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Finite element analysis of slow drug release through deformed coating film: effects of morphology and average thickness of coating film

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Abstract

This paper, a continuation of our previous work, is a presentation of the effect of the morphology and the average thickness of the deformed coating films on the slow diffusional release characteristics analyzed numerically under the constraints of the constant volume of the drug matrices and the coating films, if the films have the same average thickness. Increasing the average thickness of the coating films slows down the fractional release and the average release rate of the drug and smoothen the initial burst of the drug, as well as increase the initial lag time. The effect due to deformation of the coating films on these diffusional release characteristics are found to be less significant with the increasing average thickness of the coating films. Interestingly initial lag times are found to be the same for the coated particles having the same smallest thickness but different average thickness of coating films. The effect due to the change in the average thickness of the coating films on the characteristics of the slow controlled-release is discussed to shed light on the design of a better controlled-release device.

Keywords: Controlled-release; Deformation; Morphology; Film thickness; Coating film; Diffusional release

1. Introduction

An ideal system of controlled-release drug delivery is to deliver the drug to the site of action at a designed rate, as well as to maintain the optimal concentration level of drug in plasma within the therapeutically effective range for an extended period of time (Chien, 1992). Accordingly, the phamacokinetics and pharmacodynamics of the drug can be considerably changed compared with those by the administration in its free form. It also can decrease the needed dose of an expensive active ingredient. A few commercial products may be mentioned. (1) Norplant—a long-term contraceptive implant inserted under the skin of a upper arm and lasted for 5 years. (2) Ocusert for eye insert dosage form—releasing pilocarpine to treat glaucoma on adults for 7 days per dosage. (3)

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Nitroglycerine for extended-release oral dosage—effective for relieving angina attacks for 7–10 h.

The basic controlled-release formulation consists of an active agent (the drug and excipients) and a carrier (commonly polymeric material) (Fan and Singh, 1989). There are numerous designs using different rate-controlled mechanisms to achieve a good controlled-release. These include (1) diffusion controlled systems; (2) water penetration or solvent controlled systems; (3) chemically controlled systems; (4) regulated systems and etc. (Shinko and Kohn, 1993). Out of these systems, the diffusion-controlled systems are the most common.

Among the diffusion-controlled release of drugs, reservoir-type and monolithic devices represent the two major but fundamentally different designs (Fan and Singh, 1989). In the monolithic devices, the active agent is initially distributed in the polymeric matrix and release takes place through the bulk polymer by erosion or combination of erosion and diffusion (Higuchi, 1961, 1963; Antal et al., 1997; Ju et al., 1997; Reynolds et al., 1998; Grassi et al., 1999; Charlier et al., 2000; Kim et al., 2000; Şen et al., 2000; Reynolds et al., 2001; Rich et al., 2001). In the reservoir-type devices, more widely used in the pharmaceutical products, the active agent enclosed within the drug core or the drug matrix is diffused to the extraction medium through the membrane or coating film surrounding the core (Flynn et al., 1974; Christensen et al., 1982; Lu and Chen, 1993; Lu, 1994; Lu and Yu, 1994; Watano et al., 1995; Lee and Liao, 1995, 1997; Xu and He, 2000; Chralambopoulou et al., 2001). Two different types of controlling membrane, homogeneous or microporous, are often used in the formulations of reservoir-type systems. In such devices, the rate-controlling step is by the diffusion. The characteristics of drug release from such devices is a function of the release time, the drug diffusivity, and the drug concentration in the device as well as the layer thickness of the diffusion barrier, i.e. the thickness of the coating film in this study (Higuchi, 1961, 1963; Flynn et al., 1974; Fan and Singh, 1989). Consequently, the desired release profiles and released rates can be achieved by adjusting the geometry and the dimension of the system (Siepmann et al., 1998, 1999, 2000; Siepmann and Peppas, 2000). A detailed review on the models for diffusion-controlled release systems can be learned (Fan and Singh, 1989), while a comprehensive review of the mathematical treatments of these controlled-release problems can be found elsewhere (Flynn et al., 1974; Fan and Singh, 1989).

In all of the above analyses, however, the coated particle was assumed to be perfectly spherical, which by and large is ideal and by no means achievable practically (Jones, 1985; Mehta and Jones, 1985). Lee and Liao (1995, 1997) recently provided the first perturbation analyses on the effects of slightly deformed coating films and drug matrices on the slow release characteristics of drugs. They found the effects of shape deformations are secondary if the deformation is slight or if only the average release rate is of interest. It is noteworthy to mention that the perturbation method, which they used in their analyses, assumes only very small magnitude of shape deformation. There was still an open question on how large it is enough for the shape deformation of coating films can effectively affect the slow release characteristics of drugs through such deformed coating films.

A previous study of ours aimed to provide the answer to the aforementioned question (Chen and Lee, 2001). The combined effects of the surface morphology and the drug diffusivity in the coating films on the drug release characteristics were examined, while the initial drug loading is assumed to be saturated in the device and the average thickness of the coating films remains unchanged. The profiles of dimensionless drug concentrations and initial lag times of drug release are found to be very sensitive to the change of the perturbation parameter that is used to quantitatively describe the degree of the shape deformations on the coating films. In contrast, the effect of the shape deformation is not so substantial on the fractional release and the average release rate. Similarly, morphology of coated particles also influences the release characteristics to different extents.

It has to be pointed out that in our previous study the average thickness of coating films, i.e. the layer thickness of the diffusion barrier, re-

mains constant (Chen and Lee, 2001). Hence, it will be of fundamental interest to understand the effect of the change in the average thickness of coating films on these release characteristics.

It is thus the purpose of this work, a continuation of our previous work on the slow diffusional release of the drug (Chen and Lee, 2001), to attempt to provide insights on the combined effects of the average thickness and the morphology of the coating films on the slow controlled-release of the drug from the reservoir-type devices. The factor of varying the average thickness of the coating films is taken into account in the calculation along with the different morphology of the coating films, accordingly, at the same time as the drug diffusivity is kept constant and the initial drug concentration in the device maintains at saturation concentration. The effect due to the change in the average thickness of the coating films on the characteristics of the slow controlled-release is discussed to shed light on the design of a better controlled-release device.

2. Theoretical section

The present work is a continuation of our previous work (Chen and Lee, 2001), so there are many similarities in the logic of the equation derivations. For the sake of simplicity, only key equations that are useful in understanding the mathematical details are provided.

The geometry of the coated particles is schematically shown in the Fig. 1. A drug is dispersed in a spherical matrix with a radius b, which is coated by a thin layer (free of drug initially) to form a particle with a shape function $R(\theta)$. The initial drug concentration in the matrix is C_0 that is equal to or less than the saturation concentration. This particle is immersed in a well-stirred extraction medium of infinite volume to release the drug. This is commonly referred to as the 'perfect sink condition'. The shape function $R(\theta)$ is assumed to be symmetrical along the ϕ-coordinate while their mean value is a constant denoted as a or R_o.

