



Theoretical study of diffusional release of a dispersed solute from a hollow cylindrical polymeric matrix

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KEYWORDS

Dispersed solute;
 Hollow cylinder;
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 Exact solution;
 Moving boundary.

Abstract. The present study proposes an exact solution for the release kinetic of a solute from inside a hollow cylindrical polymeric matrix into an infinite medium when the initial concentration of the solute (A) is greater than the solubility limit (C_s). A combination of analytical and numerical methods was used to calculate the solute concentration profile and the release rate. The model was developed for two different conditions including: (1) The release medium was flowing through the hollow cylinder in which the boundary layer may be neglected, and (2) The release medium inside the hollow cylinder was stagnant where the boundary layer needed to be considered. The results indicated that the release profiles were close to the constant release rate after a typical burst release. Also, the release profile from a solid cylindrical matrix was compared to that of a hollow cylinder. The results indicated that the hollow cylindrical matrix was a promising carrier when the zero-order release was desirable. The present model demonstrated the potential of the hollow cylindrical matrix as a suitable geometry for sustained drug delivery systems.

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1. Introduction

In some cases, the treatment requires long term drug delivery to patients. Therefore, it is important to have control over the solute release mechanism of the drug delivery to patients [1]. This control requires robust and high precision modeling and solution. The dispersed matrices, in which the initial loading of solute (A) is greater than the solubility limit (C_s), represent one of the most efficient systems having the capability to be employed for control purposes. In this system, there is a moving front that separates the undissolved region of the core from the partially extracted region. The main purpose of this study is to

design a specific system to deliver solutes at a constant rate. The systems with zero-order kinetics can keep the drug concentration within required levels proper for therapeutic purposes [2].

The hollow cylindrical systems with loaded solute can be used in many applications. For instance, regenerative medicine has a good potential to build hollow cylindrical scaffolds for bone regeneration [3]. Not only these hollow implants can maintain the biomechanical strength required for load-bearing applications but also provide specific space for tissue regeneration by delivering bioactive molecules [4]. Such a hollow polymeric cylinder functions as a bone chamber because of the bone ingrowth via the perforations [5]. To stimulate bone regeneration, the inner part of the hollow scaffold can be filled with a special material capable of mimicking the natural bone tissue. The release of the desired growth factor from the outer shell may induce vascularization which plays a crucial role

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in the bone regeneration process. Moreover, the hollow cylindrical matrix can be prepared by 3D printing of biomaterials while containing growth factors [6,7]. Actually, in these systems, the solute represents the loaded growth factor in the scaffolds. The release rate of growth factor has an undeniable effect on the cells differentiation and their growth; therefore, the rate of release can be a controlled variable [8,9]. Due to the effectiveness of this factor, the high precision modeling and simulation have received a great deal of attention.

Over the past years, many efforts have been made to formulate the release kinetics of a solute from dispersed matrices [10–14]. Higuchi [12] proposed an approximate solution for dispersed planar and cylindrical geometry using pseudo-steady state assumption. However, regarding low drug loadings, his solutions were highly erroneous. Baker and Lonsdale [15] presented a solution for the planar geometry when diffusion and surface erosion simultaneously contribute to drug release. They also used pseudo-steady state assumption to find an approximate solution. Later, Paul and McSpadden [16] proposed the first exact solution for a dispersed semi-finite planar slab. Furthermore, Lee [17,18] proposed an approximate solution based on the refined integral method to model the diffusional release of a dispersed solute from planar and spherical matrices. Abdekhodaie and Cheng [11] developed an exact analytical solution for the release kinetics of a dispersed solute from a spherical matrix by using the method of combination of variables. For cylindrical geometry, Langer et al. [19] used a pseudo-steady state approach to achieve the rate of release from a hollow cylindrical matrix. Also, Zhou and Wu [20] used the finite element method to obtain the drug release from a complex matrix including a hollow cylinder when the initial concentration is less than the solubility limit. The mathematical model to simulate the release of a dispersed solute from a cylindrical polymer matrix into an infinite external volume was developed in several studies [14,21]. In a more complicated system, Jahromi et al. [13] developed a cylindrical polymeric matrix by separating baffles to achieve a zero-order release kinetic.

