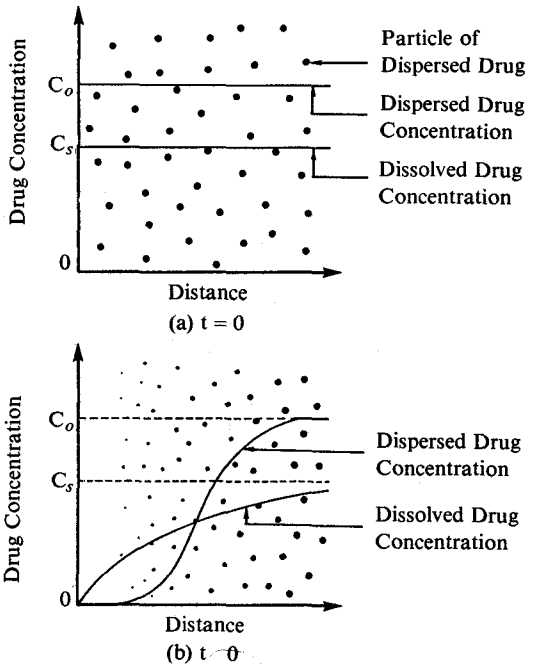

Figure 1—Drug concentration profiles within the matrix.

proposed by Aryes and Lindstrom[12]. Their model assumed that each drug particles are perfect sphere and the dispersed particles always exist in the entire matrix region.

Even the dissolution rate is slow, drug depletion generally occurs from the matrix surface. Therefore, in this study it was attempted to obtain a more general mathematical model by analyzing both the volume fraction held by dispersed drug and the local disappearance of drug particle as a function of time. Based on this model, the effect of diffusion coefficient, dissolution rate constant and particle size on drug release rate were investigated.

THEORY

Model Development

Consider one dimensional release from thin polymer slab where the drug or solute is dissolved upto its saturated concentration and the rest is dispersed in the matrix. It is assumed that the dispersed drug is in the shape of a perfect sphere and uniformly dispersed (Fig. 1(a)). When the drug starts to release, only the dissolved drug releases according to the Fick's law and a perfect sink condition is assumed. The dispersed drug is solubilized into the polymer matrix when the concentration of the dissolved drug falls below the saturated concentration. Therefore, the dispersed drug particle becomes gradually smaller and then disappears from the surface of the matrix (Fig. 1(b)).

The mass balance of dissolved and dispersed drug can be written as

$$\frac{\partial (C_{1(x,t)} V_1)}{\partial t} + \frac{\partial (C_{2(x,t)} V_2)}{\partial t} = \frac{\partial^2 (C_{1(x,t)} V_1)}{\partial x^2} \quad (1)$$

where t is time, x is distance and D is a diffusion coefficient. V_1 is a polymer volume including the dissolved drug and V_2 is the total volume including both the volume of polymer and the initial volume of the dispersed drug. C is the concentration where C_1 and C_2 refer to the concentration of dissolved and dispersed drug, respectively. It should be noted that C_1 and C_2 are defined differently as follows:

$$C_1(x,t) = \frac{M_1(x,t)}{V_1} \quad (2)$$

$$C_2(x,t) = \frac{M_2(x,t)}{V_2} \quad (3)$$

where M_1 and M_2 are the weight of dissolved and dispersed drug, respectively.

The volume fraction, ϕ, initially occupied by the dispersed drug in the polymer matrix can be written as

$$\phi = \frac{V_2 - V_1}{V_2} = 1 - \frac{V_1}{V_2} \quad (4)$$

Substituting Eqn. (1), one can obtain

$$\frac{\partial C_1(x,t)}{\partial t} + \frac{1}{1-\phi}\frac{\partial C_2(x,t)}{\partial t} = D\frac{\partial^2 C_1(x,t)}{\partial x^2} \quad (5)$$

The dispersed drug has an intrinsic dissolution rate constant to the polymer matrix. The driving force of such a solubilizing process is derived by the surface of drug particles. Since the solubilization process occurs at the surface of the dispersed particles, the change of concentration in the dispersed drug at the position, i (Fig. 2), for the time ΔT

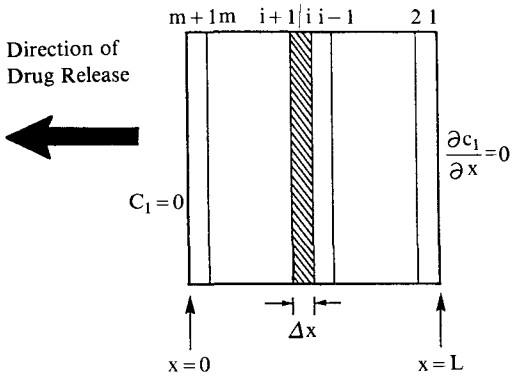

Figure 2—Schematic of the model system for the numerical simulation.

