Theoretical Study of Diffusional Release of a dispersed Solute from a Hollow Cylindrical Polymeric Matrix

Elaheh Jooybar\textsuperscript{a}, Tannaz Tajsoleiman\textsuperscript{a}, Mohammad J. Abdekhoodaie\textsuperscript{a*}

\textsuperscript{a} Department of Chemical and Petroleum Engineering, Sharif University of Technology, Tehran, Iran

\textsuperscript{*}Author to whom correspondence should be addressed (E-mail: abdmj@sharif.edu, Telephone: (+98) 21 6616 5401).
Abstract

An exact solution for the release kinetic of a solute from inside a hollow cylindrical polymeric matrix into an infinite medium has been developed, 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 strategies: 1) the release medium is flowing through the hollow cylinder in which boundary layer may be neglected, 2) the release medium inside the hollow cylinder is stagnant and the boundary layer should 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 and a hollow cylinder was compared. The results indicated that the hollow cylindrical matrix is a promising carrier when zero-order release is desirable. The present model demonstrates the potential of the hollow cylindrical matrix as a suitable geometry for sustained drug delivery systems.

**Keywords**: Dispersed solute; Hollow cylinder; Controlled release; Exact solution; Moving boundary
1 Introduction

In some therapies, it is needed to deliver a drug to the patient over a long period of time. Therefore, it is essential to have a control over a solute release mechanism for drug delivery into the human body [1]. To this end, a robust and high precision modeling and solution strategy is required. In purpose of designing a controlled release system, one of the most interesting types is the dispersed matrices in which the initial loading of solute (A) is greater than the solubility limit (Cs). In this system, there is a moving front that separates the undissolved region of the core from partially extracted region. A valuable goal is designing a specific system to deliver solutes in a constant rate. The systems with zero-order kinetics can keep the drug concentration within the therapeutic window [2].

The hollow cylindrical systems with loaded solute can be used in many applications. For instance, in regenerative medicine there is a 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 with 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 a desired growth factor from outer shell may induce vascularization which is key in bone regeneration process. Moreover, the hollow cylindrical matrix can be prepared by 3D printing of biomaterials while contained growth factors [6, 7]. Actually, in these systems, the solute is the loaded growth factors in the scaffolds. The release rate for growth factor has undeniable effect on the cells differentiation and their growth; therefore, the rate of release can be a controlled variable
By considering the effectiveness of this factor, the importance of having a high precision modeling and simulation becomes more viable.

Over the past years, an extensive amounts of work has been done to formulate the release kinetics of a solute from dispersed matrices [10-14]. Higuchi [12] first proposed an approximate solution for dispersed planar and cylindrical geometry with pseudo-steady state assumption. However, his solutions were highly erroneous in low drug loadings. Baker and Lonsdale [15] presented a solution for the planar geometry when diffusion and surface erosion simultaneously participate in 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] obtained 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 combination of variables method. For cylindrical geometry, Rhine et al. [19] used pseudo-steady state approach to achieve the rate of release from a hollow cylindrical matrix. Also, Zhou and Wu [20] applied finite element method to obtain drug release from a complex matrix including hollow cylinder when the initial concentration is less than 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. developed a cylindrical polymeric matrix with separating baffles to achieve a zero-order release kinetic [13].

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

2 Mathematical analysis

The release mechanism from a hollow cylindrical matrix is assumed to be diffusion-controlled. The mass transfer coefficient is considered to be constant and independent of the concentration, swelling is negligible, and outlet surface and end-sites are isolated. The system is analyzed under two conditions: a) diffusional release without boundary layer formation, b) 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 un-extracted core \((R < r < b)\) is constant and equal to the initial drug loading \((A)\), while there is a concentration profile in extracted region \((a < r < R)\). To obtain the concentration profile in extracted region, the Fick’s second laws are employed as follows:

\[
\frac{\partial C}{\partial t} = D \frac{\partial}{r \frac{\partial}{\partial r}} \left( r \frac{\partial C}{\partial r} \right)
\]

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:
\begin{align*}
  &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)
\end{align*}

where $C_s$ is the solubility limit of the solute in the matrix. When an external mass transfer resistance exists, the boundary layer at the surface is:

\begin{align*}
  &r = a \rightarrow -D \frac{\partial C}{\partial r} = h(C_m - 0) \quad (6)
\end{align*}