In this study, an exact analytical solution for the release kinetics of a dispersed solute from a hollow cylindrical polymer matrix in an infinite medium was developed. This study aimed to find a solution in two situations including: with boundary layer on the release surface and without boundary layer condition. The release mechanism considered in this study was a diffusion-controlled one. The predicted fractional release profiles were presented for various drug loadings and different external volumes. It was shown that the polymer matrix geometry plays a crucial role in predicting the drug release kinetics.

2. Mathematical analysis

The release mechanism from a hollow cylindrical matrix is assumed to be diffusion-controlled. The mass transfer coefficient was considered to be constant and independent of the concentration, swelling is negligible, and outlet surface and end-sites are isolated. The system was analyzed under two conditions:

- Diffusional release without boundary layer formation;
- Diffusional release with boundary layer formation.

The drug distribution in the cylinder after a certain time of release is illustrated in Figure 1 where a and b are the inner and outer radius of the hollow cylinder, respectively. R refers to the position of the diffusional front. The concentration in the unextracted core ($R < r < b$) was constant and equal to the initial drug loading (A), while there was a concentration profile in the extracted region ($a < r < R$). To obtain the concentration profile in the extracted region, the Fick second laws are employed as follows:

$$\frac{\partial C}{\partial t} = \frac{D}{r} \frac{\partial}{\partial r} \left(r \frac{\partial C}{\partial r} \right), \quad (1)$$

where D is the diffusion coefficient, r is the polar radial position, and C is the concentration of the solute in the extracted region. The initial and boundary conditions for this system in a well-agitated medium are:

$$r = a \rightarrow C = 0, \quad (2)$$

$$r = R \rightarrow C = C_s, \quad (3)$$

$$r = R \rightarrow \left(\frac{A}{C_s} - 1 \right) \frac{dR}{dt} = D \frac{\partial C}{\partial r}, \quad (4)$$

$$\tau = 0 \rightarrow R = a, \quad (5)$$

where C_s is the solubility limit of the solute in the matrix. When an external mass transfer resistance

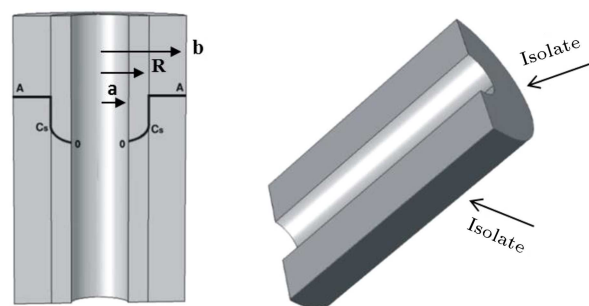


Figure 1. Schematic diagram of the solute distribution in a hollow cylinder after a certain time.

exists, the boundary layer at the surface is:

$$r = a \rightarrow -D \frac{\partial C}{\partial r} = h (C_m - 0), \quad (6)$$

where C_m is the medium concentration at the surface, and h is the mass transfer coefficient in the boundary layer. Assuming that there is equilibrium between the matrix surface and the external fluid at the surface, Eq. (6) became:

$$r = a \rightarrow -D \frac{\partial C}{\partial r} = \frac{hC}{k}, \quad (7)$$

where k is the partition coefficient between the matrix and the medium. To simplify Eq. (1), the following dimensionless variables were defined:

$$\xi = \frac{r}{a}, \quad \theta = \frac{C}{C_s}, \quad \tau = \frac{Dt}{a^2}, \quad \Gamma = \frac{R}{a}. \quad (8)$$

By using these parameters Eq. (1) is reduced to its dimensionless form:

$$\frac{\partial \theta}{\partial \tau} = \frac{1}{\xi} \left(\frac{\partial}{\partial \xi} \left(\xi \frac{\partial \theta}{\partial \xi} \right) \right). \quad (9)$$

