Mathematical Modeling and Simulation of Drug Release from Microparticles

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Abstract

In drug delivery systems, mathematical modeling plays an important role in the design of drug carrier systems and facilitates the development of new pharmaceutical products. The ultimate aim is to accurately predict the drug release profile and improve the overall therapeutic efficacy and safety of these drug carrier systems. In this project, a comprehensive review of existing mathematical models and simulations of drug release from polymeric microparticle will be conducted. Some popular drugs or proteins in the existing literature will be considered and the necessary parameter values will be gathered. The objective is to select an appropriate geometry and polymer for the drug or protein carrier system in order to meet the requirements for a specific application. The student will gain experience in modeling and simulation of drug carrier systems using MatLab.

1. Introduction

Controlled release is a technique in which an active drug is made available to a specified target at a rate and period designed to achieve an intended effect. Such controlled release drug delivery devices offer definite advantages which include i) a reduced dosing frequency, ii) a decreased incidence and/or intensity of side effects, iii) a more constant and/or prolonged therapeutic effect, and iv) an increase in cost effectiveness. In this project, students are required to develop a simple MatLab program, simulate drug release from the delivery devices and design them to meet the necessary requirements.


For diffusion-controlled microspheres, drug release profile is obtained by solving Fick’s second law of diffusion subject to appropriate boundary conditions. For one-dimensional drug release from a microsphere, the second Fick’s law of diffusion is given by:

\[
\frac{\partial C}{\partial z} = \frac{1}{r^2 \partial r} \left[ D r^2 \frac{\partial^2 C}{\partial r^2} \right]
\]  

(1)

Where D and C are the diffusion coefficient and drug concentration in the polymer matrix. The boundary conditions are influenced by the mass transfer process at the surface and the volume of the surrounding system. (Davis, 2006)

2.1. Numerical Solution for Slab Shape Drug Release

Concentration profile:

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1. Student
2. A. Professor
Drug Release Rate:

\[
\frac{m_0}{m_{\infty}} = 1 - \sum_{n=0}^{\infty} \frac{1}{\left(2n+1\right)^2 \pi^2} \exp\left(-\frac{\left(2n+1\right)^2 \pi^2 t}{4l^2}\right) \sin\left(\frac{\left(2n+1\right)\pi x}{2l}\right) \cos\left(\frac{\left(2n+1\right)\pi x}{2l}\right)
\]  

(3)

Here \(D\) is diffusivity, \(t\) is the time interval, \(l\) is half thickness of slab, \(x\) is the relative position, and \(-l < x < l\). \(C_{\text{surface}}\) is the concentration at the boundary of the particle, \(C_{\text{initial}}\) is the initial concentration of \(A\) loaded in \(B\), and \(C\) is the concentration at time \(t\), denoting the total amount of diffusing drug which has left inside the particle, and \(m_{\infty}\) is the corresponding quantity after infinite time. (Crank, 1975)

2.2. Numerical Solution for Cylindrical Drug Release

Concentration profile:

\[
\frac{c_{\text{surface}}-c}{c_{\text{surface}}-c_{\text{initial}}} = \frac{2}{\pi} \sum_{n=1}^{\infty} \frac{1}{\alpha_n} \frac{\exp\left(-\frac{D\alpha_n^2 \pi^2 t}{a^2}\right) J_0\left(\alpha_n r\right)}{J_0\left(\alpha_n a\right)}
\]  

(4)

Drug Release Rate:

\[
\frac{M_0}{M_{\infty}} = 1 - \sum_{n=1}^{\infty} \frac{1}{\pi \alpha_n^2} \exp\left(-\frac{D\alpha_n^2 \pi^2 t}{a^2}\right)
\]  

(5)

Here \(D\) is diffusivity, \(t\) is the time interval, \(a\) is the radius, \(r\) is the radial position, and \(0 < r < a\); the \(\alpha_n\) is the root of \(J_0\left(\alpha_n a\right)\), which is the zeroth order Bessel function of the first kind. \(C_{\text{surface}}\) is the concentration at the boundary of the particle, \(C_{\text{initial}}\) is the initial concentration of \(A\) loaded in \(B\), and \(C\) is the concentration at time \(t\), and position \(r\).

\(M_0\) denotes the total amount of diffusing drug which has left inside the particle, and \(M_{\infty}\) is the corresponding quantity after infinite time. (Crank, 1975)

2.3. Numerical Solution for Spherical Drug Release

Concentration profile

\[
\frac{c_{\text{surface}}-c}{c_{\text{surface}}-c_{\text{initial}}} = -\frac{2}{\pi} \sum_{n=1}^{\infty} \frac{1}{\alpha_n} \exp\left(-\frac{D\alpha_n^2 \pi^2 t}{a^2}\right) \sin\left(\frac{\alpha_n r}{a}\right) \sin\left(\frac{\alpha_n a}{a}\right)
\]  

(6)
Drug Release Rate:

\[
M_t = M_\infty - \frac{4}{\pi} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp \left( -\frac{D_n a^2 n^2}{t} \right)
\]

Here \( D \) is diffusivity, \( t \) is the time interval, \( a \) is the radius, \( r \) is the radial position, and \( 0 < r < a \).