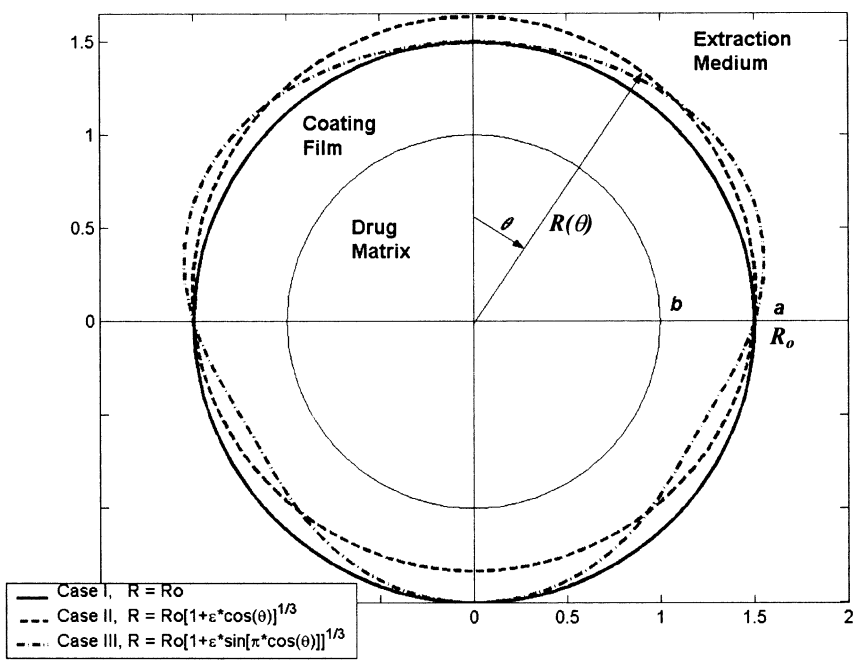

Fig. 1. Schematic drawing of the geometry of the coated particles.

2.1. Basic equations

In this work, the drug concentration is assumed to be symmetrical along the ϕ-coordinate and the drug diffusivities in the matrix D_m and in the coating film D_f are constant. The basic equation for the drug concentrations in the matrix C_m and in the coating film C_f can be simplified as follows (Crank, 1975):

$$\frac{\partial(rC_f)}{\partial t} = D_m \frac{\partial^2(rC_m)}{\partial r^2} + \frac{D_m}{r}\frac{\partial}{\partial \mu}\left[(1-\mu^2)\frac{\partial C_m}{\partial \mu}\right], \quad 0 < r < b \tag{1a}$$

$$\frac{\partial(rC_f)}{\partial t} = D_f \frac{\partial^2(rC_f)}{\partial r^2} + \frac{D_f}{r}\frac{\partial}{\partial \mu}\left[(1-\mu^2)\frac{\partial C_f}{\partial \mu}\right], \quad b < r < R(\theta) \tag{1b}$$

where $\mu = \cos(\theta)$. The initial conditions are:

$$C_m(r, \theta, 0) = C_0, \quad 0 < r < b \tag{2a}$$

$$C_f(r, \theta, 0) = 0, \quad b < r < R(\theta) \tag{2b}$$

where C_0 is equal to or less than the saturation concentration and b is the mean radius of drug matrix. The associated boundary conditions are:

$$C_m(0, \theta, t) \text{ is finite}, \tag{2c}$$

$$K_d C_f(b, \theta, t) = C_m(b, \theta, t), \tag{2d}$$

$$D_m \left.\frac{\partial C_m}{\partial r}\right|_{r=b} = D_f \left.\frac{\partial C_f}{\partial r}\right|_{r=b}, \tag{2e}$$

$$C_f(R(\theta), \theta, t) = 0 \tag{2f}$$

where K_d is the partition coefficient for drug between the drug matrix and coating film.

2.2. Equations in dimensionless forms

Dimensionless equations can provide a better view of the release characteristics, regardless of the dimensions in the physical systems. With the dimensionless groups defined below:

$$\theta_m = \frac{C_m}{C_0}, \quad \theta_f = \frac{C_f}{C_0}, \quad \tau = \frac{D_m t}{b^2}, \quad \eta = \frac{r}{b},$$

$$D_r = \frac{D_f}{D_m}, \quad L = \frac{R(\theta)}{b}, \quad \text{and} \quad L_\mu = \frac{R_\mu(\mu)}{b}$$

the basic Eqs. (1a) and (1b) can be rearranged as

$$\frac{\partial(\eta\theta_m)}{\partial \tau} = \frac{\partial^2(\eta\theta_m)}{\partial \eta^2} + \frac{1}{\eta}\frac{\partial}{\partial \mu}\left[(1-\mu^2)\frac{\partial \theta_m}{\partial \mu}\right], \quad 0 < \eta < 1 \tag{3a}$$

$$\frac{\partial(\eta\theta_f)}{\partial \tau} = D_r \frac{\partial^2(\eta\theta_f)}{\partial \eta^2} + \frac{D_r}{\eta}\frac{\partial}{\partial \mu}\left[(1-\mu^2)\frac{\partial \theta_f}{\partial \mu}\right], \quad 1 < \eta < L_0 \tag{3b}$$

while the initial conditions, Eqs. (2a) and (2b), become

$$\theta_m(\eta, \theta, 0) = 1, \quad 0 < \eta < 1, \tag{4a}$$

$$\theta_f(\eta, \theta, 0) = 0, \quad 1 < \eta < L_0 \tag{4b}$$

and the boundary conditions, Eqs. (2c), (2d), (2e) and (2f), become

$$\theta_m(0, \theta, \tau) \text{ is finite}, \tag{4C}$$

$$K_d \theta_f(1, \theta, \tau) = \theta_m(1, \theta, \tau), \tag{4d}$$

$$\left.\frac{\partial \theta_m}{\partial \eta}\right|_{\eta=1} = D_r \left.\frac{\partial \theta_f}{\partial \eta}\right|_{\eta=1}, \tag{4e}$$

$$\theta_f(L, \theta, \tau) = 0. \tag{4f}$$

where θ_m and θ_f represents for the dimensionless drug concentrations in the drug matrix and the coating films, respectively; L and L_μ are the dimensionless shape functions of the coated particle as a function of θ and $\mu = \cos(\theta)$, respectively; τ and η stands for the dimensionless unit in time and radial direction; and D_r represents the dimensionless drug diffusivity in the coating film. D_r also stands for the ratio of drug diffusivity in the coating film to that in the drug matrix. It is of note that the drug diffusivity in the drug core has been reduced to one in this dimensionless system.

To satisfy the constraint that the volume of the coated particle is maintained constant, if the average thickness of the coating film being the same, the shape functions in this study are written as follows (Chen and Lee, 2001):

Case I:

$$L_\mu(\mu) = h, \quad \text{where } h = \frac{a}{b}.$$

Case II:

$$L_\mu(\mu) = h\sqrt[3]{1 + \varepsilon \cdot \mu}$$

Case III:

$$L_\mu(\mu) = h\sqrt[3]{1 + \varepsilon \cdot \sin(\pi\mu)}$$

where ε is the perturbation parameter to quantitate the degree of the deformation of the coated sphere. Notably the shape function is not linearly proportional to ε. Case I is corresponding to the undeformed system, while Case II and III are related to the deformed systems. The shape functions are arbitrary, if they satisfy the constraint. They are deliberately chosen to simulate the possible shapes of the coated particles made by the methods of fluidized-bed coating and melting coating (Jones, 1985; Mehta and Jones, 1985; Rhodes and Porter, 1998; Chen and Lee, 2001).

The average release rate can be expressed as follows:

$$W(\tau) = -2\pi(bC_0D_m)D_r\int_{\mu=-1}^{\mu=1}\left(\eta^2\frac{\partial\theta_f}{\partial\eta}\right)\Bigg|_{\eta=L_\mu(\mu)} d\mu \quad (5)$$

Its dimensionless form can be written as

$$W_D(\tau) = \frac{W(\tau)}{\int_0^{\tau\to\infty} W(\tau)d\tau} \quad (6)$$

The fractional release is then defined as

$$F = \int_0^{\tau} W_D(\tau)d\tau = \frac{\int_0^{\tau} W(\tau)d\tau}{\int_{\tau=0}^{\tau\to\infty} W(\tau)d\tau} \quad (7)$$

Eqs. (3a) and (3b) are simultaneous two-dimensional transient diffusion equations with the boundary shape deformed as $L_\mu = L_\mu(\mu)$, and are difficult to solve analytically. Instead, they are solved numerically by the finite element method with the maximum relative error of 10^{-6}. The fractional release is calculated accordingly.

