A Thesis
entitled
Modeling of Controlled Drug Delivery from a Chitosan Microparticle
by
Niloofar Alipourasiabi
Submitted to the Graduate Faculty as partial fulfillment of the requirements for
the Master of Science Degree in
Chemical Engineering

_____________________________
Dr. Arunan Nadarajah, Committee Chair

_____________________________
Dr. Lidia Rodriguez, Committee Member

_____________________________
Dr. Maria Coleman, Committee Member

_____________________________
Dr. Amanda Bryant-Friedrich, Dean
College of Graduate Studies

The University of Toledo
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An Abstract of

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Nowadays, advanced controlled drug delivery systems have been attracted the
pharmaceutical research studies. As several experiments have to be done for
pharmaceutical approaches, mathematical modeling becomes important. Mathematical
modeling of drug release provides better understanding of controlled drug delivery system
and would help to optimize the system without huge number of expensive experiments.

Diffusion is the predominant transport phenomena of the drug delivery systems.
Therefore, optimizing the parameters related to diffusional mass transport, such as
diffusion coefficient and porosity, would be the essential key to get better controlled drug
release profile.

One of the challenges of controlled drug delivery systems is the initial burst, which
decreases the effective lifetime of drug and would cause toxicity. This challenge has been
solved by using a coating layer to control the drug release. Regarding to this issue,
promising modeling results have been shown in this study and all the modeling data have
been fitted with available experimental set of data.
The mathematical modeling results in a partial differential equation. The analytical solution for the simplified equation is provided in this study. However, the boundary condition for the outer layer is complicated and the solution for the real problem would be available by using numerical methods. Finite difference method provided the numerical solution to the real problem and MATLAB software facilitate the process of solving the equation numerically.
To my parents, who taught me everything that truly matters. And to my husband, who is always there for me.
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Graph of cumulative drug release from PLGA 85:15 coated microparticle in comparison with non-coated one. Solid line is modeling and points are experimental data. Non-coated in red and coated in blue.

Graph of cumulative drug release from PLA coated microparticle in comparison with non-coated one. Solid line is modeling and points are experimental data. Non-coated in red and coated in blue.
List of Abbreviations

FDA............................Food and drug administration
MOL............................Method of lines
ODEs...........................Ordinary differential equations
PGA............................Poly glycolic acid
PDE............................Partial differential equation
PLA............................Poly (lactic acid)
PLGA..........................Poly (lactic-co-glycolic acid)
SEM .........................Scanning electron microscope


List of Symbols

b.........................Number of microparticles
C..........................Concentration of drug
D..........................Diffusion coefficient
$D_{AB}$...................Efficient diffusion coefficient
E..........................porosity factors ratio
$G$..........................Diffusion coefficients ratio
i..........................Index for sigma in analytical method
i..........................Index for space in numerical method
j..........................Index for sigma analytical method
j..........................Index for time in numerical method
J..........................Flux of drug
K..........................Drug diffusion consumption constant
KH..........................Constant of Higuchi
$n_A$......................Mass flux of drug
$Q_t$......................Amount of drug release in time t in Higuchi model
r..........................Radius of sphere
$r_A$......................Rate of accumulation
$r^*$......................Dimensionless form of radius
t..........................time
t$^*$.......................Dimensionless form of time
u..........................Transformation function
u$^*$......................Dimensionless form of transformation function
x..........................Space in the model

$\vec{\theta}$...................Fluid velocity vector
$\rho_A$......................Mass concentration of A(drug)
$\omega_A$...................Mass fraction of A
$\varphi$......................Angle in spherical coordinate
$\theta$......................Angle in spherical coordinate
$\varepsilon$...................Porosity factor
$\theta_r$...................Fluid velocity in r direction
$\theta_\theta$................Fluid velocity in $\theta$ direction
$\theta_\varphi$................Fluid velocity in $\varphi$ direction
$\rho_{A0}$....................Initial mass concentration
$\Delta$......................Derivative operator
$\nabla$......................Partial Derivative vector operator
\( \partial \) ......................... Partial derivative operator
\( \phi_i \) ............................ Eigen function
\( \lambda_i \) ............................ Eigenvalue
Chapter 1

Introduction

Oscillation of drug levels in plasma is one of the reasons for toxicity and ineffectiveness of drugs.\textsuperscript{1} There is a maximum value above which the drug is toxic and a minimum value below which the drug is ineffective. The drug release profile has to be in this range. This is a challenge which has attracted the scientists in the pharmaceutical industry to work on controlling the administration of drugs.