(j − j + 1) can be written as follows:

$$\frac{C_2(i,j+1)A\Delta x - C_2(i,j)A\Delta x}{\Delta t} = k(C_1(i,j) - C_s)4\pi r^2(i,j)n_i \quad (6)$$

where A is area, k is dissolution rate constant, and r is radius of particle. n_i is the number of particles in one increment (A Δx in Fig. 2). Here C_s is the saturated concentration which has the same volume base as C_1 and can be given as

$$C_s = \frac{M_s}{V_1} = \frac{M_1(x,0)}{V_1} \quad (7)$$

where M_s is the weight of dissolved drug at saturated state.

It is assumed that particles are uniformly distributed in the matrix at the initial stage and the average number of particles is the same at any place. Thus, if N is the total number of particles in the matrix and L is the thickness of the matrix, one can find.

$$N = n_i\frac{L}{\Delta x} \quad (8)$$

Substituting Eqn. (8) into Eqn. (6), the following equation can be obtained.

$$\frac{\partial C_2(x,t)}{\partial t} = k(C_1(x,t) - C_s)4\pi r^2(x,t)\frac{N}{AL} \quad (9)$$

The total number of particles in the matrix, N, can also be derived as follows:

$$N = \frac{V_d}{V_o} = \frac{V_d}{\frac{4}{3}\pi r_o^3} = \frac{C_o AL}{\frac{4}{3}\pi r_o^3\rho} \quad (10)$$

where V_o is the initial volume of one particle, V_d is the initial total volume of particles, r_o is the initial radius of particle and C_o, which has the same volume base as C_2, is the initial concentration of dispersed drug. Thus C_o can be written as

$$C_o = \frac{M_2(x,0)}{V_2} \quad (11)$$

Therefore, Eqn. (9) can be given by

$$\frac{\partial C_2(x,t)}{\partial t} = k(C_1(x,t) - C_s)\, 4\pi r^2(x,t)\frac{1}{AL}\frac{C_o AL}{\frac{4}{3}\pi r_o^3\rho}$$

$$= k(C_1(x,t) - C_s)\frac{3C_o r^2(x,t)}{\gamma_o^3\rho} \quad (12)$$

Eqn. (12) suggests the mutually dependent relationship between dispersed (C_2) and dissolved (C_1) drug, i.e., the dispersed drug cannot be solubilized at the position where the dissolved drug maintains a saturated concentration ($C_1 = C_s$). Also, changes in the concentration of dispersed drug (C_2) is related to the radius of the particle(r). Thus, this relationship can be expressed as follows:

$$C_2(i,j)A\Delta x = \frac{4}{3}\pi r^3(i,j)n_i\rho \quad (13)$$

Substituting Eqn.(8) and Eqn. (10) into Eqn. (13), one can find.

$$C_2(x,t) = C_o\left(\frac{r(x,t)}{\gamma_o}\right)^3 \quad (14)$$

Therefore, the Eqns. of mass balance can be obtained as Eqn. (5), (12), and (14) with the following initial and boundary conditions:

$$C_1(x,0) = C_s$$
$$C_2(x,0) = C_o$$
$$C_1(0,t) = 0$$
$$C_2(0,t) = 0$$

$$\frac{\partial C_1(x,t)}{\partial x}\Big|_{x=L}=0$$

where x = L means the position at the matix inside of surface (Fig. 2).