3. Results

In this section, the results discussed are expressed in dimensionless units and based on the calculations from the systems of Case I, Case II and Case III with the various dimensionless radii of coated drug particles. The dimensionless radius of spherical drug matrix is always maintained constant at 1.0. The dimensionless drug diffusivity in the coating film D_r is set at 0.1 in this work, as the larger D_r will smoothen the differences on the release characteristics resulted from the effect of morphology (Chen and Lee, 2001).

Fig. 2 shows the profiles of cumulative fractional release and the average release-rates plotted, respectively, as a function of dimensionless time τ from the numerical results of the systems of Case I (undeformed systems) with the different average thickness of the coating films R_o. The drug diffusivity of the coating films $D_r = 0.1$ and the perturbation parameter $\varepsilon = 0.20$ are maintained constant for all the cases studied in the Fig. 2. With increasing the average thickness of the coating film R_o, the initial lag times on the drug release increase and it takes longer time for the coated drug particle to release the same amount of drug. For example, the initial lag times for the drug release increase from $\tau = 0.012$ with $R_o = 1.10$ to $\tau = 0.085$ with $R_o = 1.40$. It is easily understood that the drug takes time to diffuse into the extraction medium through the initially drug-free coating film. Thicker films imply longer diffusion path and more resistance in letting drugs pass through. Therefore, the initial lag times on the release profiles are more distinct among the systems with thicker films.

The dimensionless average release-rate is indeed the time-derivative of the fractional release. An increase in the average film thickness will lead to smaller initial release-rates and lesser magnitudes of average release-rates at maxima, as well as result in longer time to reach the maxima of the release-rates, as displayed on Fig. 2(b). That is, the phenomenon of the initial burst of drug is less evident in the systems with thicker coating films. For example, the magnitude of the dimensionless average release-rate at maximum is decreasing from 3.7 to 1.25, as R_o increases from 1.10 to 1.40. The corresponding time when the maximum occurs is increasing by 10-folds from 0.036 to 0.36, respectively. Times taken to reach 95% of total complete release also vary considerably. For example, the times taken to reach the 95% of the total release of the drug increase from $\tau = 0.77$ with $R_o = 1.10$ to $\tau = 1.65$ with $R_o = 1.40$. Additionally the fractional release differs significantly at shorter times.

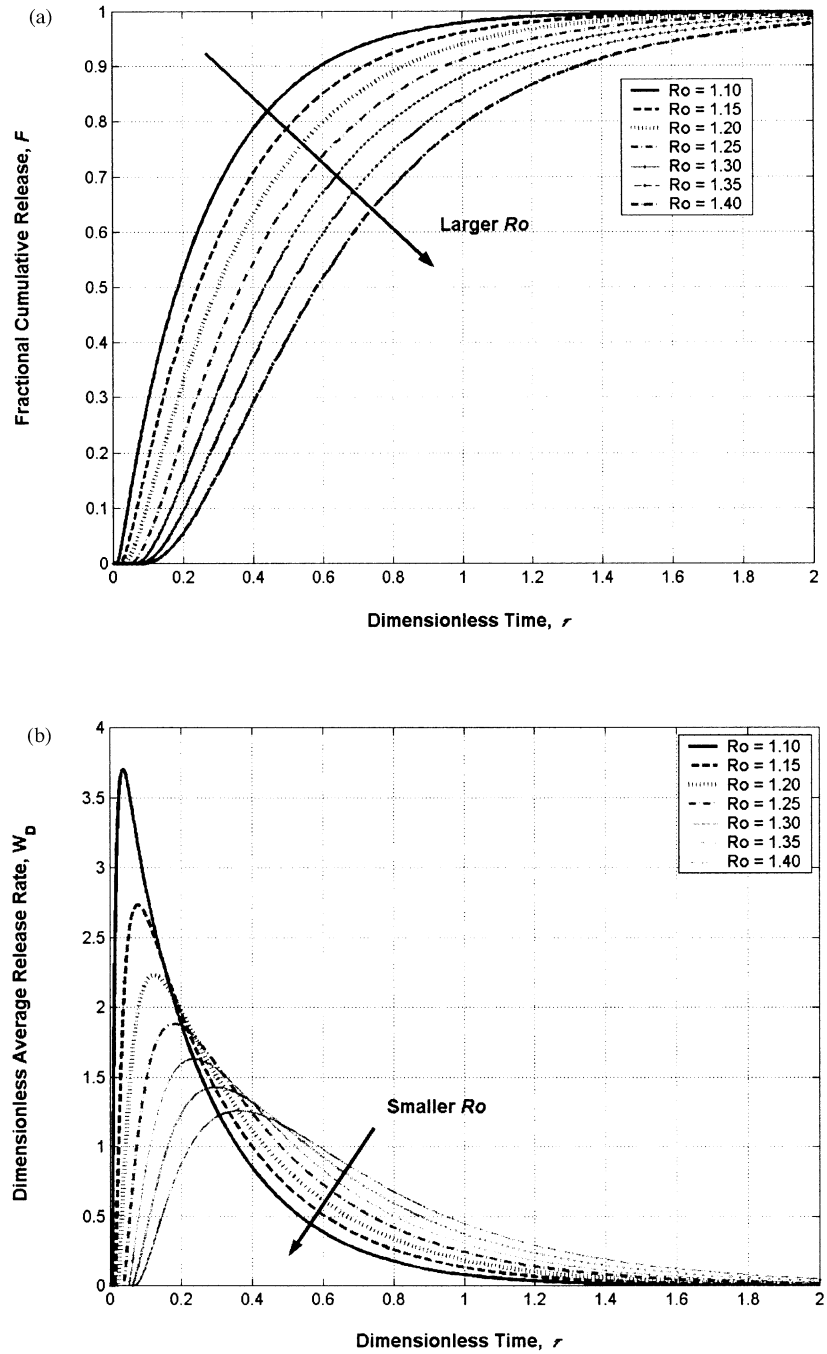

Fig. 2. Fractional release and dimensionless average release rates of the undeformed systems ($D_r = 0.1$ and $\varepsilon = 0.2$) with various average thicknesses, R_o, of the coating films. (a) Fractional release profiles. (b) Dimensionless average release rates.

The fractional release profiles and the average release-rates of the drug are drawn in the Figs. 3 and 4 for the deformed systems of Case II and Case III having the dimensionless drug diffusivity in the coating film $D_r = 0.1$ and the perturbation constant $\varepsilon = 0.2$, but with different film thickness in average. Profiles of fractional release corresponding to the undeformed system (Case I) with $R_o = 1.10$ are plotted, respectively, for comparison. The required times to reach the maxima of the average release-rates for the systems of Case II and Case III are slightly reduced to about 0.035 for both systems when $R_o = 1.10$ and near 0.34 when $R_o = 1.40$. The corresponding magnitudes of the maxima on the average release-rates are reduced slightly to 3.68 for both systems when $R_o = 1.10$, and 1.23 and 1.24 for Case II and Case III, respectively, when $R_o = 1.40$. It is clear that, similar to the undeformed systems on Fig. 2, the increasing average thickness of the coating films has also profound influence on the release characteristics in the deformed systems.

These observations are more noticeably demonstrated in the Figs. 5–7. The initial lag times are less in the deformed systems of Case II and Case III than that in the undeformed system of Case I having the same average thickness of coating films and the same dimensionless drug diffusivity in the coating films. However, the differences become less obvious for the systems with thicker coating films. It has to be declared that the results shown on Fig. 5 have been reported in our previous work (Chen and Lee, 2001). However, to demonstrate the effect of the coating films in different thickness on the characteristics of the slow diffusional release processes, it is informative to display these results again for comparisons and to demonstrate the effect of varying the average film thickness on the release characteristics.

