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Inward release polymer matrix covered by a permeable membrane: a possible zero-order controlled release device

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Abstract

An inward release polymer matrix with its aperture covered by a drug-permeable membrane is proposed as a potential zero-order controlled release device. The presence of the membrane has the effects of modifying the rate of release so that it is closer to zero order, and alleviating the problem of initial burst. Applying a Landau transformation, the present moving boundary problem is transformed in to a fixed boundary one, and the resultant problem is solved numerically by a finite difference scheme. We show that assuming drug release occurs under a pseudosteady-state condition is appropriate if the ratio (inner radius of device/outer radius of device) is small and/or the mass transfer resistance of the membrane is large. The applicability of two kinds of pseudosteady-state assumptions is discussed. The performance of the pseudosteady-state based on the rate of release is better than that based on the moving front. The region of the present device where the rate of release remains constant increases with the decrease in the ratio (inner radius of device/outer radius of device) and/or the increase in the mass transfer resistance of the membrane. Also, the higher the degree of overloading the longer the device is capable of maintaining a zero-order release rate.

Keywords: Controlled release; Zero-order kinetics; Inward release; Moving boundary problem; Polymer matrix; Drug-permeable membrane

1. Introduction

To maintain drug level in the therapeutic range, thereby avoiding the ineffectiveness or toxic effect, a zero-order controlled release device is highly desirable in drug delivery. However, the design of monolithic systems can be nontrivial. In particular, the problems of initial burst suppression and compensation for an increase in diffusion path with time are difficult to solve. Considerable works have been conducted to achieve a constant rate of release (Langer and Peppas, 1983; Pillay and Rassihi, 1999). These include, for example, swelling/erosion-controlled systems based on hydrophilic polymers (Kim, 1999), electrolyte-induced compositional heterogeneity as a peripheral matrix-stiffening phenomenon (Pillay and Rassihi, 2000), and multi-layer barriers such as Geomatrix® technology (Maggi et al., 2000). In practice, the performance of these methods depends on the nature of the drugs and polymer materials.

Monolithic systems with a simple uniform drug matrix are in fact of interest as a result of ease in manufacture for versatile classes of drugs. The changes of geometries are desirable to improve the release kinetics. Unfortunately, diffusion-controlled systems of simple geometries such as slabs, cylinders, and spheres usually do not lead to zero-order release because of the gradual decay of drug concentration with time. Inwardly releasing hemispheres (Hsieh et al., 1983; Rhine et al., 1980; Siegel, 2000), tapered disks (Bechard and McMullen, 1988), and donut-shaped tablets (Hansson et al., 1988; Kim, 1999) have been demonstrated to achieve a constant release rate. From the mathematic point of view, all of these methods belong to inward release of a part of a sphere, and the zero-order release kinetics are accomplished by an increase in the surface area of the

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dissolution front to compensate the increase of diffusion length.

In this study, an inward release polymer matrix with a drug-permeable membrane is proposed as a potential zero-order controlled release system. In addition to the merit of an inward hemispheric release device, the present device has the advantage of reducing the initial burst effect. The moving boundary problem is solved numerically and conditions under which a PSS approximation is applicable are discussed.

2. Analysis

Referring to Fig. 1, the controlled-release device considered is a fraction of sphere defined by the solid angle Ω, the inner spherical surface of radius a_i, and the concentric outer spherical surface of radius a_o. The interior of the device is a polymer matrix and all its surfaces are insulated to the drug except the inner spherical surface, which is coated with a drug-permeable membrane layer. The drug is loaded uniformly in the matrix at a concentration c_0. Let c_s be the saturated concentration with $c_0 > c_s$. As the drug is released from the device, a moving front is established. Note that if $c_0 < c_s$, then we have a fix-boundary problem. The bulk concentration of drug c_b is supposed to remain constant. To make the model development and analysis simpler, the concentration of the drug can be described in scaled forms by

$$\frac{\partial C}{\partial T} = \frac{1}{R^2}\frac{\partial}{\partial R}\left(R^2\frac{\partial C}{\partial R}\right), \tag{1}$$