Assuming perfect sink condition, the initial and boundary conditions will be as follows:

$$\xi = 1 \rightarrow \theta = 0, \quad (10)$$

$$\xi = \Gamma \rightarrow \theta = 1, \quad (11)$$

$$\xi = \Gamma \rightarrow \left(\frac{A}{Cs} - 1 \right) \frac{\partial \Gamma}{\partial \tau} = \frac{\partial \theta}{\partial \xi}, \quad (12)$$

$$\tau = 0 \rightarrow \Gamma = 1. \quad (13)$$

If the medium were not well agitated and external resistance existed, the boundary layer would be formed on the release surface. Thus, Eq. (7) becomes:

$$\xi = 1 \rightarrow \frac{\partial \theta}{\partial \xi} = \beta \theta, \quad \text{and} \quad \beta = \frac{ah}{Dk}, \quad (14)$$

where β is the Biot number. Eq. (9) is reduced to an ordinary differential equation by using the method of combination variables [22]. The combined variable was defined as:

$$\eta = \frac{\xi^2}{4\tau}. \quad (15)$$

By using η , Eq. (9) was expressed as:

$$\frac{\partial^2 \theta}{\partial \eta^2} + \left(\frac{1 + \eta}{\eta} \right) \frac{\partial \theta}{\partial \eta} = 0. \quad (16)$$

After twice integrating Eq. (16) and applying the initial and boundary conditions, the dimensionless

concentration profile for a well-agitated medium was obtained as follows:

$$\theta = \frac{Ei(\eta^+) - Ei(\eta)}{Ei(\eta^+) - Ei(\eta^*)}, \quad (17)$$

in which:

$$\eta^+ = \frac{1}{4\tau}, \quad \eta^* = \frac{\Gamma^2}{4\tau}, \quad (18)$$

$$Ei(x) = \int_x^\infty \frac{\exp^{-\eta}}{\eta} d\eta. \quad (19)$$

By using Eq. (17), and under the assumption that the boundary is at the moving front (Eq. (12)) the following equation was obtained, which gave the position of the moving front Γ versus τ :

$$\left(\frac{A}{Cs} - 1 \right) \frac{\partial \Gamma}{\partial \tau} = \frac{2}{Ei(\eta^+) - Ei(\eta^*)} \frac{\exp^{-\eta^*}}{\eta}. \quad (20)$$

Considering the boundary layer formation, the governing and moving front equations were obtained as follows:

$$\theta = \frac{2e^{-\eta^+} + \beta(Ei(\eta^+) - Ei(\eta))}{2e^{-\eta^+} + \beta(Ei(\eta^+) - Ei(\eta^*))}, \quad (21)$$

$$\frac{\partial \Gamma}{\partial \tau} = \frac{Cs}{A - Cs} \cdot \frac{2\beta}{2e^{-\eta^+} - \beta(Ei(\eta^*) - Ei(\eta^+))} \cdot \frac{\exp^{-\eta^*}}{\Gamma}. \quad (22)$$

Eqs. (20) and (22) can be solved numerically. To obtain the moving front position, an initial condition was needed for solving these ODE equations. However, the system confronted with a hurdle at $\tau = 0$ and $\Gamma = 1$, since these equations give $d\Gamma/d\tau$ to ∞ at $\tau = 0$. Therefore, another pair of initial conditions was needed to eliminate this hurdle. It is well-known that the curvature effect is negligible in the thin film and a thin spherical or cylindrical film behaves like a planar geometry. In the previous study, Abdekhodaie and Cheng [11] noticed that for a spherical matrix at small values of τ , the position of the diffusion front is very close to the release surface and the partially extracted region is very thin. Therefore, it is reasonable to expect that $\Gamma(\tau)$ at early times for planar and cylindrical geometry to be similar. For the planar geometry, Pual and McSpadden [16] presented Eq. (23) for $\Gamma(\tau)$:

$$\sqrt{\pi} \frac{(1 - \Gamma)}{2\sqrt{\tau}} \exp \left[\frac{(1 - \Gamma)}{4\tau} \right] \operatorname{erf} \left[\frac{(1 - \Gamma)}{2\sqrt{\tau}} \right] = \frac{Cs}{A - Cs}. \quad (23)$$