Fig. 5(a) and (b) exhibit the fractional release profiles and the relative deviations of the dimensionless local mass fluxes from the specifically chosen systems of Case II and Case III with $D_r = 0.1$, $\varepsilon = 0.2$ and $R_o = 1.10$. For comparison, the fractional release profile from the system of Case I with the same conditions is also depicted on Fig. 5(a). It takes 0.769 unit of dimensionless time to reach 95% of complete drug release in the undeformed system (Case I), while the deformed systems of Case II and Case III require 0.733 and 0.7 in dimensionless time unit, respectively. The initial lag times for the deformed systems of Case II and Case III are lessened from $\tau = 1.37 \times 10^{-3}$ and $\tau = 1.2 \times 10^{-3}$, respectively, to $\tau = 0.012$ for that corresponding to the undeformed system of Case I. The required times for the systems of Case I, Case II and Case III to reach the maximum average release-rates are different at $\tau =$ 0.037, 0.034 and 0.025, respectively (see Table 1).

The relative deviations in the local mass fluxes between the deformed and undeformed systems are drawn on Fig. 5(b). The relative deviation is defined in percentage as $(J - J_0)/J_0 \times 100\%$, where J and J_0 denote for the mass fluxes by diffusion of the deformed and undeformed systems, respectively. Explicitly, the deviation is the relative change of the diffusion flux of the deformed system to that of the undeformed system. It is noteworthy to mention that the magnitudes of the relative deviations in the mass fluxes shown in the Fig. 5(b) and subsequently on Fig. 6(b) and Fig.

Table 1
Times of initial lags, times taken to reach the maxima of the average release rates and times taken to reach the 95% of total complete release

		95%	Maxima	Initial lag
$R_o = 1.10$,	Case I*	0.769	0.037	0.012
$\varepsilon = 0.20$	Case II	0.733	0.034	1.37×10^{-3}
	Case III	0.700	0.025	1.20×10^{-3}
$R_o = 1.15$,	Case I*	0.926	0.079	0.020
$\varepsilon = 0.20$	Case II	0.905	0.073	3.9×10^{-3}
	Case III	0.891	0.070	3.5×10^{-3}
$R_o = 1.20$,	Case I*	1.063	0.124	0.030
$\varepsilon = 0.20$	Case II	1.057	0.116	7.0×10^{-3}
	Case III	1.042	0.115	6.3×10^{-3}

The diffusivity of the coating film is 0.1, and the perturbation parameter ε is maintained at 0.20. Case I* represents the systems coated with spherical films without deformations ($\varepsilon =$ 0). 'Maxima' represents for the times taken to reach the maxima of the average release rates and '95%' for the times required reaching 95% of total complete release rates.

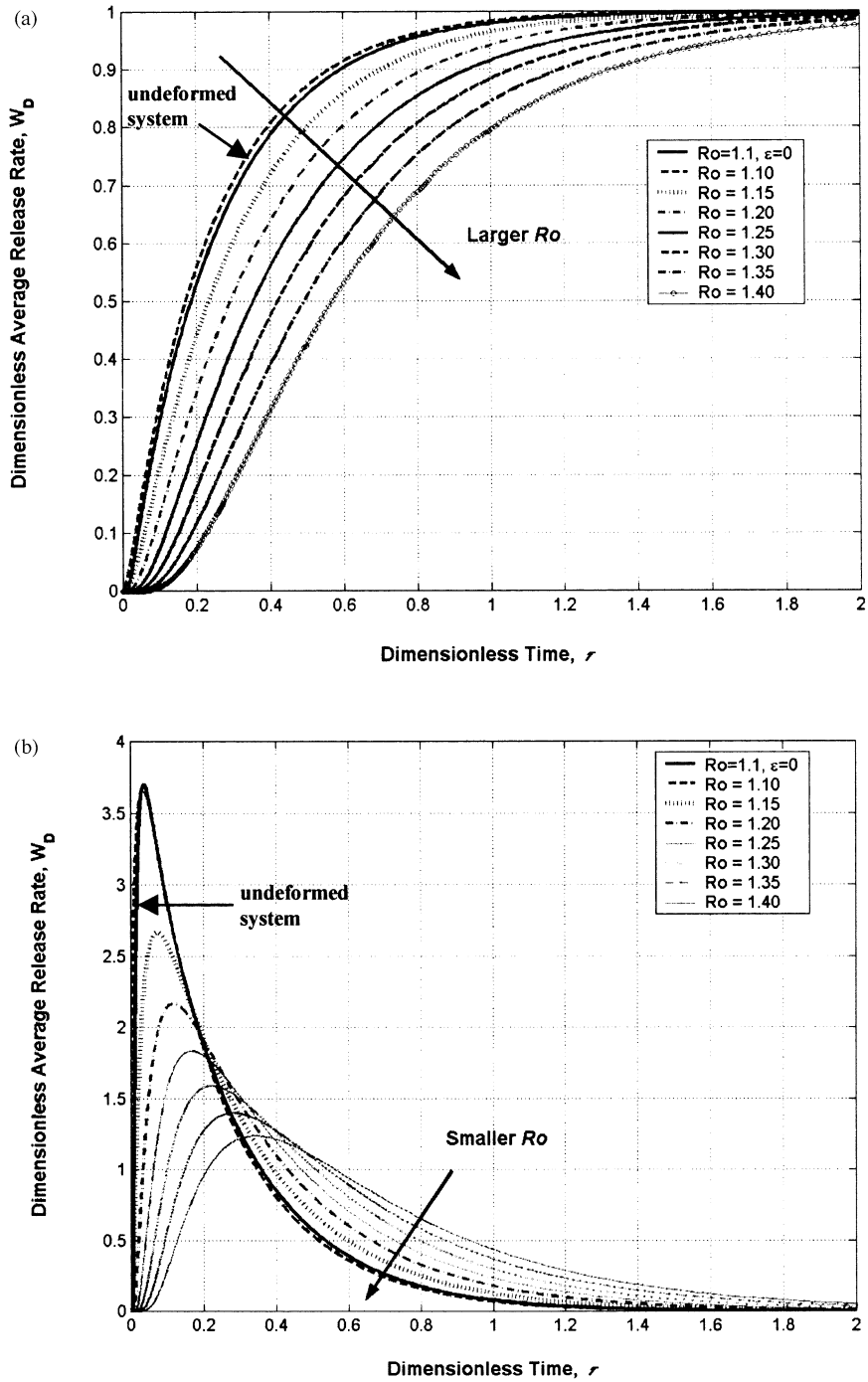

Fig. 3. Fractional release and dimensionless average release rates of the systems of Case II ($D_r = 0.1$ and $\varepsilon = 0.2$) with various average thicknesses, R_o, of the coating films. (a) Fractional release profiles. (b) Dimensionless average release rates.

