

Kinetics of Release from Polydisperse Core Particles Coated with Layers of Fine Soluble Particles

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Abstract—The kinetics of release of active material was investigated for the polydisperse core particles coated with layers of fine soluble particles dispersed in the impermeable biodegradable wax. A detailed mathematical model was developed to simulate the release kinetics governed by diffusion through the void space of the coating layer formed after the dissolution of soluble particles. The effects of the scale and shape parameters of the Rosin-Rammler type of the core size distribution were studied numerically on release profile. As a result, the low release rate was obtained for the core size distribution of large scale parameter mainly due to the small specific surface area of particles as well as for the coating layer of low volume fraction of soluble particles owing to the significant diffusional resistance.

Index Terms—Release kinetics, Coated particle, Polydisperse core, Release model.

I. INTRODUCTION

The release of active components at a controllable rate is an essential feature of advanced formulations of drug dosages [1], food ingredients [2], fertilizers and pesticides [3] etc. Several types of controlled-release particles have been proposed including embedded within an inert matrix, controlled by chemical reaction and encapsulated [4].

Encapsulated particles produced by coating of active material with polymer dissolved in organic solvent are most widely used to control the release rate. However, their application will be restricted in the near future due to environmental issues arising out of the solvent carcinogenic properties and the residual polymer left in the soil after the dissolution of the active component.

To overcome the disadvantages of such coated particles, the dry-based process was developed for coating of active core components with a layer of fine soluble [5] or permeable [6] particles dispersed in impermeable biodegradable wax.

The requirements for the total release time and the release profile vary widely in different application fields. The coating with multiple layers of different thickness and volume fractions of soluble and permeable particles has been studied to achieve an additional control over the release profile [7, 8, 9]. The released rate could also be influenced by the size distribution of core particles as suggested by Berchane et al. [10] for the matrix type of drug formulations.

The objective of the present study is to clarify the effect of the size distribution of core particles on the kinetics of release

of active material through the coating layer of fine soluble particles dispersed in impermeable wax. The mathematical modeling is applied to quantify the contribution of the coating layer thickness and the volume fraction of the soluble particles to the release rate of the active component from polydisperse core particles.

II. THEORETICAL

The release model was constructed for coated particles assuming that the diffusion of dissolved core material through the coating layer governs the release rate. When the coated particle is suspended in water in the reservoir, connected soluble particles dispersed in the coating layer dissolve creating void spaces. Water penetrates into these voids forming a water network inside the coating layer known as penetration paths. The dissolution rate of fine soluble particles is supposed to be high enough for water to reach immediately the outer surface of the core particle. Thereafter the dissolved core material diffuses to the outer surface of the coated particle through the penetration paths and releases to the reservoir.

The release of core material is considered to proceed in two consecutive time stages. The solid core gradually dissolves and shrinks in size, but is still present during the initial stage of release. The inside space between the inner surface of the coating layer and the solid core termed as an inner solution is filled with the active component dissolved in water. The volume of the inner solution increases with time until the solid core completely disappears. The second stage of release starts at this point. During this stage, the concentration of the inner solution occupying the core space decreases with time, until it equilibrates with the solution in the reservoir. The notation of the release model is illustrated in Fig. 1.

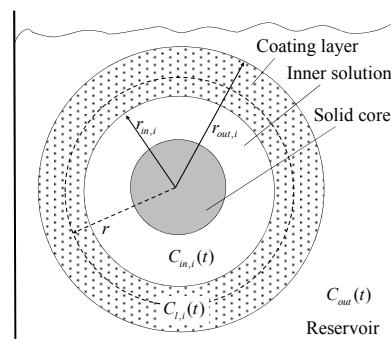


Fig. 1. Notation for release model of type i coated particle.

A. Modeling of Release Kinetics

The release kinetics of active core material by diffusion

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through the porous space of the coating layer formed after the dissolution of dispersed soluble particles could be predicted on the basis of a model developed in our previous paper [4] for monodisperse core particles. The model is further elaborated in the present study to consider the release kinetics of polydisperse core particles.