Using this equation for small values of τ , a sufficient pair for the initial condition was achieved (τ_0, Γ_0). Using these values, the Γ versus τ profile was obtained by solving Eqs. (20) and (22) for both well agitated

and unmixed mediums. The cumulative amount of solute released at any time, t , was:

$$M_t = \left[A\pi(R^2 - a^2) - 2\pi \int_a^R Cr dr \right] L, \quad (24)$$

where L is the cylinder length. The total amount of drug released at the infinite time was given by:

$$M_\infty = A\pi(b^2 - a^2)L, \quad (25)$$

where b is the outer radius of the cylinder. Therefore, the fractional release in the reduced forms for both with and without boundary layer became:

$$\frac{M_t}{M_\infty} = \frac{\Gamma^2 - 1}{\left(\frac{b}{a}\right)^2 - 1} - \frac{2C_s}{A\left(\left(\frac{b}{a}\right)^2 - 1\right)} \int_1^\Gamma \theta \xi d\xi. \quad (26)$$

3. Results and discussion

As mentioned previously, an initial condition is required to solve Eqs. (20) and (22). However, there is a hurdle under the condition $\tau = 0$ and $\Gamma = 1$. To solve this problem, in accordance with a previous study [11], it was assumed that at the beginning, the curvature effects can be neglected and $\Gamma(\tau)$ profile from the known exact solution for the planar geometry can be adopted for the cylindrical geometry. The next step is determining the point where the solution is switched to the exact one. To this end, the sensitivity analysis of the initial condition on the exact solution for two different drug loadings including; low drug loading of $A/C_s = 2$ and high drug loading of $A/C_s = 30$, was performed. Figure 2 shows the $\Gamma(\tau)$ profile for two different solute loadings and different pairs of initial conditions which were calculated from Eq. (23). In all cases, the ratio of the outer to the inner diameter of the polymer (b/a) was kept constant and equal to 3. The effect of various diameter ratios will be discussed further in this section. The results indicated that for

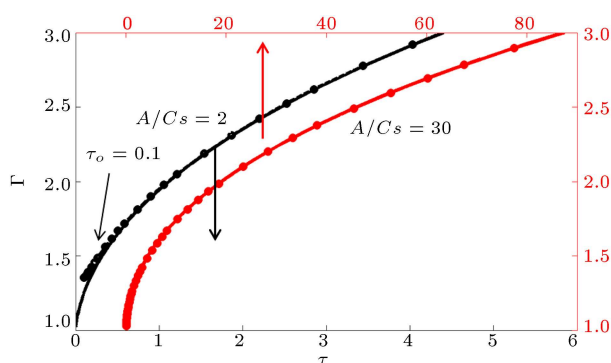


Figure 2. $\Gamma(\tau)$ profile in the hollow cylindrical matrix. The initial condition (τ_0, Γ_0) obtained from Paul and McSpadden equation for two values of A/C_s : (a) $A/C_s = 2$ and (b) $A/C_s = 30$; $\tau_0 = 0.001$ to 0.1.

$A/C_s = 30$, the $\Gamma(\tau)$ profile was insensitive to the initial condition when τ_0 ranged from 0.001 to 0.1, and all diagrams were overlapping each other. Since in lower drug loadings the velocity of the diffusional front increases, the solution is more sensitive to the initial condition. It is depicted that for $A/C_s = 2$, $\Gamma(\tau)$ profile was different when $\tau_0 = 0.1$ in comparison to smaller τ_0 , indicating the appearance of curvature effect. Therefore, considering a planar geometry at the beginning for determining the initial condition of the exact solution is not accurate when the τ_0 value is more than 0.1, for $A/C_s = 2$.

The position of the diffusional moving front for various solute loadings is depicted in Figure 3. These results were obtained using Γ values corresponding to $\tau_0 = 1 \times 10^{-3}$ from Eq. (23) as the initial conditions for Eq. (20). As it was shown, by increasing the initial drug loading (A/C_s), the velocity of the moving boundary will decrease.