$$C(R_m, T) = 1, \quad R_m < 1, \tag{2}$$

$$\left.\frac{\partial C}{\partial R}\right|_{R=R_m} = 0, \quad R_m = 1, \tag{3}$$

$$\left.\frac{\partial C}{\partial R}\right|_{R=R_i} = \Gamma C, \tag{4}$$

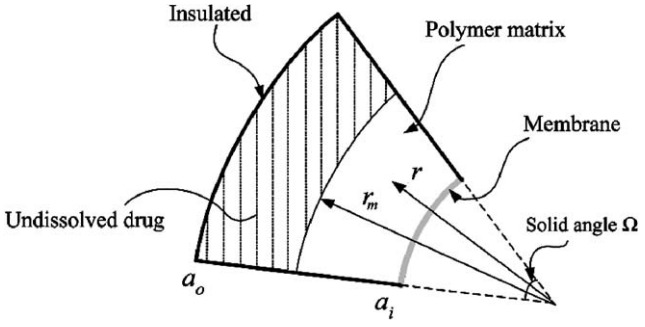

Fig. 1. The controlled-release device is a fraction of a sphere defined by the solid angle Ω, the inner spherical surface of radius a_i, and the concentric outer spherical surface of radius a_o. The interior of the device is a polymer matrix and all its surfaces are insulated to the drug except the inner spherical surface, which is coated with a drug-permeable membrane layer.

where $\Gamma = Ka_0/D$, $\rho = (c_0 - c_s)/(c_s - c_b)$, $C = (c - c_b)/(c_s - c_b)$, $T = tD/a_0^2$, $R = r/a_0$, $R_i = r_i/a_0$, and $R_m = r_m/a_0$. In these expressions, r_m denotes the position of the moving front, which separates the dissolved drug and the undissolved drug, and K is the product of the distribution coefficient and the mass transfer coefficient of the drug in the membrane. Here, Γ is a measure of the ratio (mass transfer resistance in polymer matrix/mass transfer resistance of membrane) and ρ is the ratio (maximum overloaded drug concentration difference for diffusion). The scaled temporal variation of R_m can be determined by a mass balance on the amount of drug as

$$\frac{dR_m}{dT} = \frac{1}{\rho}\left.\frac{\partial C}{\partial R}\right|_{R=R_i}, \tag{5}$$

$$R_m(0) = R_i. \tag{6}$$

The scaled rate of drug release Q can be expressed as

$$Q = \frac{q}{M_o} = \frac{3R_i^2}{(1 - R_i^3)(1 + \rho)}\left.\frac{\partial C}{\partial R}\right|_{R=R_i}, \tag{7}$$

where $M_0 = \Omega(a_0^3 - a_i^3)c_0/3$ is the total amount of drug loaded. Note that if $R_i \to 1$, the present device becomes a slab. In this case, the scaling factor a_0 should be replaced by $a_0 - a_i$. If ρ is large, the solid–liquid interface, that is, the moving front, moves slowly relative to the diffusion of the dissolved drug, and a PSS approximation is applicable. On the other hand, if ρ is small, then it is inadequate. If we let $\eta = (R - R_i)/(R_m - R_i)$ and $U = RC$, then the moving-boundary domain $\{R, T\}$ is transformed into the fixed-boundary domain $\{\eta, R_m\}$ (Landau, 1950), and it can be shown that Eqs. (1)–(7) become

$$\frac{\partial U}{\partial R_m} = \frac{\rho R_m}{(R_m - R_i)(\partial U/\partial\eta)_{\eta=1} - (R_m - R_i)^2}\frac{\partial^2 U}{\partial\eta^2} + \frac{\eta}{R_m - R_i}\frac{\partial U}{\partial\eta}, \tag{8}$$

$$\frac{\partial U}{\partial\eta} = (R_m - R_i)\left(\frac{1}{R_i} + \Gamma\right)U, \quad \eta = 0, \tag{9}$$

$$U = R_m, \quad \eta = 1 \quad \text{and} \quad R_m < 1, \tag{10}$$

$$\frac{\partial U}{\partial\eta} = (1 - R_i)U, \quad \eta = 1 \quad \text{and} \quad R_m = 1, \tag{11}$$