Suppose that there are N_i types of coated particles involved, differing in the core size, the coating layer thickness, and the volume fraction of the soluble particles dispersed in the coating layer. The number of core particles in the i -th size interval, N_i , is

$$N_i = \frac{6M_{c,T}f(x_c)dx_c}{\rho_c \pi x_{c,i}^3} \quad (1)$$

where $f(x_c)$ is the weight based distribution function of the core diameter x_c , $M_{c,T}$ is the total amount of core particles and ρ_c is the density of the core material.

The concentration of active core material $C_{l,i}(r,t)$ in the porous space of the coating layer of type i particle is given by the mass balance over the spherical shell as

$$\varepsilon \frac{\partial C_{l,i}(r,t)}{\partial t} = D_{eff} \left(\frac{\partial^2 C_{l,i}(r,t)}{\partial r^2} + \frac{2}{r} \frac{\partial C_{l,i}(r,t)}{\partial r} \right) \quad (2)$$

where r is the radius of the shell, t is the diffusion time, D_{eff} is the effective diffusivity and ε is the voidage of the coating layer. The voidage is assumed to be equal to the volume fraction of soluble fine particle dispersed in the coating layer, ϕ .

The mass transfer resistance between the liquid phase in the reservoir and the outer surface of coated particles is neglected due to the intensive mixing in the reservoir. Therefore, a boundary condition for Eq. (2) at the outer particle surface, $r_{out,i}$, is

$$C_{l,i}(r=r_{out,i},t) = C_{out}(t) \quad (3)$$

To calculate the increase in the concentration of the active component in the reservoir with time, the amount of the active material released by diffusion through the outer surface of type i particle is multiplied by the number of particles of this type, N_i , and summed up for all size intervals

$$V_{out} \frac{dC_{out}(t)}{dt} = - \sum_{i=1}^{N_i} N_i D_{eff} 4\pi r_{out,i}^2 \frac{\partial C_{l,i}}{\partial r} \Big|_{r=r_{out,i}} \quad (4)$$

where V_{out} is the reservoir volume.

The boundary condition for Eq. (2) at the inner surface of the coating layer, $r_{in,i}$, is

$$C_{l,i}(r=r_{in,i},t) = C_{in,i}(t) \quad (5)$$

where $C_{in,i}$ is the concentration of dissolved core material in the inner solution.

During the initial stage of the release when the solid core still exist, the concentration of the dissolved material in the inner solution remains constant and equal to the concentration at the saturation condition, C_{sat} ,

$$C_{in,i}(t) = C_{sat} \quad (6)$$

After the disappearance of the solid core, the concentration of the dissolved material in the inner solution decreases with elapse of time by diffusion through the inner surface of the coating layer in accordance with the following material balance equation

$$\frac{dC_{in,i}(t)}{dt} V_{core,i} = D_{eff} \frac{\partial C_{l,i}}{\partial r} \Big|_{r=r_{in,i}} 4\pi r_{in,i}^2 \quad (7)$$

where $V_{core,i}$ is the initial solid core volume, $V_{core,i} = \frac{4\pi r_{in,i}^3}{3}$.

Introducing $V_{core,i}$ into Eq. (7) and rearranging it results in

$$\frac{dC_{in,i}(t)}{dt} = \frac{3D_{eff}}{r_{in,i}} \frac{\partial C_{l,i}}{\partial r} \Big|_{r=r_{in,i}} \quad (8)$$

The initial condition for Eq. (8) is

$$C_{in,i}(t=t_{dis}) = C_{sat} \quad (9)$$

The release fraction R is defined as

$$R(t) = \frac{C_{out}(t)}{C_{out}(t=\infty)} \quad (10)$$

where $C_{out}(t=\infty)$ is the concentration of the core material in the reservoir solution at infinite time.