\( C_{\text{surface}} \) is the concentration at the boundary of the particle, \( C_{\text{initial}} \) is the initial concentration of \( A \) loaded in \( B \), and \( C \) is the concentration at time \( t \), and position \( r \).

\( M_\infty \) denotes the total amount of diffusing drug which has left the particle, and \( M_\infty \) is the corresponding quantity after infinite time. (Crank, 1975)

3. Simulation and results

The drug is uniformly distributed within the delivery device with an initial concentration of 30 mg/cm\(^3\). Once the device is injected or implanted within the human body, it begins to release the drug by a diffusion-limited process with a constant diffusion coefficient. Assume the resistance to film mass transfer of the drug through the liquid boundary layer surrounding the delivery device surface to the bulk surrounding fluid is negligible. Furthermore, assume that the drug is immediately consumed or swept away once it reaches the bulk solution so that in essence the surrounding fluid is an infinite sink. A list of drugs is given in a table as below.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Diffusion Coefficient ( \times 10^{-15} \text{ cm}^2/\text{s} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitomycin C</td>
<td>1.28</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>0.70</td>
</tr>
<tr>
<td>5-Fluorouridine</td>
<td>0.65</td>
</tr>
<tr>
<td>Goserelin acetate</td>
<td>0.59</td>
</tr>
<tr>
<td>Leuprolide acetate</td>
<td>2.50</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>1.01</td>
</tr>
<tr>
<td>Dopamine</td>
<td>0.63</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1.79</td>
</tr>
<tr>
<td>Nerve growth factor (Ficoll)</td>
<td>1.08</td>
</tr>
<tr>
<td>Bovine serum albumin</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Table 1. Drugs and Diffusion Coefficients in Polymer A.

Take Drug Adriamycin for simulation of its drug release.

The following four geometries have been proposed for the drug delivery device made of polymer Adriamycin: i) a sphere with a radius of 3 \( \mu \text{m} \), ii) a cylindrical tablet with a radius of 3 \( \mu \text{m} \) and a height of 6 \( \mu \text{m} \), iii) a cylindrical fiber with a radius of 3 \( \mu \text{m} \), and iv) a rectangular cuboids with a length, width, and height of 6, 6 and 7 \( \mu \text{m} \) respectively. It is desired to have at least 20\% of the drug being released to the body within 1 week. First of all, we try to plot the drug release profile (as a percentage of drug release) for duration of 1 week for the different geometries in a single figure:
From the simulation results, drug capsules of sphere, finite cylinder and cuboids meet the release requirement of 20% in one week. Hence, we can determine the geometries appropriate for this particular application are sphere, finite cylinder and cuboids.

After the geometries of the drug capsule are determine, we further study the drug release process within the drug carrier. By applying the above literature equations in MatLab, we are able to plot the drug concentration profile (as a function of drug concentration against relative position within the device) for the different geometries in a single figure at a time of

I) 1 week:

Figure 2. First week drug concentration profile within the microparticle
II) 2 weeks:

Figure 3. Second week drug concentration profile within the microparticle

III) 4 weeks:

Figure 4. Second week drug concentration profile within the microparticle

4. Discussion
From the plots of above, at a relative position nearer to the center, the four geometries have almost the same concentration values. When it moves further away from the center, at the same relative position, the cuboids have the highest concentration, followed by finite cylinder, infinite cylinder, and the sphere has the lowest concentration. What is more, the larger diffusion coefficient of the drug in the carrier, the more differences exhibit in the concentration profiles of the four geometries. This may due to different surface-to-volume ratios of the different microparticle geometries where surface-to-volume ration of spherical drug carriers is $3 \ r^{-1}$, $2 \ r^{-1}$ for infinite cylinder, $2h^{-1} + 2 \ r^{-1}$ for finite cylinder and $(2ab+2ac+2bc)/abc$ for cuboids (a b c stands for side length, h stands for height of cylinder and r stands for radios).

5. Conclusion

This project models the situation when the drug capsule is injected into human body, the drug slowly releases into the cancer cells by an unsteady state diffusion. Assume the surrounding fluid has a negligible resistance to the film mass transfer of the drug through the boundary layer of the drug capsule. Moreover, the drug is immediately consumed when it reach the bulk fluid which is an infinite reservoir. Then it comes to a design problem that we are required to apply current numerical solutions to select an appropriate geometry of the polymer to be the drug carrier to meet certain drug release requirement and incorporated with MatLab to simulate the dosage process. In the future, the relationship between the carrier dimensions and diffusivity would be investigated and correlations could be applied to real life drug delivery experiment.

References