$$\frac{dT}{dR_m} = \frac{\rho R_m}{1/(R_m - R_i)(\partial U/\partial\eta)|_{\eta=1} - 1}, \tag{12}$$

$$Q = \frac{3\Gamma R_i}{(1 - R_i^3)(1 + \rho)}U(\eta = 0). \tag{13}$$

After solving Eq. (8) for U, the cumulative fraction of release F can be evaluated by

$$F = \frac{R_m^3 - R_i^3}{1 - R_i^3} - \frac{3(R_m - R_i)}{(1 - R_i^3)(1 + \rho)} \times \int_0^1 (\eta(R_m - R_i) + R_i)U \, \mathrm{d}\eta. \quad (14)$$

The governing equations, Eqs. (8) and (12), are solved numerically subject to the boundary conditions, Eqs. (9)–(11) and (6), by a finite difference method. Note that U has a singular point at $R_m = R_i$, i.e., at the beginning of the drug-release process. This difficulty can be circumvented by solving Eqs. (2), (4), and (5) to obtain the initial relation between T and R. We obtain

$$\frac{\mathrm{d}T}{\mathrm{d}R_m} = \frac{\rho}{\Gamma}. \quad (15)$$

This expression can be used to estimate the initial relation between T and R_m during a very short period, and the singularity problem is circumvented. The concentration at R_i is first solved by Eq. (4); then, the initial distribution of drug in the interval $[R_i, R_m]$ can be estimated by interpolation. Note that if the interval $[R_i, R_m]$ is sufficiently small, the distribution of the drug in the interval $[R_i, R_m]$ is close to C_s, and the interpolation is appropriate. Once the singularity problem is solved, Eqs. (8) through (12) can be solved by a standard finite difference scheme.

3. Results and discussion

According to Eq. (5), if ρ is large, the solid–liquid interface represented by R_m moves slowly relative to the diffusion of dissolved drug, and the left-hand side of Eq. (1) can be ignored, i.e., a PSS approximation is applicable. In this case, it can be shown that

$$C = \frac{((1 + \Gamma R_i)R - \Gamma R_i^2)R_m}{((1 + \Gamma R_i)R_m - \Gamma R_i^2)R}, \quad R_i \leqslant R \leqslant R_m. \quad (16)$$

Substitution of this expression into Eq. (14) yields the cumulative fraction of release under PSS approximation

$$F = \frac{1}{(1 - R_i^3)(1 + \rho)(1 + \Gamma R_i - \Gamma R_i^2/R_m)} \times \left(\left(\rho(1 + \Gamma R_i) - (1 + \rho)\frac{\Gamma R_i^2}{R_m} \right)(R_m^3 - R_i^3) - \frac{3\Gamma R_i^2}{2}(R_m^2 - R_i^2) \right). \quad (17)$$

Here, F is expressed as a function of R_m. Note that the solution obtained under PSS approximation cannot be used directly to estimate the rate of drug release and the position of the moving front simultaneously since the mass of the drug is not conserved under PSS approximation. Therefore, the relationship between R_m and T can be determined either by a combination of Eqs. (7) and (17) or by Eq. (5) directly. In the first approach, the scaled rate of drug release is

$$Q = \frac{3\Gamma R_i^2}{(1 - R_i^3)(1 + \rho)(1 + \Gamma R_i - \Gamma R_i^2/R_m)}. \quad (18)$$

Following the treatments of Bechard and McMullin (Bechard and McMullen, 1988), Eq. (17) is differentiated with respect to R_m and the resultant expression is divided by Eq. (18). The expression thus obtained is integrated with respect to R_m using the initial condition equation (6). We obtain

$$T = \frac{1 + \Gamma R_i}{3\Gamma R_i^2}\rho(R_m^3 - R_i^3) - \frac{3\rho - 1}{6}(R_m^2 - R_i^2) - \frac{\Gamma R_i^2}{6(1 + R_i)}(R_m - R_i) - \frac{\Gamma^3 R_i^4 \mathrm{Ln}(R_m/R_i) + (2R_i + 3\Gamma R_i^2)\,\mathrm{Ln}(1 + \Gamma R_i - \Gamma R_i^2/R_m)}{6\Gamma(1 + R_i)^2}. \quad (19)$$