B. Modeling of Size Distribution of Core Particles

The size distribution of core particles is assumed to be of the Rosin-Rammler type [11]. The cumulative oversize distribution, $F(x_c)$, is

$$F(x_c) = \exp \left\{ - \left(\frac{x_c}{x_e} \right)^n \right\} \quad (11)$$

where x_e is the scale parameter and n is the shape parameter. The scale parameter is the characteristic value of the distribution and the shape parameter controls the width of the frequency distribution of sizes with the higher value corresponding to the narrower distribution.

The frequency distribution, $f(x_c)$, is

$$f(x_c) = \frac{n}{x_e} \left(\frac{x_c}{x_e} \right)^{n-1} \exp \left\{ - \left(\frac{x_c}{x_e} \right)^n \right\} \quad (12)$$

III. METHODS

The influence of the core size distribution on the release kinetics of coated particles was analyzed with the help of the developed above model. The system of model equations, Eqs.

(1) - (12), was solved numerically using a method of lines [12]. A second-order central-differencing scheme was utilized to discretize the space derivatives in Eq. (2). Then, the solution of resulting system of ordinary differential equations was carried out employing Gear's method [13].

The total amount of the active core material was kept constant for all simulations. The reference value of parameters used in simulation are as follows: the thickness of the coating layer was assumed to be proportional to the core size with the ratio of the layer thickness to the core radius equal to 0.0077 and the volume fraction of the soluble particles in the coating layer is presumed to be equal 0.3.

IV. RESULTS AND DISCUSSION

The effect of the scale parameter of Rosin-Rammler distribution of core sizes on the release profile is illustrated in Figs. 2 and 3.

The distributions of core particle sizes were generated by varying x_e in Eq. (11) at the fixed value of n , $n = 3$, as demonstrated in Fig. 2 (a) by the cumulative oversize distribution functions and in Fig. 2 (b) by the frequency distribution functions.

The release profiles differ significantly with the scale parameter and the release rate decreases for core particles of the size distribution of larger x_e , as shown in Fig. 3. With

increasing x_e , the core size distribution shifts to the larger sizes. Since the thickness of the coating layer is assumed to be proportional to the core size, the larger particles are coated with the thicker layer. Thus, the core material dissolved in the inner solution has to diffuse a long distance inside the thick coating layer to reach the outside surface. The large core particles are also of a small specific surface area that limits supply of the active component from the inner solution to the coating layer through the inner surface according to Eq. (8). Therefore, both the thick coating layers and the small specific surface area of large particles contribute to the decrease of release rate.

To clarify contributions of the layer thickness and the surface area to the release rate, simulations were also carried out for the core particles coated with layers of the same thickness of 100 μm . As illustrated in Fig. 3, the release curve for core particles of a wide size distribution, $x_e = 3000$, coated with layers of variable thickness almost coincide with the curve for layers of constant thickness. Therefore, the decline in the specific surface area is mainly responsible for the reduction of the release rate of large particles.

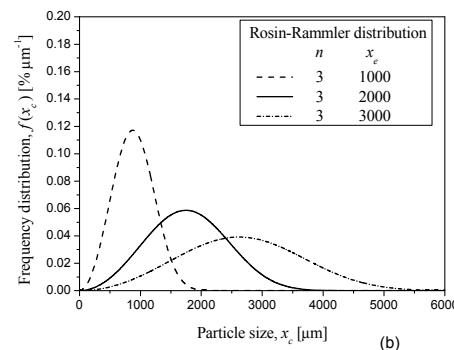
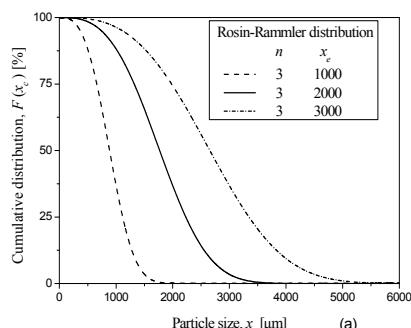


Fig. 2. Rosin-Rammler distributions of core particles for various scale parameters: (a) cumulative oversize distributions, (b) frequency distributions.