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

\begin{align*}
  &r = a \rightarrow -D \frac{\partial C}{\partial r} = \frac{hC}{k} \quad (7)
\end{align*}

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

\begin{align*}
  &\xi = \frac{r}{a} \quad \theta = \frac{C}{C_s} \quad \tau = \frac{Dt}{a^2} \quad \Gamma = \frac{R}{a} \quad (8)
\end{align*}

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

\begin{align*}
  &\frac{\partial \theta}{\partial \tau} = \frac{1}{\xi} \left( \frac{\partial}{\partial \xi} \left( \xi \frac{\partial \theta}{\partial \xi} \right) \right) \quad (9)
\end{align*}

Assuming perfect sink condition, the initial and boundary conditions are:

\begin{align*}
  &\xi = 1 \rightarrow \theta = 0 \quad (10)
\end{align*}
\[ \xi = \Gamma \rightarrow \theta = 1 \]  

(11)

\[ \xi = \Gamma \rightarrow \left( \frac{A}{Cs} - 1 \right) \frac{\partial \Gamma}{\partial \tau} = \frac{\partial \theta}{\partial \xi} \]  

(12)

\[ \tau = 0 \rightarrow \Gamma = 1 \]  

(13)

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

\[ \xi = 1 \rightarrow \frac{\partial \theta}{\partial \xi} = \beta \theta \quad \text{and} \quad \beta = \frac{a h}{D k} \]  

(14)

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

\[ \eta = \frac{\xi^2}{4 \tau} \]  

(15)

By using this variable, equation (9) was expressed as:

\[ \frac{\partial^2 \theta}{\partial \eta^2} + \left( 1 + \frac{\eta}{\xi^2} \right) \frac{\partial \theta}{\partial \eta} = 0 \]  

(16)

After twice integrating equation (16) and applying the initial and boundary conditions, the dimensionless concentration profile for a well agitated medium was obtained as follows:

\[ \theta = \frac{Ei(\eta^*) - Ei(\eta)}{Ei(\eta^*) - Ei(\eta^* \xi^2)} \]  

(17)

in which:

\[ \eta^* = \frac{1}{4 \tau} \quad \text{and} \quad \eta^* = \frac{\xi^2}{4 \tau} \]  

(18)
By using equation (17), and the boundary condition at the moving front (equation (12)) the following equation was obtained, which gave the position of the moving front $\Gamma$ versus $\tau$:

\[
\left(\frac{A}{Cs} - 1\right) \frac{\partial \Gamma}{\partial \tau} = \frac{2}{Ei(\eta^+) - Ei(\eta)} \frac{\exp^{-\eta}}{\eta}
\]  

(20)

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

\[
\theta = \frac{2e^{-\eta} + \beta(Ei(\eta^+) - Ei(\eta))}{2e^{-\eta} + \beta(Ei(\eta^+) - Ei(\eta^+))}
\]

(21)

\[
\frac{\partial \Gamma}{\partial \tau} = \frac{Cs}{A - Cs} \frac{2\beta}{2e^{-\eta} - \beta(Ei(\eta^+) - Ei(\eta^+))} \frac{\exp^{-\eta}}{\Gamma}
\]

(22)

Equations (20) and (22) can be solved numerically. To obtain the moving front position, an initial condition is needed for solving these ODE equations. However, system confronted to a hurdle at $\tau = 0$ and $\Gamma = 1$, since these equations give $d\Gamma/d\tau \to \infty$ at $\tau = 0$. Therefore, another pair of initial condition is needed to eliminate this hurdle. It is well-known that curvature effect is negligible in thin film such that a thin spherical or cylindrical film behaves similarly to a planar geometry. In the previous study, Abdekhoadaie and Cheng [11] considered that for a spherical matrix at small values of $\tau$, 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 is similar. For the planar geometry, Pual and McSpadden [16] presented equation (23) for $\Gamma(\tau)$:
\[
\sqrt{\pi} \frac{(1-\Gamma)}{2^{\sqrt{\tau}}} \exp \left[ \frac{(1-\Gamma)}{4\tau} \right] \text{erf} \left[ \frac{(1-\Gamma)}{2\tau} \right] = \frac{Cs}{A-Cs}
\]  