This expression is an extension of Higuchi model (Higuchi, 1961) to the case of a spherical inward release device. If the moving front is estimated based on a PSS assumption, then its temporal variation is obtained by substituting Eq. (16) into Eq. (5). We obtain

$$\frac{\mathrm{d}R_m}{\mathrm{d}T} = \frac{\Gamma R_i^2}{\rho((1 + \Gamma R_i)R_m - \Gamma R_i^2)R_m}. \quad (20)$$

Integrating this expression and applying Eq. (6), we obtain

$$T = \frac{(1 + \Gamma R_i)\rho}{3\Gamma R_i^2}(R_m^3 - R_i^3) - \frac{\rho}{2}(R_m^2 - R_i^2). \quad (21)$$

The results based on the above two PSS approximations are illustrated in Figs. 2 and 3. These figures reveal that the deviations of the results based on PSS approximation are appreciable when the level of overloaded drug ρ is small and/or the mass transfer resistance of the membrane $1/\Gamma$ is small. If ρ or $1/\Gamma$ is large, assuming that the PSS condition is appropriate, as illustrated in Fig. 3(b), implies that the PSS approximation is more appropriate when a membrane is present than when it is absent. Figs. 2 and 3 also reveal that the performance of the PSS based on the rate of release rate, Eq. (26), is better than that based on the moving front, Eq. (28).

The influence of the mass transfer resistance of the membrane on the release behavior is illustrated in Fig. 4. As can be seen in these figures, if the radius ratio R_i is small, the solid curve almost coincides with the dashed curve, i.e., the influence of Γ on the temporal variation of F is negligible. In other words, if R_i is small, whether the membrane is present or not is unimportant. As R_i increases, the dashed curve begins to separate from the solid curve, and the larger the R_i the more the difference between the two curves, that is, the more significant the presence of the membrane.