In order to transform these mass balance equations to dimensionless equations, the dimensionless groups are established as follows:

$$\tau=\frac{Dt}{L^2}$$

$$\eta=\frac{x}{L}$$

In addition, C_1, and C_2 and C_0 can be expressed by

$$\theta_1(\eta,\tau)=\frac{C_1(x,t)}{C_s}$$

$$\theta_2(\eta,\tau)=\frac{C_2(x,t)}{C_s}$$

$$\xi=\frac{C_o}{C_s}$$

Therefore, Eqn. (5) can be expressed as

$$\frac{\partial\theta_1(\eta,\tau)}{\partial\tau}+\frac{1}{1-\phi}\frac{\partial\theta_2(\eta,\tau)}{\partial\tau}=\frac{\partial^2\theta_1(\eta,\tau)}{\partial\eta^2} \quad (15)$$

Eqn. (12) also can be given as Eqn. (16) with the following dimensionless groups.

$$\nu=\frac{k/r_o}{D/L^2}$$

$$\Phi=C_o/\rho$$

$$\pi=\frac{r(x,t)}{\gamma_o}$$

$$\frac{\partial\theta_2(\eta,\tau)}{\partial\tau}=3\nu\Phi(\theta_1(\eta,\tau)-1)\pi^2(\eta,\tau) \quad (16)$$

Eqn. (14) can be written as

$$\theta_2(\eta,\tau)=\xi\pi^2(\eta,\tau) \quad (17)$$

Initial and boundary conditions can be given as

$$\theta_1(\eta,0)=1$$
$$\theta_2(\eta,0)=0$$
$$\theta_1(0,\tau)=0$$
$$\theta_2(0,\tau)=0$$

Table I—*Input values for variable and transport parameters.*

Diffusion coefficient (D)	1.464×10^{-8}cm^2/sec
Initial dispersed drug concentration (C_o)	0.02 g/cm^3
Saturated concentration (C_s)	0.01 g/cm^3
Initial radius of drug particle (r_o)	5 um
Matrix thickness (L)	0.01 cm
Drug density (e)	1.368 g/cm^3

$$\frac{\partial\theta_1(\eta,\tau)}{\partial\tau}\Big|_{\eta=1}=0$$

These dimensionless equations are simulated numerically. Since C_1 was not defined by total volume V_2 but by V_1, the flux should be corrected by volume fraction as shown in Eqn. (18).

$$F(t)=D\frac{\partial C_1(x,t)}{\partial x}\Big|_{x=0}(1-\phi) \quad (18)$$

Therefore, flux can be written with dimensionless groups as follows:

$$F(t)=\left\{\frac{\partial\theta_1(\eta,\tau)}{\partial\eta}\Big|_{\eta=0}\right\}\left(\frac{DC_s}{L}\right)(1-\phi) \quad (19)$$

RESULTS AND DISCUSSION

Dimensionless Variables

In this study, there are several important factors such as k, r_0, D, L, C_0, C_s, p which affect the drug release pattern. These factors transformed into five dimensionless variables such as θ, Π, Φ, ν, ξ (see Eqns. (15), (16), (17)). The θ, Π are the dimensionless variables related to the drug concentration and the size of dispersed drug particles, respectively. The ϕ is the volume fraction of dispersed drug in the matrix, and the ξ is connected to the drug particle property. The ν implies the relationships of dissolution constant (k), diffusion coefficient (D) and particle size (r_0). Therefore, the ν is the most important variable in investigation of the effect of particle size and dissolution rate constant on the drug release pattern. As can be seen in Eqn. (16), ν is the ratio of k/r_0 and D/L^2. The k/r_0 is the dis-