Multiple dosages of conventional forms of drugs in a day are required to achieve a sustained therapeutic plasma concentration. One way to solve the problem is by using biodegradable polymer microspheres containing dispersed medication.\textsuperscript{2} In this case, diffusion of drug through the polymer matrix, controls the release process. As the diffusion process is slow, it decreases the oscillation and the drug release profile is within the therapeutic range.

One of the main properties of polymers in drug delivery, is the biodegradability because they are removed by normal metabolic pathway and are not harmful for human health. In recent years, biodegradable polymers have been used as the carriers of drugs to achieve the desired drug release profile. Chitosan is a natural polysaccharide which is one of the most common used carriers to control drug diffusion in blood. Chitosan is helpful
for maintaining drug in the therapeutic range in which the level of drug is effective and non-toxic.

Controlled drug release from a single administration, reduces the side effects related to high concentration and repeated administration of drug. Nowadays, around sixty million people, who fight with several illnesses such as cancer, have been supported by advanced drug delivery systems. In other words, conventional drug therapy regimens have been replaced by their controlled release drug delivery alternatives such as Chitosan, poly (lactic acid) (PLA) and poly (lactic-co-glycolic acid) (PLGA) microspheres.

1.1 Biodegradable polymers for drug delivery

Numerous studies has been done on application of biodegradable polymers in drug delivery area since it was found that these polymers are bioresorbable functional devices in surgery. Biodegradable materials categorize in natural and synthetic polymers. They degrade enzymatically or non-enzymatically or both with non-toxic by-products which are removed by normal metabolic pathway. Hence, their process of degradation is biocompatible and non-toxic. Chitosan is in the family of natural biodegradable polymers whereas PLA and PLGA are in the synthetic group.
1.1.1 Chitosan

The structure of Chitosan polysaccharide is similar to cellulose. This compound is produced from the deacetylation of chitin by using sodium hydroxide as a reagent and water as solvent. Chitin is a natural product and highly available biocompatible polysaccharide. On the other hand, application of chitin is restricted comparing to chitosan because the chitin is chemically inert. In comparison to chitin, chitosan is reactive and different forms of it can be obtained such as powder, paste, etc.\textsuperscript{6}

![Chitosan structure]

**Figure 1-1.** Chitosan structure

Chitosan has several advantages that made it one of the best polymers for controlled drug release. It is non-toxic and biodegradable in a way that it breaks down to amino sugars in the human body. The low cost of it is another reason for the huge usage in biomedical industry.\textsuperscript{1}
1.1.2 Poly (lactide acid)

Lactic acid is the monomer of poly lactide acid and can be obtained from renewable sources. Corn is the most common feedstock to produce the precursor of PLA. PLA as a biodegradable polymer decomposes into carbon dioxide and water.

![PLA structure]

Figure 1-2. PLA structure

1.1.3 poly (lactide-co-glycolide)

PLGA is a copolymer of two different acids: poly glycolic acid (PGA) and PLA. Weight percentage of each polymer, defines the copolymer. For instance, an 85:15 PLGA contains 85 percent of PLA and 15 percent of PGA.
PLGA has been used for different commercial and research controlled drug delivery approaches. This polymer is physically strong, biodegradable and biocompatible which has been approved by FDA.

Existence of esters in these polymers’ (PLA and PLGA) backbone made them biodegradable. In addition, they are capable to form thin layers which are needed for pharmaceutical coating purposes.

1.2 Methods of controlled drug-delivery

Langer classified the polymeric drug delivery systems to four categories: swelling controlled, diffusion controlled, chemically controlled and magnetically controlled. Among these, swelling controlled and diffusion controlled systems have been employed in most of the experimental and modeling studies.

Diffusion controlled system contains two devices: the reservoir system and the porous network monolithic matrices.
1.2.1 Reservoir system

Reservoir drug delivery devices contain a membrane which enclosing the drug. Dissolution into the polymer following by diffusion through the polymer membrane is the process for drug release of reservoir controlled system. Saturating the membrane prior to drug release happens in the storage and is one of flaws for the reservoir systems. As the drug has been already diffused into the surface of the membrane, it will be immediately released by placing the system into the release media. As a result, a sudden release of drug happens.