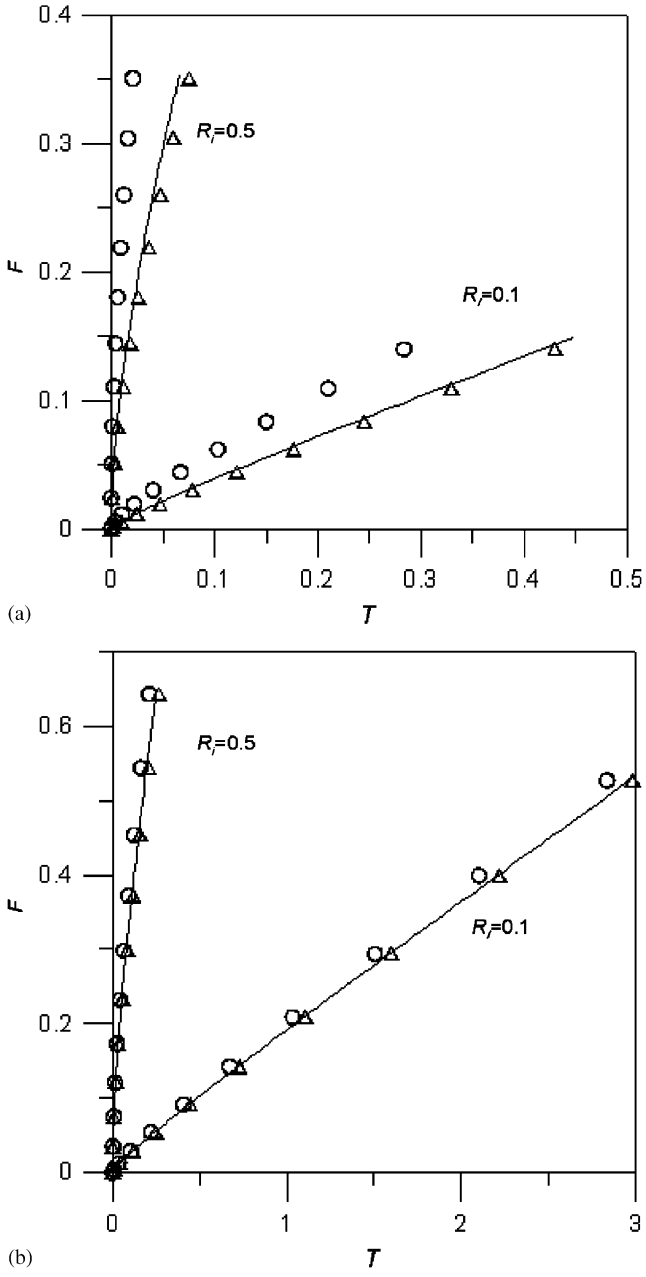

Fig. 2. Variations of cumulative release fraction F as a function of scaled time T at different R_i and ρ for the case when $\Gamma = 10^9$. (a) $\rho = 0.1$; (b) $\rho = 1$. Solid curve, exact solution, △, pseudosteady-state approximation based on Eqs. (17) and (19), ○, pseudosteady-state approximation based on Eqs. (17) and (21).

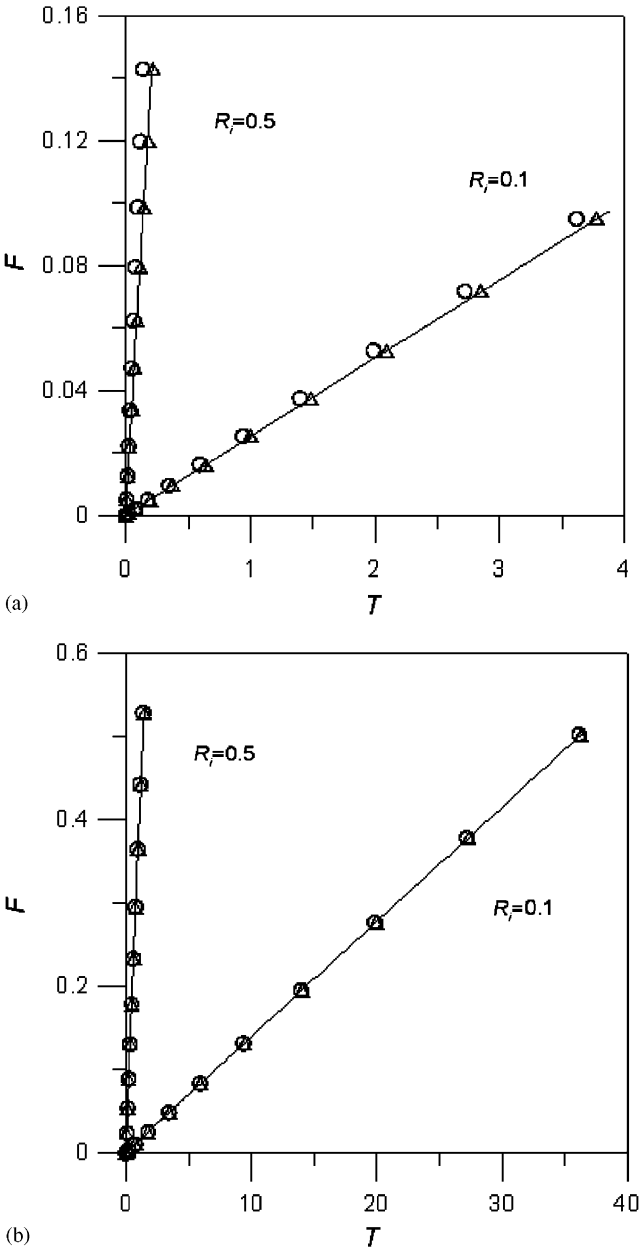

Fig. 3. Variations of cumulative release fraction F as a function of scaled time T for the case of Fig. 2 except that $\Gamma = 1$.