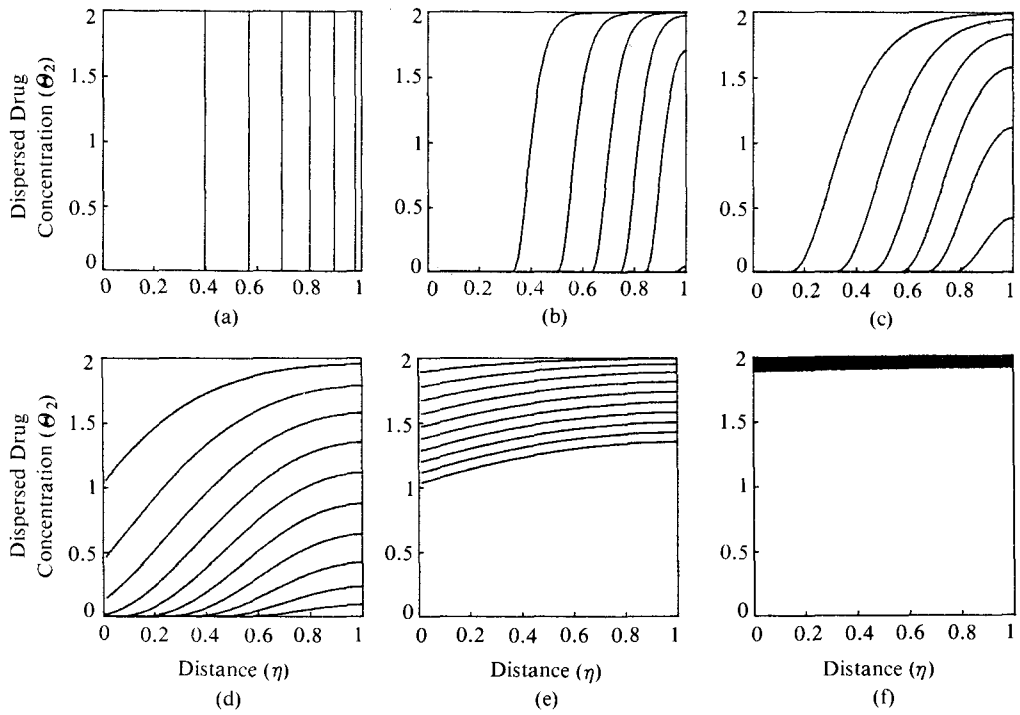

Figure 3—Profiles of dispersed drug concentration-distribution in the matrix with dimensionless time (τ: 0-2; time interval is 0.2); (a) Higuchi's model, (b) $\nu = 1.366 \times 10^4$, (c) $\nu = 1.366 \times 10^3$, (d) $\nu = 1.366 \times 10^2$, (e) $\nu = 1.366 \times 10$, (f) $\nu = 1.366$.

solution rate per unit particle size and the D/L^2 is the permeation rate per unit matrix thickness. Thus ν can represent the ratio between diffusion time constant and dissolution time constant.

As shown in Table 1, the values of variables were fixed by the experimental data of B. Farhadieh[13], who investigated the dispersed matrix system and also reported his experimental results were consistent with Higuchi's model[1]. However, the dissolution rate (k) and the particle size (r_0) were not considered in his study[13], his experiment cannot be the representative of general case of dispersed matrix system. Hence, the concentration profiles of drug in the polymer matrix in our study were simulated according to the changes in k value. The k value was changed from 10^{-3} to 10^{-7}, and the resulting ν value varies from 1.366×10^4 to 1.366. The dimensionless time covered from 0 to 2 at the time interval of 0.2.

Drug Concentration Profiles

Fig. 3 and Fig. 4 show the concentration profiles of dispersed and dissolved drug in the polymer matrix, respectively. The profiles of total drug (dispersed + dissolved) concentrations are shown in Fig. 5.

a. High ν value ($>10^4$)

In this case the dissolution time constant (r_0/k) is at least 10^4 times greater than the diffusion time constant (L^2/D). This means the dissolution of drug into the polymer matrix is sufficient enough to replace a depletion zone of dissolved drug which has occurred by diffusion. Thus, the pseudo-steady state condition can be accepted between a dissolution and diffusion transport. As can be seen in the Fig. 3(b) and Fig. 5(b), when the ν is greater than 10^4, the profiles of dispersed drug concentration show almost steep vertical line and also show 5(a)). Additionally, the profiles of dissolved drug concentration (Fig. 4(b)) show almost straight line like Higuchi's model case (Fig. 4(a)). Therefore, in this case ($\nu = 1.366 \times 10$), assumptions of both pseudo-steady state condition between dissolution and diffusion and diffusion transport, and the linearity in concentration profiles can be accepted if the matrix