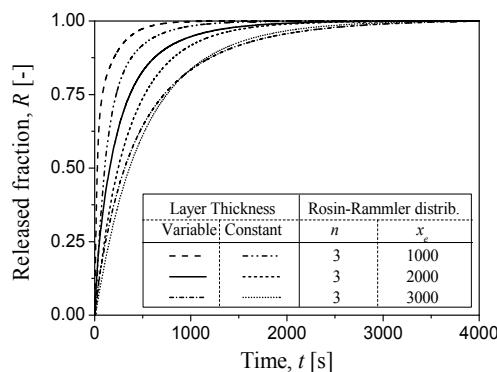


Fig. 3. Effect of scale parameter of core size distribution on the release profile.

A specific surface area of a particle in the i -size ratio is calculated as

$$S_i = \frac{\pi x_{c,i}^2}{\pi x_{c,i}^3} = \frac{6}{x_{c,i}} \quad (13)$$

The total specific surface area is

$$S = \sum_{i=1}^{N_t} N_i S_i = \sum_{i=1}^{N_t} N_i f_n(x_{c,i}) dx_{c,i} \cdot \frac{6}{x_{c,i}} = 6 N_T \sum_{i=1}^{N_t} \frac{f_n(x_{c,i})}{x_{c,i}} dx_{c,i} \quad (14)$$

where N_T is the total number of particles, $N_T = \sum_{i=1}^{N_t} N_i$, and $f_n(x_c)$ is the number based frequency distribution of core particles which is converted from the mass based distribution defined by Eq. (12).

The total specific surface areas calculated by Eq. (14) for various size distributions are summarized in Table I.

TABLE I: THE TOTAL SPECIFIC SURFACE AREA OF PARTICLES

Scale parameter of Rosin-Rammler distribution, x_e [μm]	Total specific surface area of particles, S [m^2/m^3]
1000	9276
2000	4419
3000	2854

The effect of the shape parameter of Rosin-Rammler distribution of core sizes on the release profile is illustrated in Figs. 4 and 5. The size distributions of core particles of the same scale parameter, $x_e = 2000$, and various values of shape parameter used in the simulation of release kinetics are shown in Fig. 4. Inspection of Fig. 5 indicates that the release rate only slightly decreases with increasing shape parameter.

The effect of the volume fraction of soluble particles dispersed in the coating layer on the kinetics of release was studied by varying the volume fraction, $\phi = 0.1, 0.2, 0.5$, for polydisperse core particles coated with impermeable layers of the thickness proportional to the core diameter. The effective diffusivity of the coating layer, D_{eff} , was estimated from the volume fraction of soluble particles by using an empirical equation [14]

$$D_{eff} = [a \ln(b\phi^2 + c) + d]\phi \quad (15)$$

where a, b, c and d are the fitting parameters.

This equation was derived by fitting the results of Monte-Carlo simulations of the transport of active species by diffusion in the three-dimensional porous structure formed after the dissolution of soluble particles. The values of the effective diffusivity used in the simulation of release kinetics are summarized in Table II.

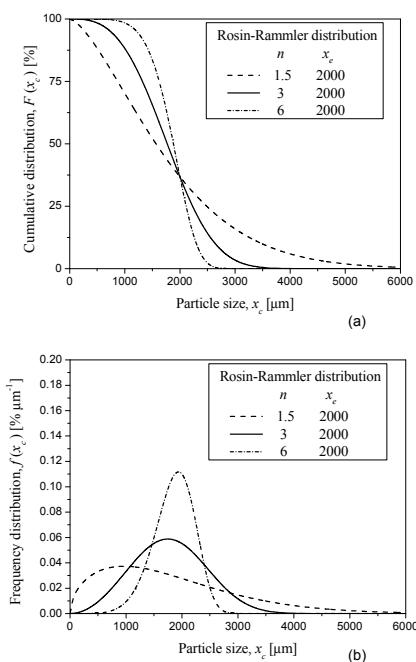


Fig. 4. Rosin-Rammler distributions of core particles for various shape parameters: (a) cumulative oversize distributions, (b) frequency distributions.