In fact, if R_i becomes large, the mass transfer resistance provided by the membrane helps the present device in achieving a zero-order release behavior, as illustrated in Fig. 5, where the scaled release rate, Q, is plotted against the cumulative release fraction, F. Fig. 5 shows that Q is nearly constant when R_i and/or Γ is small, i.e., the smaller the ratio (a_i/a_0) and/or the greater the mass transfer resistance of the membrane the closer the release rate to a constant. The observation that the larger the R_i (or smaller the a_0) of a device the greater the deviation of its release mechanism from zero order is because its geometry is closer to a plate. In fact, regardless of the magnitude of R_i, the plate-like behavior always exist except that the smaller the R_i the less appreciable this behavior. For a fixed a_i, a small R_i implies a large a_0. From the mass transfer point of view, whether a_0 is large or not will not affect the qualitative behavior of the present dissolution phenomenon until the moving front reaches a_0. Note that because the area of the moving front in the present inward release device increases with the increase in the diffusion length, it has the potential to achieve zero-order release kinetics. Fig. 5 also indicates that the problem of initial burst can be alleviated by a large mass transfer resistance provided by the membrane.

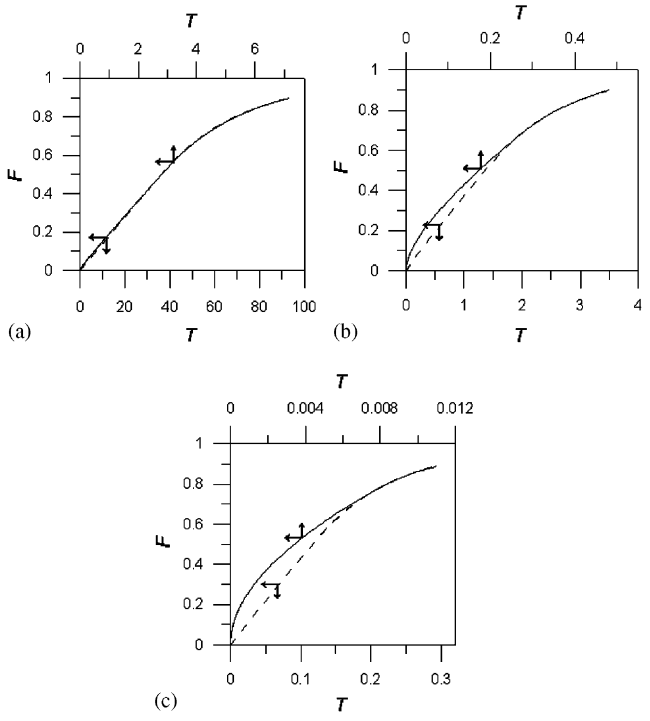

Fig. 4. Variations of cumulative release fraction F as a function of scaled time T for various R_i at two levels of Γ for the case when $\rho = 1$. (a) $R_i = 0.1$; (b) $R_i = 0.5$; (c) $R_i = 0.9$. Solid curve, $\Gamma = 10^9$; dashed curve, $\Gamma = 1$.

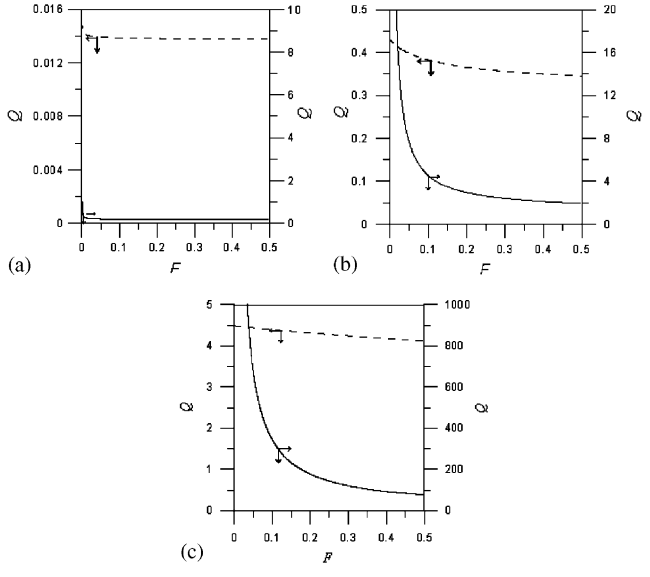

Fig. 5. Variations of scaled release rate Q as a function of F for various R_i at two levels of Γ for the case when $\rho = 1$. (a) $R_i = 0.1$; (b) $R_i = 0.5$; (c) $R_i = 0.9$. Solid curve: $\Gamma = 10^9$; dashed curve: $\Gamma = 1$.

