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Controlled Release from Coated Polydisperse Particles

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Abstract. In this study, the application of core particles of tailored size distribution coated with layer of soluble particles dispersed in the impermeable biodegradable wax was investigated for controlling the release rate of active material. A detailed mathematical model was developed to simulate the release kinetics of polydisperse particles governed by diffusion through the penetration paths inside the coating layer. 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.

Keywords: controlled release, coated particle, polydisperse core, release model

1. Introduction

The release of active components at a controllable rate is an essential feature of advanced formulations of drug dosages, food ingredients, fertilizers and pesticides etc.

Encapsulated particles produced by coating of active material with polymer dissolved in organic solvent are widely used to control the release rate. However, their application will be limited in the near future due to the solvent carcinogenic properties and the residual polymer.

To overcome the disadvantages of such coated particles, we developed the dry-based process for coating of active core components with a layer of fine soluble [1] or permeable [2] particles dispersed in impermeable biodegradable wax.

The requirements for the total release time and the release profile widely vary 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 [3, 4, 5]. The released rate could also be influenced by the size distribution of core particles as suggested by Berchane *et al.* [6] 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 release rate of active material through the coating layer of fine soluble particles dispersed in impermeable wax.

2. 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, water penetrates into the void spaces of the coating layer. Connected soluble particles dissolve forming penetration paths. The dissolution rate of fine soluble particles is supposed to be high enough for water to reach the outer surface of the core particle immediately. Thereupon the dissolved core material diffuses to the outer surface of the coated particle through the penetration paths and releases to the reservoir.

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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 second stage starts when the core completely disappears. 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.

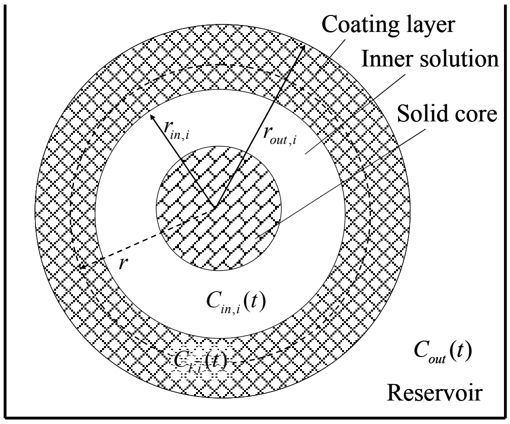


Fig. 1: Notation for release model of type i coated particle.

2.1. Modeling of release kinetics

The release kinetics of active core material by diffusion 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 of the polydisperse core particles.

Let us assume that there are N_t types of coated particles involved, differing in the core size and the coating layer thickness. The number of core particles in the *i*-th size interval, N_i, is

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

where $f(x_c)$ is the weight 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

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

where r is the radius of the shell, t is the diffusion time, D_{eff} is the effective diffusivity and ε is the void fraction of the coating layer.

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

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

To calculate the increase in the concentration of active component with time in the reservoir, 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

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

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

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

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 space between the shrinking core and the inner boundary of the coating layer remains constant and equal to the concentration at the saturation condition, C_{sat},

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

After the disappearance of the solid core, the concentration of the dissolved material in the inner solution decreases with elapse of time due to diffusion through inner surface according to the following equation

$$\frac{dC_{in,i}(t)}{dt} = \frac{3D_{eff}}{r_{in,i}} \left.\frac{\partial C_{l,i}}{\partial r}\right|_{r=r_{in,i}}\,. \tag{7}$$

The initial condition for Eq. (7) is

$$C_{in,i}(t = t_{dis}) = C_{sat}\,. \tag{8}$$

The release fraction R is defined as

$$R(t) = \frac{C_{out}(t)}{C_{out}(t=\infty)}\,. \tag{9}$$

2.2. Modeling of size distribution of core particles

The size distribution of core particles is assumed to be of the Rosin-Rammler type [7]. The cumulative oversize distribution, $F(x_c)$, is

$$F(x_c) = \exp\left\{-\left(\frac{x_c}{x_e}\right)^n\right\}, \tag{10}$$

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

$$f(x_c) = \frac{n}{x_e}\left(\frac{x_c}{x_e}\right)^{n-1} \exp\left\{-\left(\frac{x_c}{x_e}\right)^n\right\} \tag{11}$$