Figure 1-4. Reservoir system

1.2.2 Monolithic System

Monolithic drug delivery systems contain uniformly dispersed drug in a porous polymer. The hydrogels are the swellable monolithic systems which has attracted the
pharmacological industry. The monolithic system is more common than the reservoir system because of the possible defects in the membrane of reservoir system. These defects may result in higher sudden drug release which is undesirable.

![Figure 1-5. Monolithic System](image)

1.3 Initial burst

Some of the drugs need prolonged treatment but their short biological half-life makes it difficult to achieve the effective drug release profile. Controlling the release of drugs over a long period of time is the main advantage of injectable polymer microspheres. However, there is a technical problem with these polymers. In the first day of administration and in the early stage of drug release process, most of the drug releases from the microsphere into the human body. This dose dumping, which is called “initial burst”,

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cause serious problems such as toxicity and decreasing the drug efficiency. Hence, it is an important issue to work in the area of controlled drug delivery.\textsuperscript{10}

The initial burst release diminishes the effective lifetime of the polymeric drug delivery device. In addition, the high initial concentration may reach to the toxic level of drug in the patient’s body. This phenomenon is neglected in most mathematical models because the initial burst takes place in very short time in comparison with the total release of the drug.\textsuperscript{8}

Burst release can be a surface phenomenon.\textsuperscript{8} It is mentioned in several studies that the fast drug release from the surface of the microsphere is the reason for the initial burst.\textsuperscript{10} Therefore, an outer layer coating would prevent the initial burst in the drug release process.\textsuperscript{8}

1.4 Proposed research

1.4.1 Experiments

Controlled drug delivery is a method with preset rate of drug release in a determined period of time.\textsuperscript{9} There are two categories for controlled drug delivery: Sustained and targeted drug delivery. In this study, the focus was on sustained drug delivery over a period of time. One of the aims for this drug delivery system is to increase patient compliance by fewer effective doses of drug.

In experimental data which were acquired by Dr. Rodriguez\textsuperscript{1}, several methods have been tried to find an optimum controlled drug delivery. Based on the experimental data,
increasing the amount of crosslinking results in slower drug release. However, it also causes reduction in drug loading efficiency.

An optimization was done to maintain the balance between loading efficiency and drug release rate but even the optimum one was not desired. The reason is that the positive effect of decreasing initial burst is negligible in comparison with the downside of reduction in drug loading efficiency. Hence, a novel method was used to achieve the desired results.

In the novel approach, the reservoir and monolithic system were combined in one polymeric drug delivery device. As a result, the drawbacks of each system were mitigated. In this method, the drug was dispersed in the chitosan matrix (monolithic system) and a biopolymer coating surrounded this matrix (reservoir system). In other words, this method is the surface modification of the chitosan microparticles using a coating of another biopolymer.

**Figure 1-6.** Combination of reservoir and monolithic system.
Chitosan has been studied as the polymer matrix in this research. Poly (lactide acid) and poly (lactide-co-glycolide) were used as the coating materials. Coated microparticles have shown better results in sustainability and decreasing the initial burst. The drug release was done in five days sustainably.\textsuperscript{1}

One of the advantages of this system is the improvements in the reservoir system. In the case of mechanical defects in the biopolymer layer, the drug will not release immediately because it is dispersed in the monolithic system. In addition, maximum amount of the drug can be loaded in the chitosan matrix without the need of high crosslinking agent. Another advantage of using protective coating is the enhancement in the mechanical properties. Existence of coating provides higher mechanical strength which is as functional as crosslinking.

1.4.2 Modeling Research objectives

There is an essential need to do several experiments for pharmaceutical objectives. Mathematical modeling facilitates the development process of drug release without the need to perform vast number of experiments.

Three different mechanisms of diffusion, swelling and erosion are considered for controlled drug delivery in most of the pharmaceutical studies. In this research, the focus is on the diffusion part and it has been shown that the diffusion process is the most important fact. Hence, the interest in the present work is in drug diffusion from polymeric device. As a matter of fact, any other effects such as degradation of the polymeric matrix were ignored.
In the present study, numerical solution has been used to model the drug diffusion through the porous media and polymer coating, and MATLAB software facilitate the simulation of it.