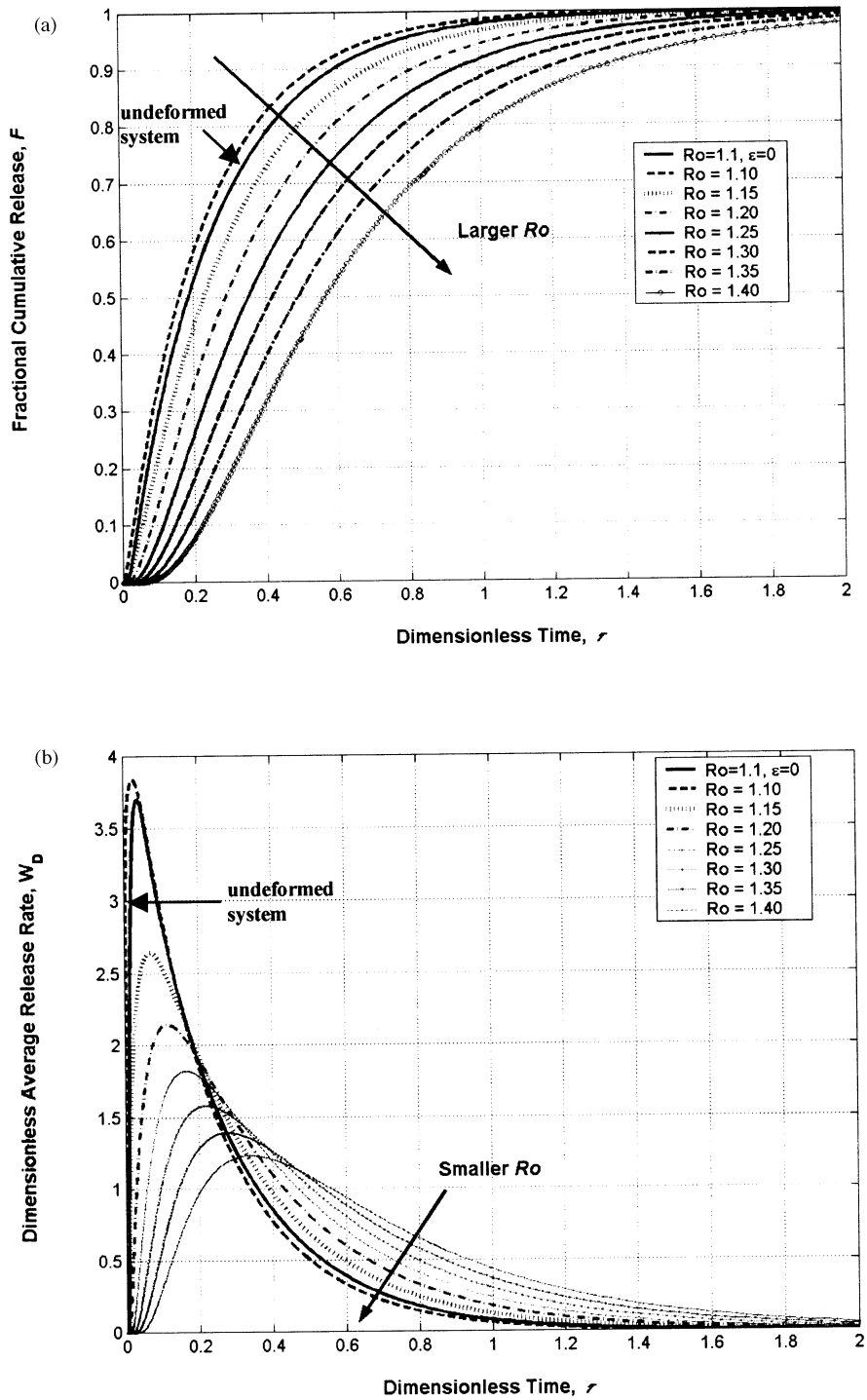

Fig. 4. Fractional release and dimensionless average release rates of the systems of Case III ($D_r = 0.1$ and $\varepsilon = 0.2$) with various average thicknesses, R_o, of the coating films. (a) Fractional release profiles. (b) Dimensionless average release rates.

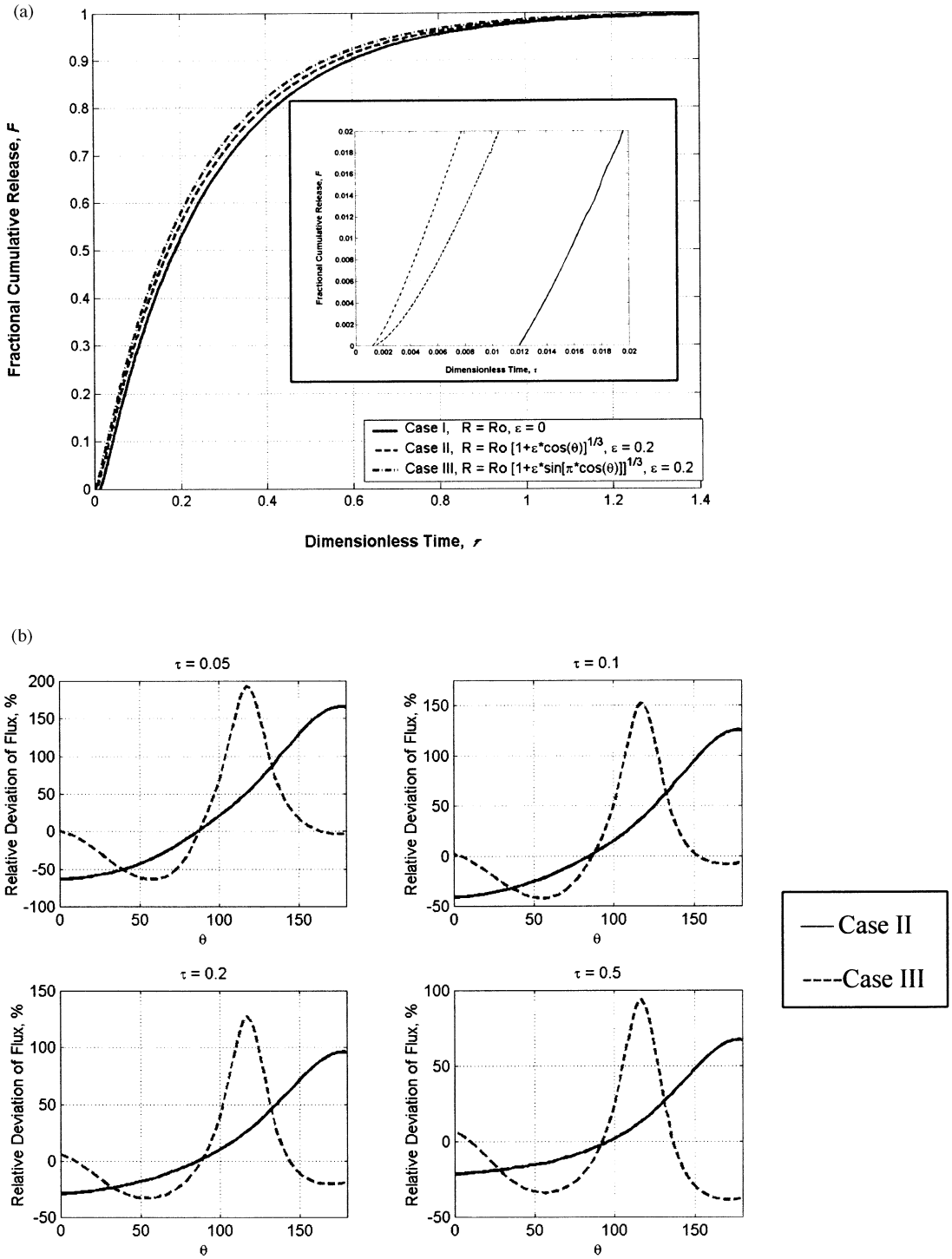

Fig. 5. Comparisons of fractional release profiles and deviations in the local dimensionless mass fluxes of the systems with $R_o = 1.10$, $D_r = 0.1$ and $\varepsilon = 0.2$. (a) Comparisons of fractional release. (b) Deviations in the dimensionless local mass fluxes.

7(b) are functions of time τ and angle θ. The greatest deviation in the mass fluxes happens at/near the South Pole (i.e. $\theta = 180°$) for the coated particles with the shape functions described by Case II. Its corresponding magnitude of the mass flux is enlarged by about 160% at $\tau = 0.05$. In contrast, the North Pole (i.e. $\theta = 0°$) always observes the minimum flux and the corresponding magnitude of the minimum flux is lessened only by about 60%. Likewise, it takes place at $\theta = 120°$ for the maximum flux in the system of Case III and the corresponding maximum flux is amplified by about 195% at $\tau = 0.05$, while the minimum happens at $\theta = 60°$ and the magnitude of the flux is declined by about 60%, too.