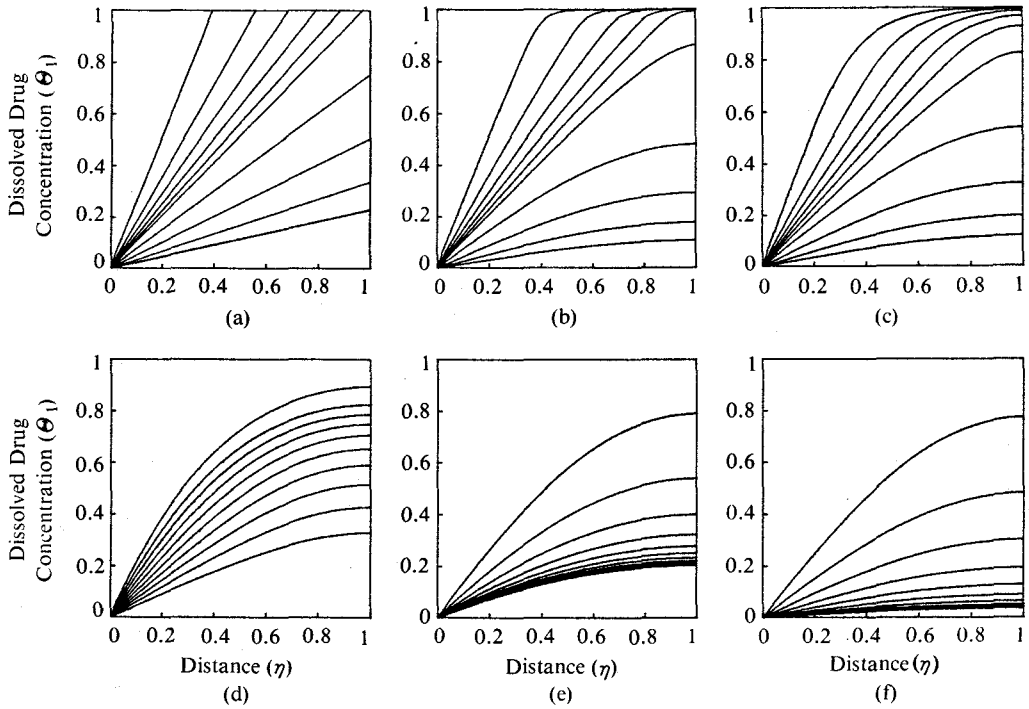

Figure 4—Profiles of dissolved drug concentration-distribution in the matrix with dimensionless time (τ: 0-2; time interval is 0.2); (a) Higuchi's model, (b) $\nu = 1.366 \times 10^4$, (c) $\nu = 1.366 \times 10^3$, (d) $\nu = 1.366 \times 10^2$, (e) $\nu = 1.366 \times 10$, (f) $\nu = 1.366$.

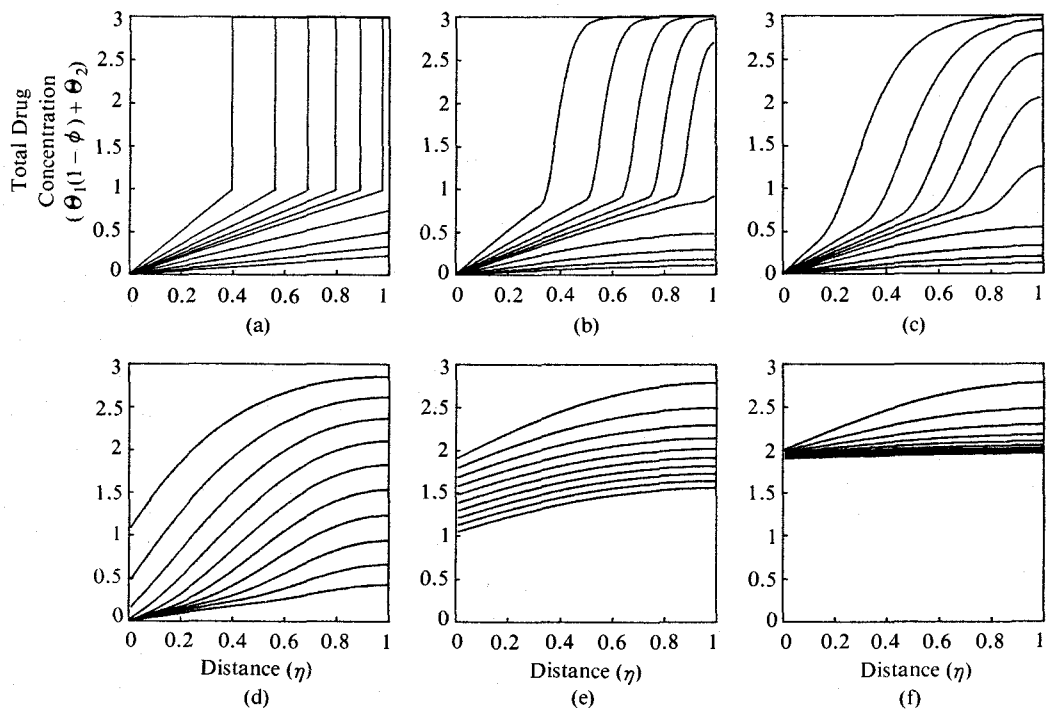

Figure 5—Profiles of total drug concentration-distribution in the matrix with dimensionless time (τ: 0-2; time interval is 0.2); (a) Higuchi-s model, (b) $\nu = 1.366 \times 10^4$, (c) $\nu = 1.366 \times 10^3$, (d) $\nu = 1.366 \times 10^2$, (e) $\nu = 1.366 \times 10$, (f) $\nu = 1.366$.