In conclusion, the objective of this research is to develop a model for the drug release from an optimized drug delivery system. By mathematical modeling, the equation of diffusion has been acquired and numerical method has been used as a tool to solve the governed equation.
Chapter 2

Development of the mathematical modeling

Pre-designed manner of drug release in controlled drug delivery systems provides the efficient therapeutic results along with patient compliance. Scientific understanding of the mass transport mechanism of drug release is provided by mathematical modeling which can help to improve future drug delivery systems. Although a mathematical model predicts drug release mechanism only for a particular pharmaceutical system, it will be helpful to provide general guidelines to design various kinds of drug delivery systems.

There are some specific drugs which must be received very often because they have short therapeutic life time. In these cases, controlled drug delivery offers better drug efficiency and patient satisfaction. Drug release at controlled rate, time, and concentration has been provided by localized drug delivery system.

Clinical experiments are expensive and time consuming. Mathematical modeling provides better understanding of the drug release mechanism which will facilitate the observations of various hypotheses before performing any clinical experiments.11
2.1 Literature review on Mathematical modeling:

2.1.1 Higuchi Model

Higuchi\textsuperscript{12} proposed a model for the drug release based on Fick’s law in 1963. This model is one of the popular models that most of the mathematical modeling articles have been discussed it. The mathematical expression is:

\[ Q_t = KH\sqrt{t} \quad (2-1) \]

Here, the t is time, \( Q_t \) is the amount of drug release in time t and KH is the constant of Higuchi.

There are several assumptions which Higuchi considered for describing this model:

1. There is a perfect sink in the diffusion environment.
2. Device swelling and eroding can be ignored.
3. The drug diffusion is in one dimension.
4. Diffusion coefficient of the drug is assumed to be constant.
5. Size of drug particles are much smaller than the thickness of system.
6. The initial concentration of drug in the matrix is much higher than solubility of the drug.
2.1.2 Two dimensional model

Another approach to do the modeling,\textsuperscript{11} is to consider convection and diffusion in the mass transport of drug release. The two dimensional model equation for drug delivery system is given below:

\[
\frac{\partial C}{\partial t} + \vec{\vartheta} \Delta C = \nabla (D \nabla C) - KC
\]  

(2-2)

where \( C \) is concentration of drug, \( t \) is time, \( K \) is drug consumption constant, \( D \) is diffusion coefficient, and \( \vec{\vartheta} \) is fluid velocity vector.

The effect of convection is ignored and the continuity equation is used for the mathematical model of the system. There is no fluid flow in the system and also, the temperature change has been neglected. Therefore, \( \vartheta = 0 \) and \( K = 0 \). The simplified equation is:\textsuperscript{11}

\[
\frac{\partial C}{\partial t} = \nabla (D \nabla C)
\]  

(2-3)

2.1.3 One dimensional method

Using Fick’s law of diffusion in another attempt for modeling,\textsuperscript{13} provided best description of drug diffusion in one dimension. For the reservoir system, Fick’s law of diffusion describes the drug release through the membrane which surrounds the drug.
\[ J = -D \frac{dc}{dx} \]  

(2-4)

J is the flux of the drug, D is the drug diffusion coefficient, and C is the drug concentration. The drug diffusion coefficient is considered as constant. In addition, the flux has been considered for mass average velocity of the system.

The equation for monolithic system is defined by Fick’s second law:

\[ \frac{dc}{dt} = \frac{Da^2c}{dx^2} \]  

(2-5)

This equation achieved by assuming the constant diffusion coefficient.

2.2 Need for new model

As explained in the section 2.1, the models for drug delivery systems are considered in Cartesian system. However, the geometry of the drug delivery systems is spherical and the simplifying assumptions for the system would cause some errors in the final model. Although achieving the sphere geometry for all the microparticles is ideal and might not be possible, considering spherical geometry is more accurate than Cartesian.

There are more assumptions for the existing models. One of the main simplifying assumptions considered in these models, is the perfect sink in the diffusion environment. This assumption plays an important role in the model as it describes the boundary condition
in the outer layer of sphere. Therefore, there is a need to consider the real boundary condition to acquire the more precise model.