Both deformed systems of Case II and III have the minima or the maxima of the relative deviations in the local mass fluxes occurring at the locations where the thickest or the thinnest coating films are found. At the same release time, the magnitude of the maximum flux in the system of Case II is always slightly smaller than that in the system of Case III, while the magnitude of the minimum remains approximately the same. As a result, the drug is released faster in the system of Case III releases than in the system of Case II. However, the absolute magnitude of the increase in the maximum flux is always greater than that of the decrease in the minimum flux in all the systems.

Similar profiles of fractional release from the cases on Fig. 5(a) but with larger $R_o = 1.15$ and $R_o = 1.20$ are depicted as Fig. 6(a) and Fig. 7(a), respectively. The differences among fractional release profiles become less significant on Fig. 7(a) as the average film thickness increases. To reach 95% of total release, it takes a dimensionless time of 1.063 for the system of the Case I, and 1.057 for that of Case II and 1.042 for that of Case III. The times reaching maxima of the average release rates are $\tau = 0.124$, $\tau = 0.116$ and $\tau = 0.115$, and the corresponding times of initial lags are $\tau = 0.030$, $\tau = 0.007$ and $\tau = 0.0063$ for the systems of Case I, Case II and Case III, respectively (Table 1). It is clear that increasing the average film thickness significantly increases the initial lag times and the times taken to reach the maxima of average release rates or the 95% of the complete release. Likewise, despite not being shown here for $R_o = 1.40$, the initial lag times and the required times taken to reach the 95% of total release or the maxima of the average release rate increases significantly. However, the differences in the release characteristics due to the effects arising from the different morphology of the coated particles become less evident with increasing average thickness of the coating films. That is, the effects on these release characteristics are smoothened by increasing the average film thickness, similar to those due to the increase in the film diffusivities if the average thickness of the coated spheres is maintained constant.

Compared with a 160% increase in the maximum flux in the system of Case III at $\tau = 0.05$ on Fig. 5(b) and Fig. 6(b), the corresponding increase in the same system but with $R_o = 1.20$ at the same time on Fig. 7(b) is about 325%, while the deviations at larger times ($\tau \geq 0.2$) on Fig. 7(b) are lower than those on Fig. 5(b) at the same corresponding times. Interestingly, the relative deviations of the local mass flues shown on Fig. 6(b) fall between the values on Fig. 5(b) and Fig. 7(b) at the same corresponding times. At shorter release times, the relative deviations on Fig. 6(b) are closer to those on Fig. 5(b), in contrast that the values on Fig. 6(b) are closer to those on Fig. 7(b) at latter times during the course of release process. It is possibly attributed from the delay in the drug release in the systems with the thicker coating films, which is consistent to the observation on the larger initial lag times in the same systems. However, at larger times, the average release rates are slower in the systems with thicker films, which accounts for the less deviations in the local mass fluxes on Fig. 7(b) than that in the Fig. 5(b) at the same corresponding times. The locations of the maximum and minimum fluxes in both systems take place at the same spots as those on Fig. 5(b).

In general, the fastest dissolution of drug takes place in the systems of Case III among all the systems studied in this work, which have the same drug diffusivity, the same average film thickness and the same perturbation parameter.

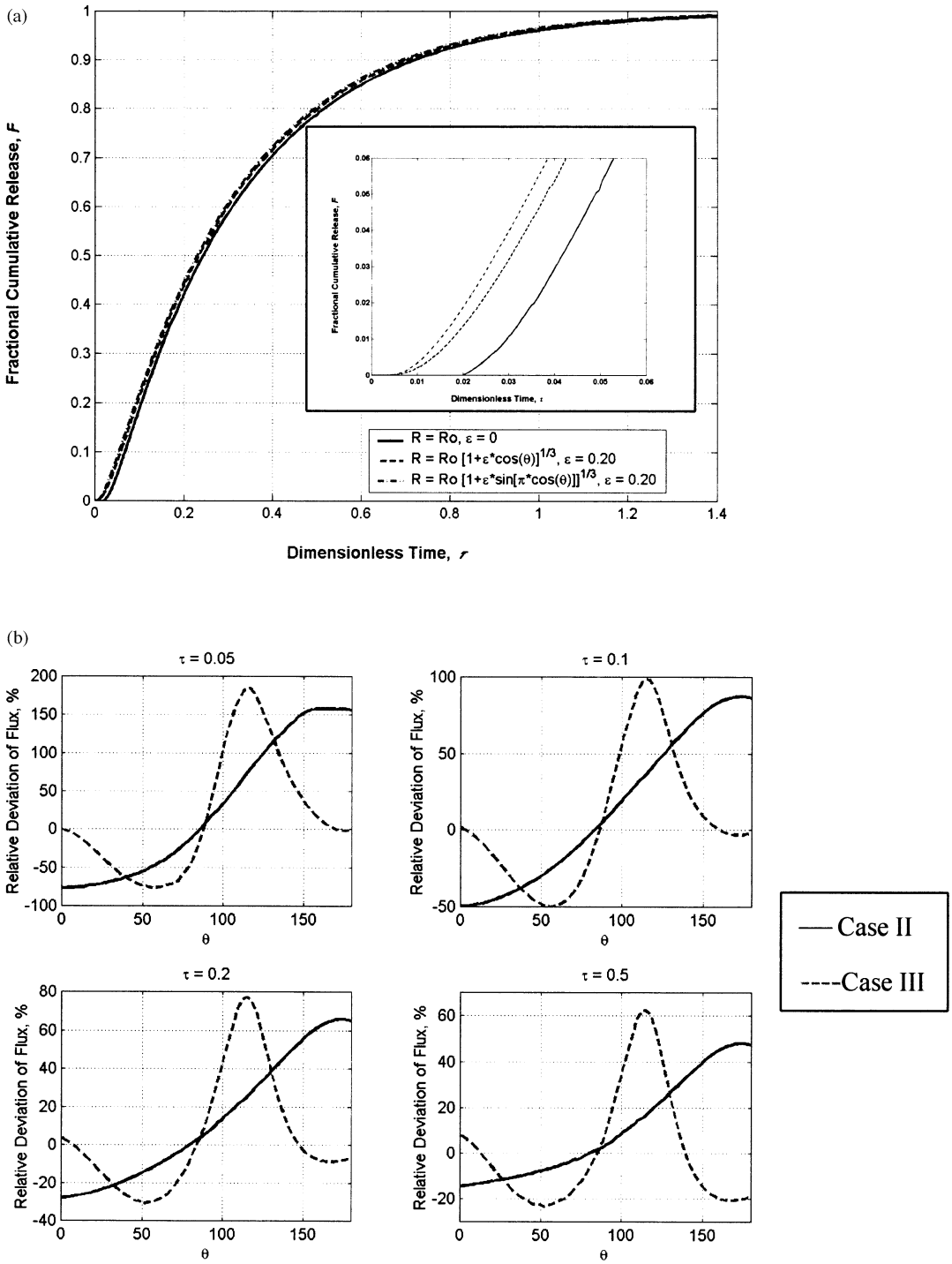

Fig. 6. Comparisons of fractional release profiles and deviations in the local dimensionless mass fluxes of the systems with $R_o = 1.15$, $D_r = 0.1$ and $\varepsilon = 0.2$. (a) Comparisons of fractional release. (b) Deviations in the dimensionless local mass fluxes.