(23)

Using this equation for small values of \( \tau \), a sufficient pair for initial condition was achieved \((\tau_0, \Gamma_0)\). Using these values, the \( \Gamma \) versus \( \tau \) profile was obtained by solving equations (20) and (22) for both well agitated and unmixed mediums. The cumulative amount of solute released at any time, \( t \), was:

\[
M_t = \left[ A\pi(R^2 - a^2) - 2\pi \int_a^R Crdr \right] L
\]

(24)

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

\[
M_\infty = A\pi(b^2 - a^2)L
\]

(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:

\[
\frac{M_t}{M_\infty} = \frac{\Gamma^2 - 1}{(\frac{b}{a})^2 - 1} - \frac{2Cs}{A((\frac{b}{a})^2 - 1)} \int_1^\Gamma \theta \xi d\xi
\]

(26)

3 Results and discussion

As mentioned previously, an initial condition is required to solve the equations (20) and (22). However, there is a hurdle at condition of \( \tau=0 \) and \( \Gamma=1 \). To solve the problem, according to 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, low drug loading of \( A/Cs=2 \) and high drug loading of \( A/Cs=30 \), was
performed. Figure 2 shows the $\Gamma(\tau)$ profile for two different solute loadings and different pairs of initial conditions which were calculated from equation (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 indicate that for $A/Cs=30$, the $\Gamma(\tau)$ profile is insensitive to the initial condition when $\tau_0$ ranged from 0.001 to 0.1, and all diagrams are 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 $A/Cs=2$, $\Gamma(\tau)$ profile is different when $\tau_0=0.1$ in comparison to smaller $\tau_0$, that shows 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 $\tau_0$ value is more than 0.1, for $A/Cs=2$.

The position of the diffusional moving front for various solute loadings is depicted in Figure 3. The results presented were obtained using $\Gamma$ values corresponding to $\tau_0=1\times10^{-3}$ from Eq. (23) as the initial conditions for Eq. (20). As it was shown, by increasing the initial drug loading ($A/Cs$), 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 which are obtained by applying the exact solution for the dispersed matrix with hollow cylinder geometry illustrate that after a typical initial burst release an approximate zero-order release kinetic is obtained. This behavior is more substantial in higher solute loadings. As the $A/Cs$ increases, the cumulative fractional release curves become increasingly sustained, and the constant release rate takes place in larger period of time. When the moving front reaches the end of the polymer, the system behaves like a dissolved matrix. It is also possible to pre-release the hollow matrix to avoid the most nonlinear portion of the initial solute release.
The fractional release profile from hollow cylinder into a well agitated medium was compared with a dispersed cylindrical matrix in which solute releases from the outer surface based on the Khamene and Abdekhodaie’s 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 hollow cylinder was kept constant at 3. Considering these conditions, the \(A/Cs\) ratio for the hollow cylinder and the rigid cylindrical matrix was 12.6 and 101, respectively. Figure 5 illustrates that the solute release rate from the hollow cylindrical matrix is lower than the cylindrical one, and is more close to the zero order kinetics. Therefore, by a simple change in the geometry a release profile which is very close to zero order will be achieved. Figure 6 shows another comparison between the fractional release from hollow cylindrical matrix and solid cylindrical polymer matrix for two different values of \(A/Cs\). 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 show that for the same initial solute loading the hollow cylindrical matrix provides a more sustained release than cylindrical matrix. It should be noticed that as the total solute amount in the hollow cylinder is less than \(\pi b^2 LA\), the proposed fractional release \(\left(\frac{M_r}{\pi b^2 LA}\right)\) does not reach unity, like in cylindrical matrix. The hollow cylindrical matrix is an appropriate geometry for simulating artery stent which has been loaded with drug, and the drug is released from the inner surface to the lumen. In this specific case the blood flow makes an agitated media inside the polymer matrix which prevents 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 release rate. When the moving front met the outer surface of the matrix, the system behaves like a dissolved matrix. Therefore, an obvious change appeared in the fractional release profile.