One of the other objectives of writing a new model, is to develop the model for the combination of monolithic and reservoir system. Current studies are focused on one of the systems mostly monolithic system as it is more common in the controlled drug delivery. In this study, the monolithic system is modeled as the first attempt and then, the combination of it with reservoir system is achieved.

2.3 Development of the model

The microparticle in this study, is a polymer sphere with drug dispersed in it. This polymer is highly porous in a way, which it is assumed that the diffusion is happening all over the sphere. In reality, the diffusion occurs only through the pores, but as this chitosan polymer is highly porous, it can be considered as a homogenous sphere carrying the drug. In addition, it is assumed that all the particles are in the same size and the average radius of the particles considered to be the radius of each particle. During the time, the drug diffuses out to the environment. The diffusion environment is well mixed. As a result, the diffused mass considered to be homogenous all over the environment.

The early stage of drug release process is accompanied by a significant release of the drug. Decreasing this initial burst is one of the main objectives of this study because the decrease keeps drug in therapeutic range and in an efficient way. In order to decrease the amount of initial burst in drug release process, the description of the associated physics of drug diffusion in mathematical terms is needed. First, finding an appropriate equation is
necessary. Defining boundary conditions and initial condition is next step to start the modeling.

2.3.1 Equation

Conservation equation of mass is written in the spherical coordinate. The purpose of writing this equation, is to express the variation of mass concentration \( \rho \) in the control volume over time. \( \rho \) is governed by conservation principle that indicates:

\[
\text{Accumulation of } \rho \text{ in the control volume over time } Dt \\
= \text{transport rate of mass in} - \text{transport rate of mass out} \\
+ \text{generation of } \rho \text{ inside control volume}
\]

There is no generation of mass in the spherical hydrogel. As a result, the accumulation term is zero.
By considering the differential mass which is shown in the figure (2-1), the equation of continuity for the drug A, in terms of $\rho$ for constant $\rho D_{AB}$ has been derived:\textsuperscript{14}

\begin{equation}
\rho \left( \frac{\partial \omega_A}{\partial t} + \partial_r \frac{\partial \omega_A}{\partial r} + \frac{\partial \theta}{r} \frac{\partial \omega_A}{\partial \theta} + \frac{\partial \varphi}{r \sin \theta} \frac{\partial \omega_A}{\partial \varphi} \right) = \rho D_{AB} \left[ \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial \omega_A}{\partial r} \right) + \frac{1}{r^2 \sin \theta} \frac{\partial}{\partial \theta} \left( \sin \theta \frac{\partial \omega_A}{\partial \theta} \right) + \frac{1}{r^2 \sin^2 \theta} \frac{\partial^2 \omega_A}{\partial \varphi^2} \right] + r_A
\end{equation}

Or
\[
\left( \frac{\partial \rho_A}{\partial t} + \frac{\partial}{\partial r} \frac{\varrho \rho_A}{r} + \frac{\partial}{\partial \theta} \frac{\rho_A}{r \sin \theta} + \frac{\partial}{\partial \varphi} \frac{\rho_A}{r \sin \theta} \right) = D_{AB} \left[ \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \left( \frac{\partial \rho_A}{\partial r} \right) \right) + \frac{1}{r^2 \sin \theta} \frac{\partial}{\partial \theta} \left( \sin \theta \frac{\partial \rho_A}{\partial \theta} \right) + \frac{1}{r^2 \sin^2 \theta} \frac{\partial^2 \rho_A}{\partial \varphi^2} \right] + \tau_A
\]
(2-7)

\( \omega_A = \) mass fraction of A

\( \rho_A = \) mass concentration of A

\( \varphi = \) arc tan \( y/x = \) angle in spherical coordinates

\( \theta = \) arc tan \( \sqrt{x^2 + y^2}/z = \) angle in spherical coordinates

The term of \( D_{AB} \) is the diffusion coefficient. As this study focus on porous hydrogels, the more accurate definition of this term would be efficient diffusion coefficient which include porosity term in it.

\[ D_{AB} = \frac{D \epsilon}{\tau} \]  
(2-8)

Where the \( \epsilon \) is the porosity factor of hydrogel and \( \tau \) is the tortuosity which considered to be one. Hence, the product of diffusion coefficient and porosity factor is considered as the definition of efficient diffusion coefficient.