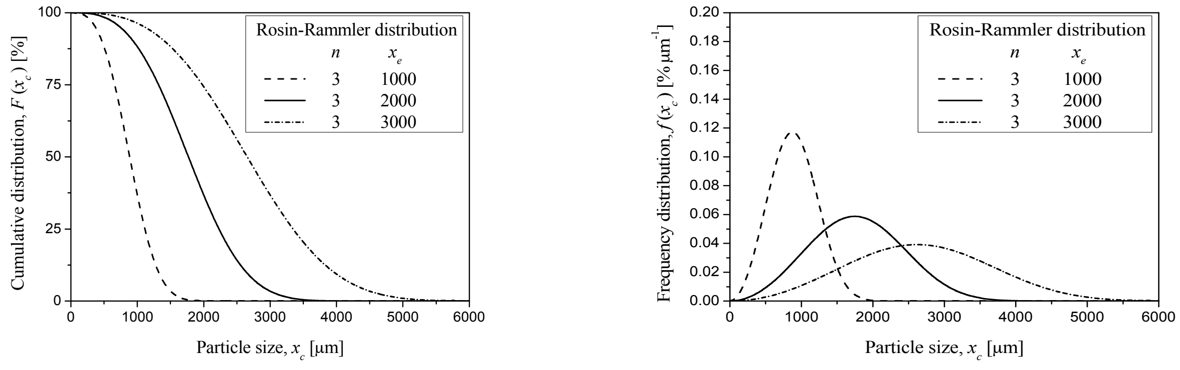
3. Methods

The influence of the core size distribution on the release kinetics of coated particles was analyzed with the help of developed above model. The system of model equations, Eqs. (1) - (11), was solved numerically using a method of lines [8]. 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 [9].

The total amount of the active core material and the volume fraction of the soluble particles in the coating layer were kept constant for all simulations. 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.

4. 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. (10) at the fixed value of n, 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 the size distributions of larger x_e, as shown in Fig. 3. With increasing x_e, the core size distribution shifts to the larger sizes. Therefore, the thick coating layer as well as the smaller specific surface area of large particles contributes to the decrease of release rate. To clarify the contribution of the layer thickness and the surface area to the release rate, simulations were also carried out for core particles coated with layers of the same thickness of 100 μm. As illustrated in Fig. 3, the decline in specific surface area is mainly responsible for reduction of release rate of large particles. The total specific surface area is 9276 m^2/m^3 for core particles of $x_e = 1000$, 4419 m^2/m^3 for $x_e = 2000$ and 2854 m^2/m^3 for $x_e = 3000$, correspondingly.



(a) (b)

Fig. 2: Rosin-Rammler distributions of core particles for various scale parameters:

(a) cumulative oversize distributions, (b) frequency distributions.

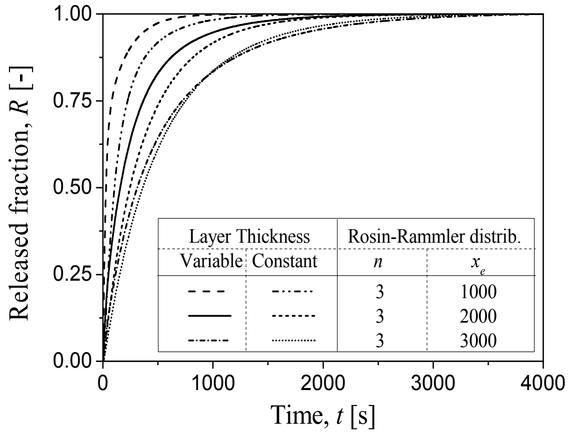
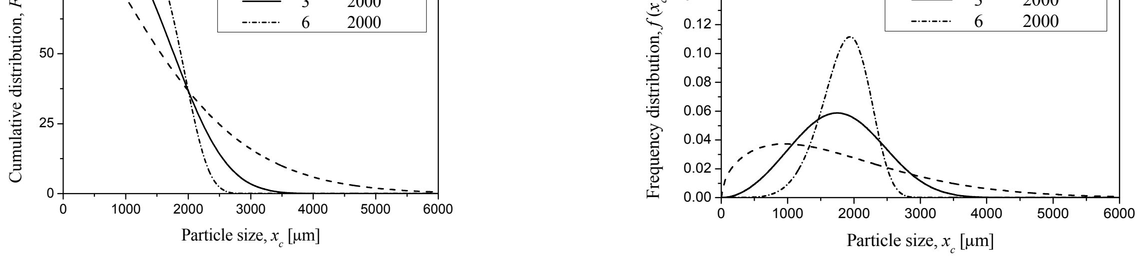


Fig. 3: Effect of scale parameter of core size distribution on the release profile.



(a) (b)

Fig. 4: Rosin-Rammler distributions of core particles for various shape parameters:

(a) cumulative oversize distributions, (b) frequency distributions.

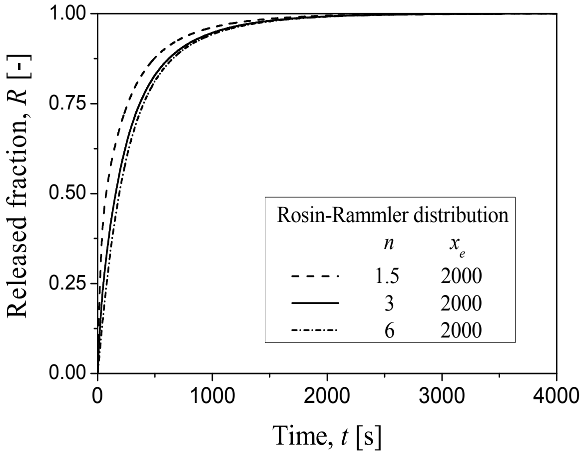


Fig. 5: Effect of shape parameter of core size distribution on the release profile.

The effect of the shape parameter of core size distribution 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 simulations are shown in Fig. 4. Inspection of Fig. 5 indicates that the release rate only slightly decreases with increasing the shape parameter.

5. Conclusions

The application of core particles of tailored size distribution coated with layers of 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. As a result, the low release rate 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.

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