When the release medium is not well agitated, the boundary layer is formed on the release surface. This layer resists to the mass transfer, therefore, the rate of release and moving front velocity decreases. The fractional release of the solute into a medium with boundary layer is illustrated in Figure 8. As the dimensionless Biot number ($\beta = \frac{ah}{Dk}$) increases, the mass transfer coefficient and the rate of release increase. Therefore, the medium can be considered as a well agitated medium for the sufficiently great values of $\beta$. The results indicate that for small values of $\beta$, the cumulative release is more sensitive to Biot number. However, as the value of $\beta$ increases, the relevant fractional release approaches to a similar profile. In the presence of boundary layer, the release profiles become more sustained as the $A/Cs$ increases. For sufficiently high values of $\beta$, 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 is diffusion controlled the release rate from an inwardly releasing cylinder is near to zero-order, particularly at higher solute loadings. Comparison between 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 with the ability of sustained release of a solute.
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List of Variables

\begin{itemize}
  \item \( A \) Initial solute loading per unit volume
  \item \( a \) Inner diameter of the hollow cylindrical matrix
  \item \( b \) Outer diameter of the hollow cylindrical matrix
  \item \( C \) Solute concentration in the matrix at any time
  \item \( C_s \) Equilibrium solute solubility in the matrix
  \item \( D \) Solute diffusion coefficient in the matrix
  \item \( h \) Mass transfer coefficient
  \item \( L \) Length of cylinder
  \item \( k \) Partition coefficient between the matrix and medium
  \item \( M_t \) Cumulative amount of solute released
  \item \( M_\infty \) Total amount of solute released at infinitive time
  \item \( r \) Spatial coordinate
  \item \( R \) Position of diffusion moving front
  \item \( t \) Release time
  \item \( \xi \) Dimensionless spatial coordinate defined by Eq (8)
  \item \( \tau \) Dimensionless time defined by Eq (8)
  \item \( \Gamma \) Dimensionless moving from position defined by Eq (8)
  \item \( \theta \) Dimensionless concentration defined by Eq (8)
  \item \( C_m \) Medium concentration
\end{itemize}
References


**Elaheh Jooybar:**

Elaheh Jooybar obtained her BSc, MSc, and PhD in Chemical engineering with biomedical engineering direction from Sharif university of Technology. She is now working in tissue engineering field specially cartilage and bone tissue engineering. Also, she is working in theoretical field like mathematical modeling in biological systems.

**Tannaz Tajsoleiman:**

Tannaz Tajsoleiman is an industrial Post-doctoral researcher at Freesense ApS, Denmark. She holds a Ph.D. in chemical and biochemical engineering from the Technical University of Denmark and obtained her BSc and MSc from Sharif University of Technology. The focus of her research is the application of computational modelling and simulation techniques in the characterization of various bioprocesses.

**Mohammad Jafar Abdekhodaie:**

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 bachelor and master’s degree in chemical engineering from Sharif University of Technology and received his PhD degree from University of Toronto.
Figure legends:

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

Figure 2. \( \Gamma(\tau) \) profile in the hollow cylindrical matrix. The initial condition \((\tau_0, \Gamma_0)\) obtained from Paul and McSpadden equation for two values of \(A/C_s\), (a) \(A/C_s=2\); (b) \(A/C_s=30\); \(\tau_0=0.001\) to 0.1.

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

Figure 4. Fractional release profiles versus \(\tau\) from a hollow cylindrical matrix at various drug loadings in a well agitated medium, \(\tau_0\) 0.001.

Figure 5. Comparison between diffusional release from a hollow cylinder (present model ×) and a cylindrical matrix (Khamene et. al –) 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 between diffusional release from a hollow cylinder (present model ●) and a cylindrical matrix (Khamene et. al –) for two different drug loadings, a) \(A/C_s=7\), b) \(A/C_s=101\). The outer diameter of the hollow cylinder and the diameter of the solid cylindrical implant are the same. The outer to inner diameter ratio \((b/a)\) was equal to 3, \(\tau_0= 0.001\).

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) \(A/C_s=60\), \(\tau_0= 0.001\).
Figure 1
Figure 3.
Figure 4.
Figure 5.

![Graph showing two curves labeled with A/Cs = 101 and A/Cs = 12.6. The y-axis represents \( M(t)/M_\infty \) and the x-axis represents \( \tau \).]
Figure 6.
Figure 7.
Figure 8.