Assumption is to ignore the diffusion in \( \theta \) and \( \varphi \) directions and velocity in \( r \) direction is assumed to be zero. In addition, the rate of accumulation is zero. Hence, the simplified equation will be:

\[ \frac{\partial \rho_A}{\partial t} = D_{AB} \left[ \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \left( \frac{\partial \rho_A}{\partial r} \right) \right) \right] \]  
(2-9)
This is the original diffusion equation which is used to find the diffusion rate of drug from chitosan microparticle. The mass concentration is defined as “concentration” in this study.

### 2.3.2 Initial and boundary conditions

The beginning concentration in the microsphere has been considered as constant value of $\rho_{A0}$ in all over the particle. In the center of sphere, the concentration is considered to be finite.

The concentration in the outer boundary layer is assumed to be zero. This assumption is only correct if the outside fluid velocity is high enough that there is no observed diffused mass in the boundary. However, this boundary condition for the radius of ‘a’, the radius of spherical particle, and time $t$ is not the real one. This is one of the assumptions that has been modified in the modeling of real problem. The zero boundary condition in the time of $t$ and radius of $a$ will be considered only for simplifying the initial steps of modeling.

The solution domain of the equation (2-9) formed by an initial boundary condition and is developing by time steps and two specified boundary conditions are limiting it.\(^{15}\)

The simplified initial and boundary conditions to solve the governed equation are:

\[
\frac{\partial \rho_A}{\partial t} = D_{AB} \frac{1}{r^2} \left( \frac{\partial}{\partial r} \left( r^2 \frac{\partial \rho_A}{\partial r} \right) \right) \quad (2-10)
\]

\[
\rho_A(r, a) = \rho_{A0}
\]
\[ \rho_A(a, t) = 0 \]
\[ \rho_A(0, t) = \text{finite} \]

In order to solve this equation, it is helpful to transform the (2-10) equation using the transformation of \( u(r, t) = r \rho(r, t) \). The transformed equation is:

\[
\frac{\partial u}{\partial t} = D_{AB} \frac{\partial^2 u}{\partial r^2} \tag{2-11}
\]

In order to develop the complicated real model, it is better to start with the simplified conditions to evaluate the selected solving method for the advanced model. Therefore, the initial steps of modeling started with the simplified assumptions. The simplified initial condition and boundary conditions are:

\[ u(r, 0) = r \rho_{A_0} \]
\[ u(a, t) = 0 \]
\[ u(0, t) = 0 \]
\[ u(o, t) = 0 \]

Which are used to solve the problem analytically.

2.4 Analytical solution

The transport equation of (2-11) is categorized as a Partial differential equation (PDE). This category of equations is one of the most applicable one in engineering and
science. In most of the solving approaches, the PDEs were transformed to ordinary differential equations (ODEs) to make them simpler. In this part, the goal is to solve the PDE equation with the simplified boundary conditions assumptions.

Regarding to type of initial and boundary conditions, there are different PDE equations forms. Hence, it is important to define various kinds of partial differential equations. 16

The PDE equations are classified in three different categories: Hyperbolic, Parabolic and Elliptic. The equation of (2-11) is a parabolic partial differential equation. In order to solve it analytically, Eigen function were used. Here is the analytical procedure of solving the equation with simplified boundaries:

\[
u(r, t) = \sum_{i=1}^{\infty} \langle u, \Phi_i \rangle \Phi_i\]  

(2-12)

The definition for \( \langle \phi_i, \phi_j \rangle \) would be:

\[
\langle \phi_i, \phi_j \rangle = \int_0^a \phi_i \phi_j dr = \delta_{ij}
\]

(2-13)

Before any further proceeds, the \( \phi_i \) has to be known. Using the following equation,

\[
\frac{\partial^2 \phi}{\partial t^2} = -\lambda_i^2 \Phi
\]

(2-14)

And the solution for \( \Phi \) would be in this form:

\[
\Phi = A \sin \lambda r + B \cos \lambda r
\]

(2-15)

By the following boundary conditions, the \( \Phi \) equation is simplified:

\[
\Phi(0) = 0 \quad \Rightarrow \quad B=0
\]
The simplified equation for $\Phi$ is:

$$\Rightarrow \Phi_i = A_i \sin(\lambda_i r) = A_i \sin\left(\frac{i\pi}{a} r\right) \quad (2-16)$$