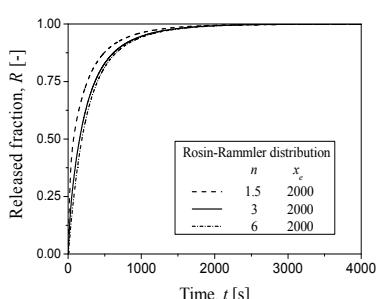


Fig. 5. Effect of shape parameter of core size distribution on the release profile.

TABLE II: EFFECTIVE DIFFUSIVITIES FOR VARIOUS VOLUME FRACTIONS OF SOLUBLE PARTICLES

Volume fraction of soluble particles, $\phi [-]$	Effective diffusivity, D_{eff} [m ² /s]
0.1	2.8×10^{-11}
0.3	7.0×10^{-11}
0.5	9.1×10^{-11}

The release profiles of polydisperse core particles coated with layers of various volume fractions of dispersed soluble particles are shown in Figs. 6 (a) and (b) for core size distributions of Rosin-Rammler type of $x_e = 1000$ and $x_e = 3000$, respectively.

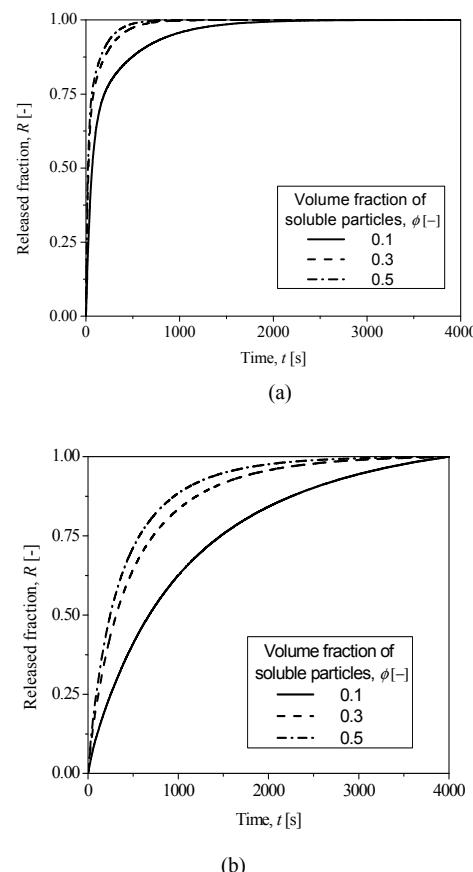


Fig. 6. Effect of volume fraction of soluble particles on release profile.

Rosin-Rammler distribution of core particles with $n = 3$ and

$$(a) x_e = 1000, (b) x_e = 3000$$

The release rate reduces significantly when the volume fraction decreased from $\phi = 0.3$ to $\phi = 0.1$ especially for the core particles of wide size distribution, $x_e = 3000$. The diffusion of the active material is hindered in the coating layer of low volume fraction of soluble particles as the restricted porous space is formed in place of the dissolved soluble particles due to the small contact area of neighbor soluble particles and the low number of percolation paths. However, the release rate of particles coated with layers of $\phi = 0.3$ only slightly decreases in comparison with one for $\phi = 0.5$, as the broad porous network already exists in the coating layer of $\phi = 0.3$.

V. CONCLUSIONS

The application of core particles of tailored size distribution coated with layers of fine soluble particles dispersed in the impermeable wax was proved to be useful for controlling the release rate of active material.

The detail mathematical model was constructed to simulate the release kinetics of polydisperse core particles governed by diffusion through the penetration paths inside the coating layer formed in place of dissolved soluble particles.

As a result, the low release rate of the active core material was obtained for the core size distribution of Rosin-Rammler type with the large scale parameter mainly due to the small specific surface area of large size particles. The release rate was also low for the core particles coated with layers of low volume fraction of soluble particles due to the hindered diffusion in the restricted space of percolation paths.

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