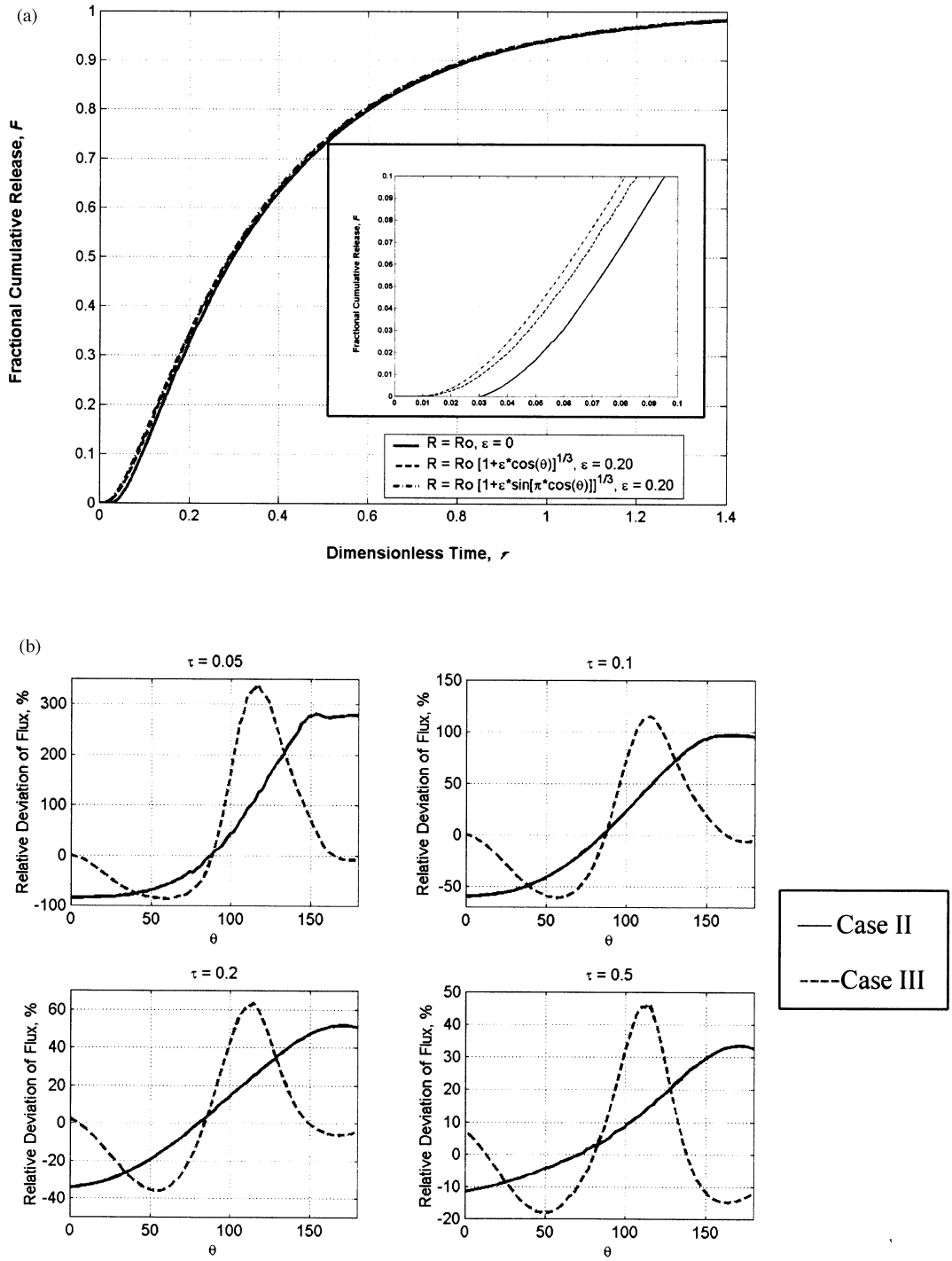

Fig. 7. Comparisons of fractional release profiles and deviations in the local dimensionless mass fluxes of the systems with $R_o = 1.20$, $D_r = 0.1$ and $\varepsilon = 0.2$. (a) Comparisons of fractional release. (b) Deviations in the dimensionless local mass fluxes.

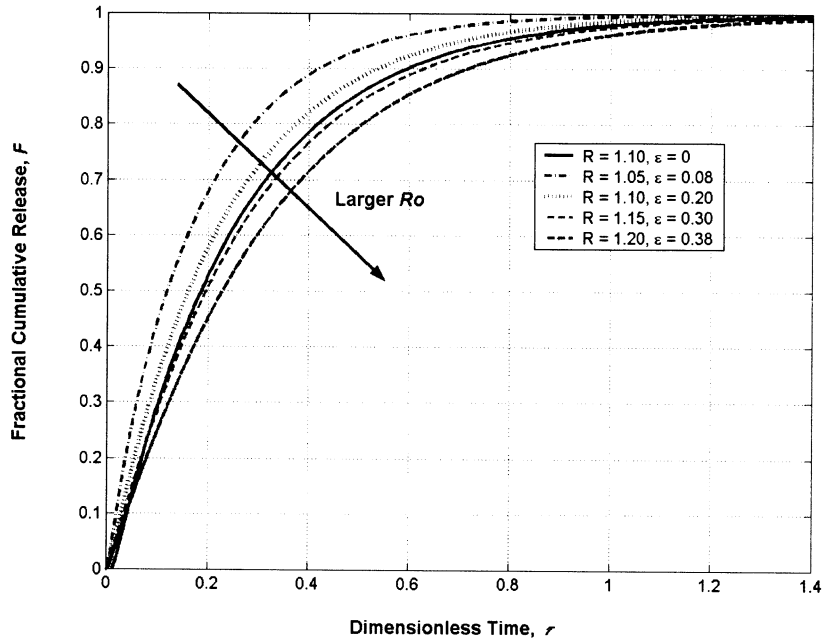

Fig. 8. Comparisons of fractional release profiles of the systems of Case III ($D_r = 0.1$) with the coating films having the same smallest thickness.

Fig. 8 shows the profiles of the fractional releases from the systems of the Case III ($D_r = 0.1$) having different average thickness of the coating films but the same minimum thickness. That is, the smallest thickness of these coating films is deliberately maintained at the same value by varying the perturbation parameters ε and the average thickness of the coating films. Release characteristics from these systems have been examined. Interestingly, the initial lag times are found to be equal. However, the rest of the release characteristics differ. The system with the smallest average thickness of the coating film releases the drug much faster than the other systems. It is clearly demonstrated that the initial lag time is dominated 'locally' by the scale of the smallest thickness of the coating films in the deformed systems, while the rest are determined 'globally' by the whole coated particles.

4. Discussion

It is interesting to observe that the locations of the maximum and minimum relative deviations of local fluxes, which is equivalent to the maximum and minimum local flux, occurs at the regions where the thickest and the thinnest coating films are located on the deformed coated particles. In addition, plateau on the curves of the relative deviations of local mass fluxes near the maxima are observed in the deformed systems, especially in those of Case II. The mass flux by diffusion, $-D\nabla C$, is not only inversely proportional to the distance of diffusion path, but also proportional to the difference of drug concentrations. Initially the concentration difference is the same throughout the coating films. The maximum and minimum relative deviations will take place at the regions having the thickest and thinnest films. For example, in the system of Case II, the fastest depletion of drug is taking place initially at $\theta = 180°$ (the South Pole). Thus, the difference in the drug concentrations through the coating film at that point is also decreasing. As a result, the mass fluxes near the South Pole have to become smaller and, therefore, the region with the maximum mass flux

has to expand to regions corresponding to the smaller θ, i.e. regions with thicker coating films.

In this work the amount of the drug in the drug matrix is deliberately kept constant. The amount of fractional release is indeed the time integral of the average release rate. That is, the area between the curves of the dimensionless average release-rate and the abscissa (the axis of dimensionless time) should be conserved as constant equal to the amount of the drug initially present. If a coated particle release drug faster initially and hence has a larger magnitude of the average release rate at maximum. At the latter times during the course of release process, its average release rate has to fall below that of the other coated particle that has smaller average release rate initially. These are clearly observed on Fig. 2(b), Fig. 3(b) and Fig. 4(b).