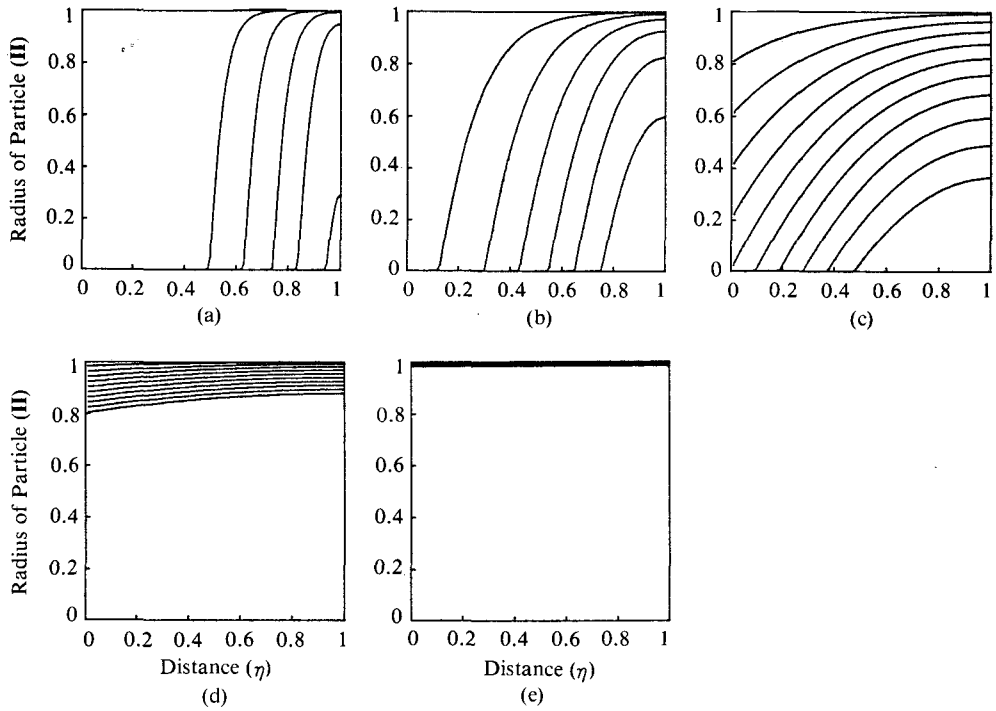

Figure 6—Profiles of particle size distribution in the matrix with dimensionless time (τ: 0-2; time interval is 0.2, k = 10^{-4} cm/sec): (a) $r_o = 5 \times 10^{-2}\,\mu$m, (b) $r_o = 5 \times 10^{-1}\,\mu$m, (c) $r_o = 5\,\mu$m, (d) $r_o = 50\,\mu$m, (e) $r_o = 500\,\mu$m.

thickness is infinite.

b. Medium ν values ($10^2 < \nu < 10^3$)

In these cases, the profiles of dispersed drug concentration become broaden with decreasing of ν value (Fig. 3(c)-(d), Fig. 5(c)-(d)). These results indicated that the pseudo-steady state cannot be assumed when the dissolution rate is not sufficient enough to replace the depletion zone of dissolved drug which has occurred by diffusion. The profiles of dissolved drug concentration gradually changed to the convex curves (Fig. 4(c)-(d)). Especially, the decreasing degree of dissolved drug concentration level at the initial release stage was remarkable with decreasing ν value. It is thought that this non-steady state is probabley the general case in the dispersed matrix.

Also, in this range of ν value, the concentrations of dissolved and total drug in a surface of inner matix changed from the initial release state. This change means that the matrix thickness greatly influence upon the drug release pattern. Therefore, the thickness of matrix is an important consideration factor for both the duration and the flux of drug in the state where the pseudo-steady state assumption cannot be accepted between diffusion and dissolution transport. In addition, this phenomena can explain why the matrix thickness L is an important variable for flux in the Eqn. (19).

c. Low ν value ($\nu < 10$)

In the case of the extremely low ν value, the profiles of dissolved drug concentration are almost same as those in the matrix system containing only dissolved drug, and the effect of dispersed drug is negligible (Fig. 3(e),(f), Fig. 4(e),(f), and Fig. 5(e), (f)).