The fractional release profile for various solute loadings in a well-agitated medium is shown in Figure 4. The results obtained by applying the exact solution for the dispersed matrix with hollow cylinder

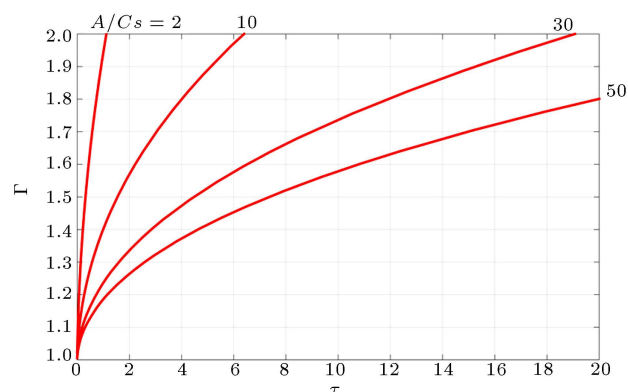


Figure 3. Position of the diffusional moving front (Γ) versus τ for various drug loadings. As A/C_s increases, the moving boundary moves slower, $\tau_0 = 0.001$.

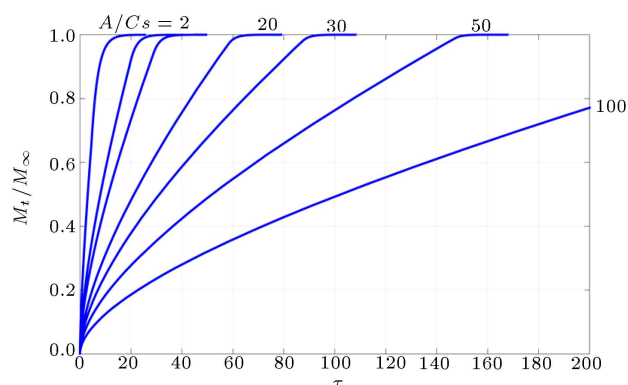


Figure 4. Fractional release profiles versus τ from a hollow cylindrical matrix at various drug loadings in a well-agitated medium, $\tau_0 = 0.001$.

geometry illustrated that after a typical initial burst release, an approximate zero-order release kinetic was obtained. This behavior is more substantial in higher solute loadings. As the A/C_s increased, the cumulative fractional release curves became increasingly sustained, and the constant release rate takes place in a larger period. When the moving front reached the end of the polymer, the system behaved like a dissolved matrix. It was also possible to pre-release the hollow matrix to avoid the most nonlinear portion of the initial solute release.

The fractional release profile from the hollow cylinder into a well-agitated medium was compared with a dispersed cylindrical matrix in which the solute releases from the outer surface followed the Khamene and Abdekhodaie model [21]. The amount of solute loaded in both systems was the same, and the outer surface area of the cylinder matrix was equal to the inner surface area of the hollow cylindrical matrix. The outer diameter to inner diameter ratio (b/a) for the hollow cylinder was kept constant at 3. The A/C_s ratio for the hollow cylinder and the rigid cylindrical matrix was 12.6 and 101, respectively. Figure 5 illustrates

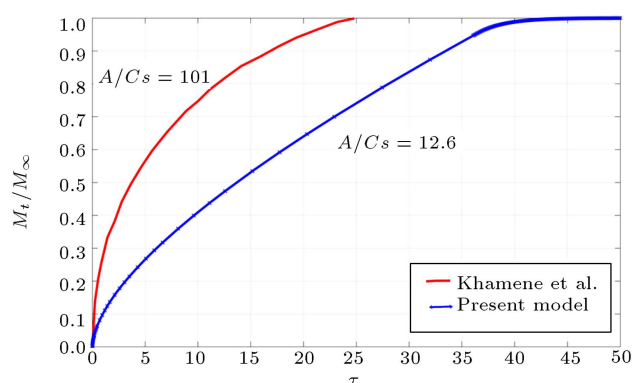


Figure 5. Comparison of diffusional release from a hollow cylinder (present model) and a cylindrical matrix (Khamene et al. [21]) with the same amount of loaded solute and release surface. The outer to inner diameter ratio (b/a) was equal to 3, $\tau_0 = 0.001$.