As mentioned and discussed in our previous work (Chen and Lee, 2001), a possible conjecture is proposed here to explain the effects on the release characteristics owing to the different thickness and morphology of the coating films. The mass flux due to diffusion and the effective surface area for mass-transfer between coated particle and the extraction medium are the two main factors influencing most of the release characteristics. The average release rate of the coated drug particle is the product of the above two factors and its time integral gives the amount of fractional release.

With concentrations kept constant at both ends of diffusion path, shorter path will give a larger diffusion flux. That is, the reciprocal of the film thickness could be regarded as an indicator on the magnitude of the diffusion flux (Chen and Lee, 2001). The maximum diffusion flux in the deformed system is always greater that that of the undeformed system, as the thinnest thickness of the coating film is always less than that of the undeformed system of which film thickness is equal to the average thickness for both deformed systems. That is, the driving force due to diffusion for the drug is much larger over there. Under these circumstances, the drug diffuses faster and travels shorter to the extraction medium at the thinnest regions. As a result, the deformed systems will have less initial lag times on the release processes.

The aforementioned explanation can be successfully to elucidate the discoveries on Fig. 8, which clearly demonstrates that the initial lag times are governed 'locally' by the magnitude of the shortest diffusion path over the coating films and have the same values for all the cases having the same values of the smallest thickness of the coating films despite the different average thickness and the different morphology. In other word, the systems in the Fig. 8 have the same shortest diffusion path in the coating films or, equivalently, the equal driving potential on diffusion, i.e. the equal diffusion flux, initially. Therefore, the drug will take the same time to reach the extraction media initially. It is noteworthy of mentioning that fact that the curves of the fractional release of the drugs indeed differ a lot after the initial lag times.

Additionally on Fig. 8, the magnitudes of the diffusion fluxes initially at the thinnest points of the coating films, which is proportional to the reciprocal thickness, are about 2.4 times than that of the average initially with $R_o = 1.05$, about 4.7 times with $R_o = 1.10$, about 7.1 times with $R_o = 1.15$ and about 9.5 times with $R_o = 1.20$. If the release behaviors of the drugs in the systems of the Fig. 8 are all dominated by the fastest release at the regions near the thinnest thickness, the release behaviors should hold the same. Indeed, the fractional release of the drug on the system with $R_o = 1.05$ is the fastest one. One possible reason is that the coating films on such system ($R_o = 1.05$) are considerably thin compared with the other systems. The drug will not diffuse out only from the thinnest region but also somewhere on the coating films, as they will not encounter higher resistance to diffuse through the coating films. Interestingly the initial lag time is more dominated locally by the smallest thickness of the coating films, while other characteristics of the drug release are dependent globally on the physical characteristics of the coating films, such as the average film thickness and the film morphology as well as the drug diffusivity and the degree of shape deformation.

In the previous work (Chen and Lee, 2001), it demonstrated that the deformation and the morphological difference of the coating films would enhance the diffusional releases of the drugs at the systems with the smaller drug diffusivities in the coating films. The effects due to the larger deformations of the coating films give rise to the much faster diffusion fluxes, which could compensate for the slight loss in the effective area for mass transfer. Similar to the effects resulting from the larger drug diffusivities in the coating films, the differentiations among the fractional release curves are smoothen out with the increasing average thickness of the coating films. It is possibly due to the smaller magnitudes of the diffusion fluxes with thicker films. One may argue that the effective area for mass transfer, indeed, increases with the larger coated spheres. That is true, however, under the conditions of the 'perfect sink', the drugs have to diffuse out radially for effective drug release (see the appendix of reference by Chen and Lee, 2001, for proof). Increasing the film thickness will increase the effective area for the mass transfer but decreases the magnitude of the diffusion flux. Ideally, the rates of the controlled-release will remain constant if the drug diffusivity in the coating film is equal to that of the drug matrix. However, due to the different morphology, it creates the heterogeneity on the mass fluxes. Under these circumstances, the drugs will preferentially diffuse out through the regions that allow the faster release. Similarly, increasing the film thickness will reduce the magnitudes of the mass fluxes and, thus, reduce the heterogeneity of the fluxes, which eventually lead to no difference in the fractional release of the drugs in the system of Case II and III having the same drug diffusivity and the perturbation parameter but larger average thickness of the coating films.

Finally, the ideal controlled-release device is designed to obtain the desirable zero-order release kinetics, in which the release amount is linearly proportional to the release time. However, the diffusional release is of the first-order. It goes after an initially high release-rate followed by the fast declining rate of drug release (Higuchi, 1961, 1963). That is, the initial burst effect is inevitable in such diffusional release, which is undesirable and can be possibly reduced by increasing the average thickness of the coating film. By combining the knowledge from the effects of morphology and the shape deformations as well as the drug diffusivity in the coating films on the characteristics of drug release, one may possibly design a controlled-release device with near zero-order release.

5. Conclusions

The effect of the morphology and the average thickness of the coating films on the slow diffusional release characteristics have been analyzed numerically under the constraints that the volume of the drug matrices is maintained constant and that the volume of the coating films is kept the same for the coated particles with the same average thickness of coating films. Increase in the average thickness of the coating films retards the fractional release and average release rate of the drug and level out the initial burst of the drug as well as delays the initial release of the drug. For example, increasing the film thickness from that equal to 10% of the radius of the drug matrix to 40% of that, the fractional release of the drug is slowed down as much as from 0.92 to 0.55 at the dimensionless time $\tau = 0.6$, while the initial lag times increase significantly as much as from $\tau = 0.001$ to $\tau = 0.035$.

The results of this study demonstrate that the variations of the average release rate and the fractional release remain unaffected among the deformed and undeformed systems, if the average film thickness is large enough (for example, $R_o \geq 1.20$ for $\varepsilon = 0.20$ and $D_r = 0.1$). That is, the effect due to the increase in the average film thickness will become less effective on differentiating the drug release characteristics resulted from the morphological change of the coating films.

Interestingly initial lag times, unlike other release characteristics, are found to be influenced only by the magnitude of the smallest thickness of the coating films. That is, the initial lag times will be the same for the coated particles having the same drug diffusivity and the same smallest thickness but different average thickness of coating films.

To design a good controlled-release device, any factor in the film thickness, the drug diffusivity in the coating film, the film morphology and the degree of shape deformation cannot be left out as, indeed, all of them are coupled together.

6. Nomenclature

a, R_o mean radius of the coated particle (m)
b mean radius of drug core (m)
C_i drug concentration; $i = $ m, f denoted for that in drug core and that in coating film; $i = 0$ denoted for initial drug concentration (kg mol/m^3)
D_i drug diffusivity; $i = $ m, f for that in drug core and that in coating film (m^2/s)
D_r dimensionless drug diffusivity in the coating film ($= D_f/D_m$) (−)
F fractional cumulative release (−)
J the mass flux by diffusion in the deformed system (−)
J_0 the mass flux by diffusion in the undeformed system (−)
K_d distribution constant for drug core and coating ($= C_m(R(\theta), t)/C_f(R(\theta), t)$) (−)
$L(\theta)$ $R(\theta)/b$ (−)
$L_\mu(\mu)$ $R_\mu(\mu)/b$ (−)
r radial element in spherical polar coordinate (−)
$R(\theta)$ deformed shape function as a function of θ (m)
$R_\mu(\mu)$ deformed shape function as a function of μ, m; $R(\theta) = {}_\mu(\mu)$
t time (s)
W average release rate (kg mol/s)
W_D dimensionless average release rate (−)

Greek letters

ε perturbation parameter (−)
ϕ one of the angular elements in spherical polar coordinate (−)
η dimensionless radius $= r/b$ (−)
μ $\cos(\theta)$ (−)
θ polar angle and one of the angular elements in spherical polar coordinate (−)
θ_i dimensionless drug concentration; $i = $ m, f denoted that in the drug core and that in the coating film (−)
τ dimensionless time, ($D_m t/b^2$, −)

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