Particle Size

Fig. 6 shows the change of relative particle size compared to the initial one. The k was fixed for 10^{-4} cm/sec, and the initial particle size varied from 0.05 μm to 500 μm.

As can be seen in Fig. 6, even if the non-steady state conditions were existed between dissolution and diffusion transport, pseudo-steady state might be achieved by reducing the particle size (see Fig.

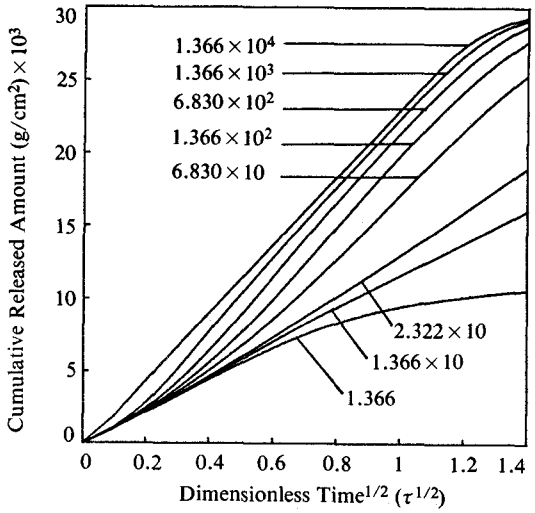

Figure 7—Plots of cumulative drug released amount from dispersed matrix. Each curve is carrying its respective ν value.

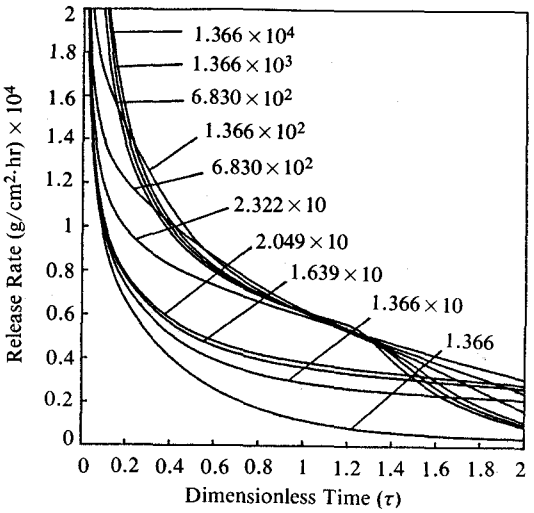

Figure 8—Comparison of drug release rate with the ν value. The number assigned to each curve express its own ν value.

6(a),(b)), since the dissolution rate could be increased by the increasing the surface area of drug particles, as a consequence of reducing particle size.

The Released Amount

Fig. 7 shows the cumulative released amount of drug with the square root of time as ν value changes. When the ν is greater than 10^4, the released amount of drug is linearly dependent on the

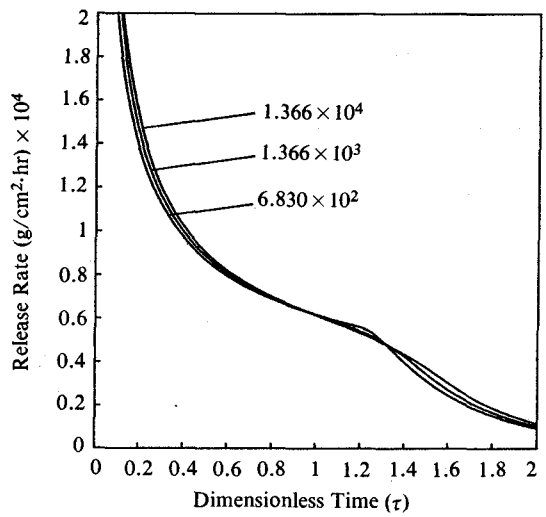

Figure 9—Plots of drug release rate from the matrix, when $\nu > 5 \times 10^2$. The number assigned to each cruve express its own ν value.

square root of time as far as dispersed drug exist. With analyzing in the concentration profiles of drug, these results are same with those of Higuchi's model. As the ν decreases, the curves of drug released amount gradually exhibit the deviation from the linear dependence on $t^{1/2}$ and the release order varies from 0.5-1.0.