A constant release rate can be expected from the present controlled-release device if the key parameters are properly chosen, namely, ρ is large, R_i is small, and/or Γ is small. This is illustrated in Fig. 6 where a linear relation between F and T is observed during most of the release process. When

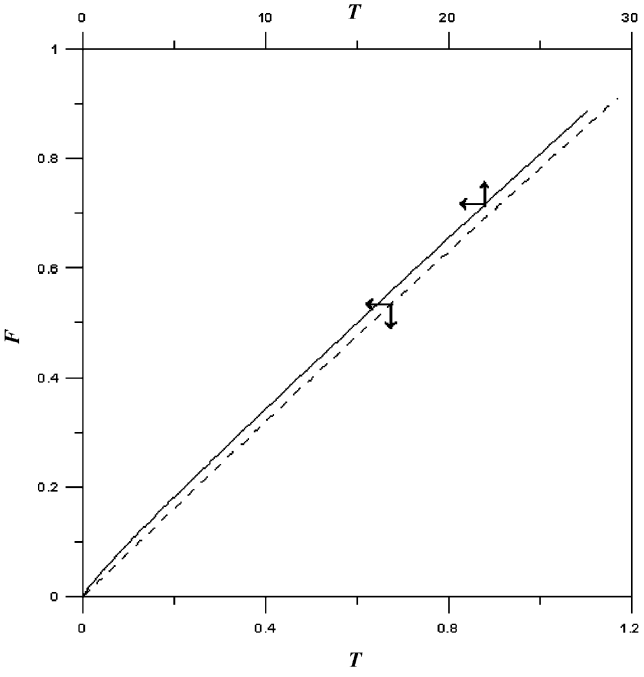

Fig. 6. Temporal variation of cumulative release fraction F at different combinations of R_i and Γ for the case when $\rho = 10$. Solid curve, $R_i = 0.1$ and $\Gamma = 10^9$, dashed curve, $R_i = 0.9$ and $\Gamma = 1$.

the moving front reaches a_0, the constant release rate behavior no longer exists. This is because the rate of release is mainly controlled by the diffusion of drug in the polymer matrix after $R_m = 1$. In this case, because the driving force for diffusion declines with time, so does the release rate. Since a zero-order release kinetics can be approximated by choosing appropriate R_i and Γ for $R_m \leqslant 1$ only, the objective of maintaining the time interval in which an approximate zero-order kinetics occurs at a maximum needs to be achieved by increasing the amount of drug released before $R_m = 1$. This can be accomplished by raising the value of ρ. In practice, a device with a small R_i implies that its aperture is small and is relatively difficult to manufacture, and a device with a small Γ leads to a small release rate. Therefore, a proper combination of R_i and Γ needs to be determined in the design stage so that an approximate zero-order controlled release can be achieved.

4. Conclusion

In summary, an inward release polymer matrix with its aperture covered by a drug-permeable membrane is proposed as a potential zero-order controlled release device. The performance of the device is evaluated through numerical simulation, and the performance of the results based on a pseudosteady-state assumption (PSS) is examined. We obtain the following conclusions: (1) The presence of the membrane has the effects of modifying the rate of

release so that it is closer to zero order, and alleviating the problem of initial burst. (2) The smaller the ratio (inner radius of device/outer radius of device) and/or the greater the mass transfer resistance of the membrane, the closer the release rate to a constant. (3) If both the geometry of a device and the membrane are chosen appropriately, a zero-order behavior can be achieved for most of the release process when the loading drug in polymer matrix is high. (4) The PSS approximation may be appropriate, if the ratio (inner radius of device/outer radius of device) is small, the mass transfer resistance of the membrane is large, and/or the loading drug in the polymer matrix is high.

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