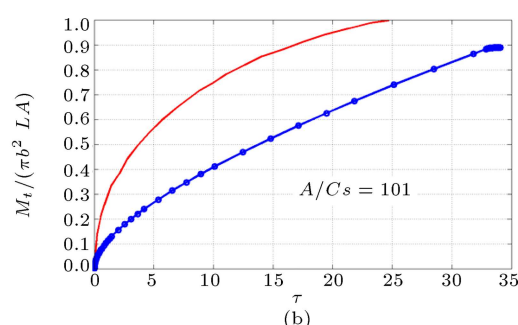
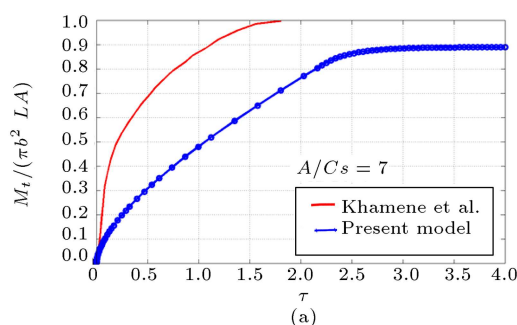


Figure 6. Comparison of diffusional release from a hollow cylinder (present model) and a cylindrical matrix (Khamene et al. [21]) for two different drug loadings: (a) $A/C_s = 7$ and (b) $A/C_s = 101$. The outer diameter of the hollow cylinder and the diameter of the solid cylindrical implant is the same. The outer to inner diameter ratio (b/a) was equal to 3, $\tau_0 = 0.001$.

that the solute release rate from the hollow cylindrical matrix was lower than the cylindrical one, and was more close to the zero-order kinetics. Therefore, by a simple change in the geometry, a release profile that is very close to zero-order will be achieved. Figure 6 shows another comparison between the fractional release from the hollow cylindrical matrix and solid cylindrical polymer matrix for two different values of A/C_s . In this condition, it was assumed that the outer diameter of the hollow cylinder (b) was equal to the solid cylindrical matrix diameter. The results showed that for the same initial solute loading, the hollow cylindrical matrix provided a more sustained release compared to the cylindrical matrix. It should be noticed that as the total solute amount in the hollow cylinder was less than $\pi b^2 LA$, the proposed fractional release ($M_t/(\pi b^2 LA)$) has not reached the same degree of unity of cylindrical matrix. The hollow cylindrical matrix was an appropriate geometry for simulating artery stent which has been loaded with a drug, and the drug was released from the inner surface to the lumen. In this specific case, the blood flow provided an agitated media inside the polymer matrix which prevented the boundary layer to be formed on the release surface.

Figure 7 shows the fractional release profile for different ratios of the outer diameter to the inner diameter of the hollow cylindrical matrix at various initial solute loadings. It was shown that as the b/a ratio increased, the release profile became more sustained and a near zero-release kinetic was achieved. Therefore, the diameter ratio can be set as a controlling parameter for the release rate. When the moving front met the outer surface of the matrix, the system behaved like a dissolved matrix. Therefore, an obvious change occurred in the fractional release profile.

When the release medium was not well agitated, the boundary layer was formed on the release surface. This layer resisted to the mass transfer, therefore, the rate of release and moving front velocity decreased. The fractional release of the solute into a medium with a boundary layer is illustrated in Figure 8. As