The Release Rate

The drug release rate for the various v values are shown in Fig. 8. The release pattern of drug were very complicated with respect to the ν. Therefore, we have tried to analyze by dividing the ν value into three categories. In the case where ν is greater than 10^3, the release rate shows the typical 0.5 order release pattern, and the flux is almost unchanged (Fig. 9). This can be explained by the high dissolution rate compared to the diffusion of drug through matrix. Thus, the change of the diffusion rate of dissolved drug was very small. The break points in Fig. 9 occur when the dispersed drug depleted.

The curves of release rate when the ν values are in the range of 10^3 to 10^2 are shown in Fig. 10. The changes in flux are complicated and irregular in this range and the durations of dimensionless time which requires the disappearance of dispersed drug at the matrix surface also change with ν values. It is

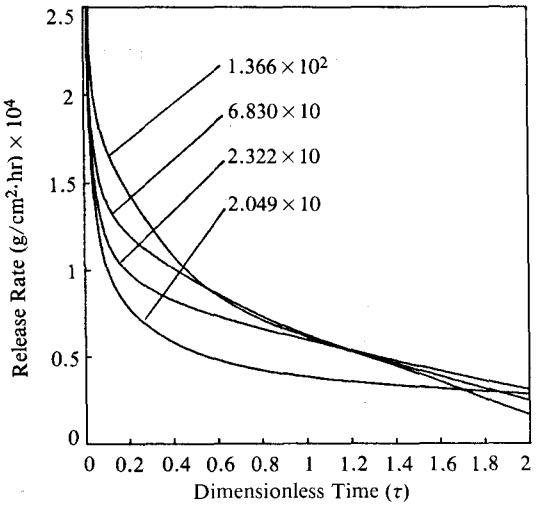

Figure 10—Plots of drug release rate from the matrix, when $2.5 \times 10 < \nu < 5 \times 10^2$. The number assigned to each curve express its own ν value.

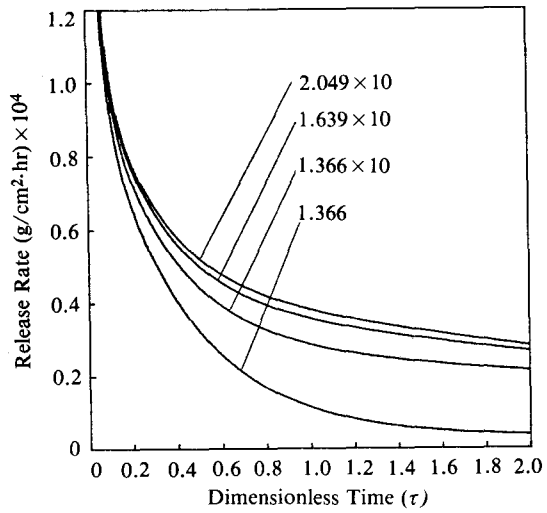

Figure 11—Plots of drug release rate from the matrix when $\nu < 2.5 \times 10$. The number assigned to each curve express its own ν value.

thought that the complication of changes in flux is due to the disappearance of dispersed drug at the matrix surface. The existance of dispersed drug at the surface greatly influenced on the flux since the flux was mainly controlled by the surface layer of matrix.

Fig. 11 shows the changes in flux where ν is less than 10. In this range the flux is getting lower as the ν become smaller. This effect might also be explained the that the flux become smaller as the particle size is larger. This result was same as Aryes[12] and Chandrasekaran[14]'s model studies where the dispersed drug always remains intact size throughout the experiment and the drug release is only dissolution controlling mechanism.

CONCLUSION

A mathematical model of dispersed matrix was developed. This model permits the analysis of change and/or disappearance of dispersed drug particle in the matrix as a function of time. The theory explains the transport process in terms of four basic parameters; diffusion coefficient D, particle size r_o, dissolution constant k and the thickness of polymer matrix L. Also the volume fraction of dispersed particle, ϕ, was considered. Our mathematical model is able to explain general case and covers the complete range between the dissolution and diffusion controlling transport.

The profiles of dispersed drug concentration in the matrix show vertical straight line with high ν value but they become broaden and parallel with decreasing of ν values. Therefore, one should be very careful to assume the pseudo-steady state between dissolution and diffusion transport in the dispersed matrix.

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