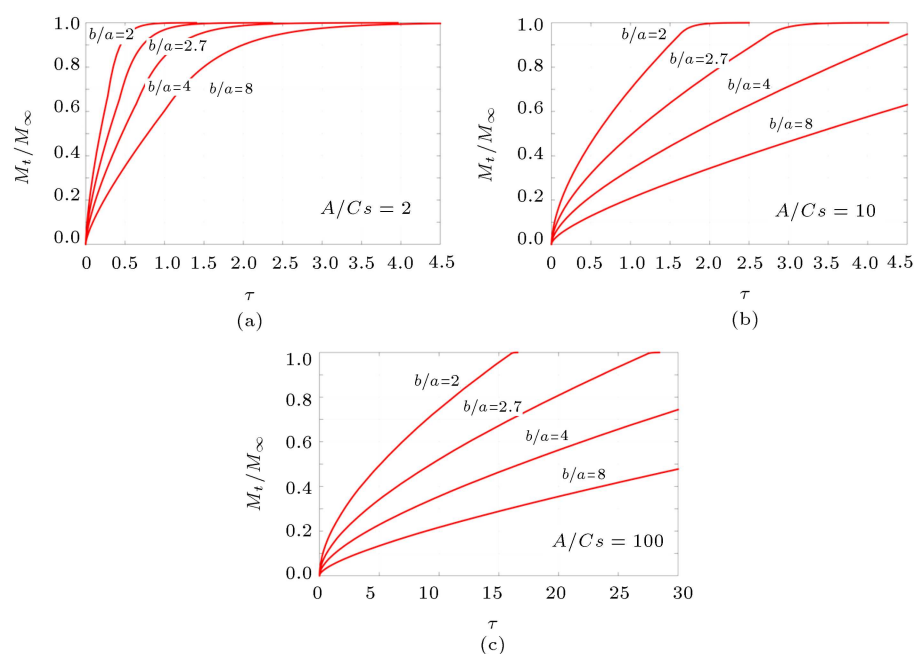


Figure 7. Fractional release from a hollow cylinder for different ratios of inner diameter to the outer diameter, and various initial solute loadings: (a) $A/C_s = 2$, (b) $A/C_s = 10$, and (c) $A/C_s = 100$, $\tau_0 = 0.001$.

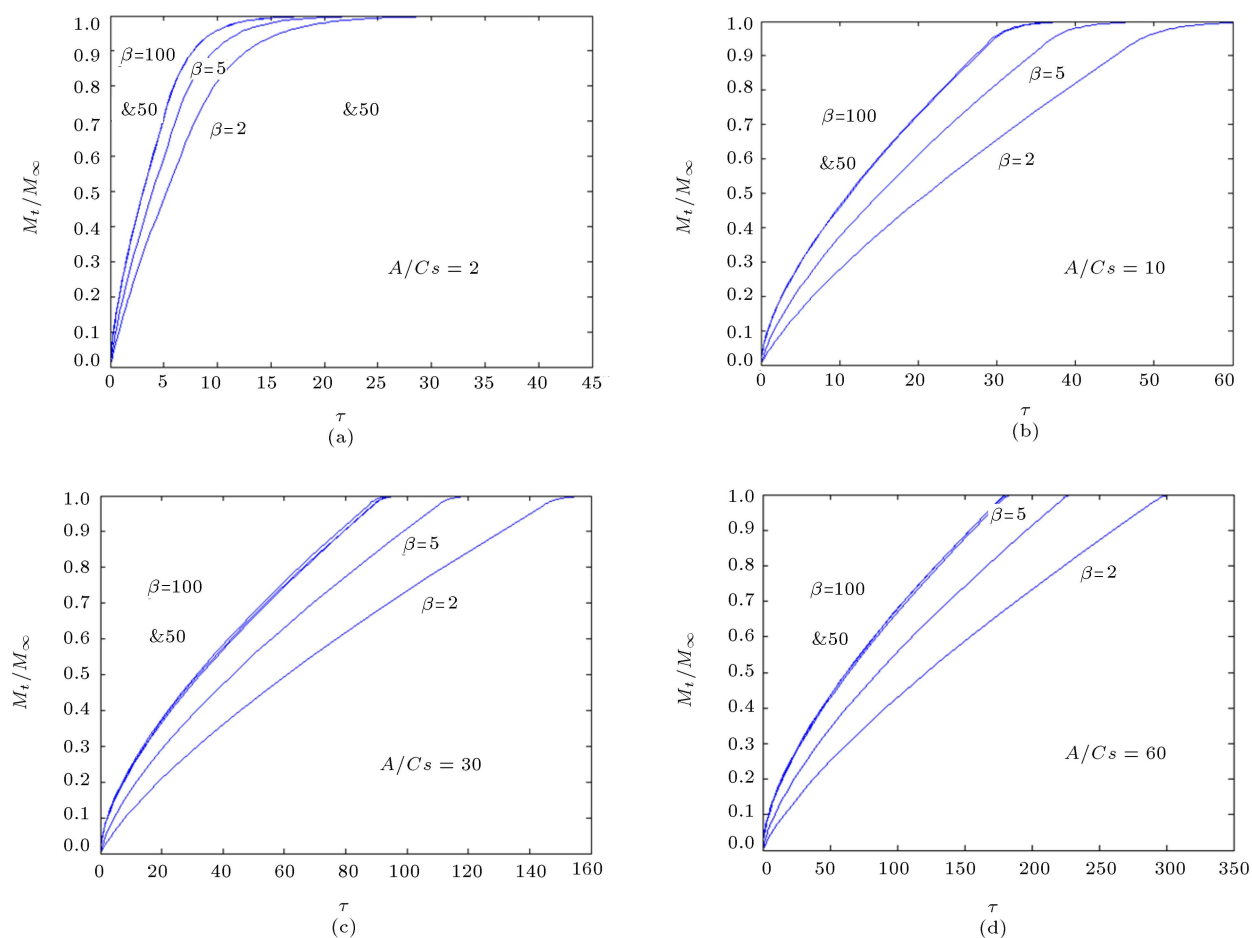


Figure 8. Fractional release for a dispersed solute from a hollow cylindrical matrix at various drug loadings and different Biot numbers: (a) $A/C_s = 2$, (b) $A/C_s = 10$, (c) $A/C_s = 60$, and (d) $A/C_s = 60$, $\tau_0 = 0.001$.

the dimensionless Biot number ($\beta = \frac{ah}{Dk}$) increased, the mass transfer coefficient and the rate of release increased. Therefore, the medium can be considered as a well-agitated medium for the sufficiently great values of β . The results indicated that for small values of β , the cumulative release was more sensitive to the Biot number. However, as the value of β increased, the relevant fractional release approached a similar profile. In the presence of the boundary layer, the release profiles became more sustained as the A/C_s increased. For sufficiently high values of β , the boundary layer effect can be neglected and the fractional release approaches to that in the well-agitated medium.

4. Conclusions

An exact analytical solution for the diffusional release of a dispersed solute from a hollow cylindrical matrix into an infinite medium was presented. When the release mechanism was diffusion-controlled, the release rate from an inwardly releasing cylinder was near to zero-order, particularly at higher solute loadings. The comparison between a hollow cylindrical matrix and a solid cylindrical one indicated that by a simple change in the geometry, a more sustained release kinetics will be achieved. The hollow cylindrical implant may have applications in making stents, tissue engineering scaffolds, and a drug delivery vehicle used to provide the sustained release of a solute.

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Nomenclature

A	Initial solute loading per unit volume
a	Inner diameter of the hollow cylindrical matrix
b	Outer diameter of the hollow cylindrical matrix
C	Solute concentration in the matrix at any time
C_s	Equilibrium solute solubility in the matrix
D	Solute diffusion coefficient in the matrix
h	Mass transfer coefficient
L	Length of cylinder
k	Partition coefficient between the matrix and medium
M_t	Cumulative amount of solute released

M_∞	Total amount of solute released at infinitive time
r	Spatial coordinate
R	Position of diffusion moving front
t	Release time
ξ	Dimensionless spatial coordinate defined by Eq. (8)
τ	Dimensionless time defined by Eq. (8)
Γ	Dimensionless moving from position defined by Eq. (8)
θ	Dimensionless concentration defined by Eq. (8)
C_m	Medium concentration

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Mohammad Jafar Abdekhodaie is a Professor at Sharif University of Technology where he leads a multidisciplinary team focusing on tissue engineering, drug delivery, and mathematical modeling in biological systems. He obtained his BSc and MSc degrees in Chemical Engineering from the Sharif University of Technology and received his PhD degree from the University of Toronto.