In order to find $A_i$, the equation (2-13) is used:

For $i=j$:

$$1 = \int_0^a \Phi_i^2 \, dr = A_i^2 \int_0^a \sin^2 \left(\frac{i\pi}{a} r\right) \, dr = \frac{A_i^2}{2} \int_0^a \, dr - \frac{A_i^2}{2} \int_0^a \cos \left(\frac{2i\pi}{a} r\right) \, dr$$

$$1 = \frac{A_i^2 a}{2} - \frac{A_i^2 a}{2\pi} \sin \left(\frac{2i\pi}{a} r\right) \bigg|_0^a$$

As the term of $\sin \left(\frac{2i\pi}{a} r\right) \bigg|_0^a$ equals to zero, the $A_i$ would be:

$$A_i = \sqrt{\frac{2}{a}}$$

Regarding to $A_i$, the $\Phi_i$ would be:

$$\Phi_i = \sqrt{\frac{2}{a}} \sin \left(\frac{i\pi}{a} r\right) \quad (2-14)$$

Additionally, these equations are provided to solve the equation:

$$\frac{\partial}{\partial t} (u, \Phi_i) = \left(\frac{\partial u}{\partial t} , \Phi_i\right) = D_{AB} \left(\frac{\partial^2 u}{\partial t^2} , \Phi_i\right) \quad (2-15)$$

Based on the equation of (2-13), the term of $\left(\frac{\partial^2 u}{\partial r^2} , \Phi_i\right)$ can be obtained in this way:

$$\frac{\partial^2 u}{\partial r^2} \frac{\partial^2 u}{\partial r^2} \Phi_i \, dr = \frac{\partial u}{\partial r} \left[\Phi_i \right]_0^a - \int_0^a \frac{\partial u}{\partial r} \frac{\partial \Phi_i}{\partial r} \, dr = -u \frac{\partial \Phi_i}{\partial r} \bigg|_0^a + \int_0^a u \frac{\partial \Phi_i}{\partial r} \, dr$$
Since the following terms would be zero,

\[ \frac{\partial u}{\partial r} \phi_i \bigg|_0^a = 0, \quad -u \frac{\partial \phi_i}{\partial r} \bigg|_0^a = 0 \]

This equation is achieved:

\[ \langle \frac{\partial^2 u}{\partial r^2}, \phi_i \rangle = \langle u, \frac{\partial^2 \phi_i}{\partial r^2} \rangle \quad (2-16) \]

As a result, the chain of equations will be completed in this way:

\[ \frac{\partial}{\partial t} \langle u, \Phi_i \rangle = \langle \frac{\partial u}{\partial t}, \Phi_i \rangle = D_{AB} \langle \frac{\partial^2 u}{\partial t^2}, \Phi_i \rangle = D_{AB} \langle u, \frac{\partial^2 \phi_i}{\partial t^2} \rangle = -\lambda_i^2 D_{AB} \langle u, \Phi_i \rangle \quad (2-17) \]

Now, the aim is to solve the following equation:

\[ \frac{d}{dt} \langle u, \phi_i \rangle = -\lambda_i^2 D_{AB} \langle u, \phi_i \rangle \quad (2-18) \]

The solution for this equation is provided as follows:

\[ \langle u, \phi_i \rangle = \langle u, \phi_i \rangle \bigg|_{t=0} e^{-\lambda_i^2 D_{AB} t} \quad (2-19) \]

Based on the equation (2-13), the solution for the (2-19) equation would be:

\[ \langle u, \phi_i \rangle \bigg|_{t=0} = -A_i \rho A_0 \frac{-a^2}{i \pi} (-1)^i \quad (2-20) \]

Considering equations of (2-19) and (2-20), the final result is as follows:

\[ \langle u, \phi_i \rangle = \langle u, \phi_i \rangle \bigg|_{t=0} e^{-\lambda_i^2 D_{AB} t} = -\frac{2}{\sqrt{a}} \rho A_0 \frac{a^2 (-1)^i}{i \pi} e^{-\lambda_i^2 D_{AB} t} \quad (2-21) \]

Therefore, based on the equation of (2-12), the analytical solution for the simplified conditions would be:

\[ u = -\frac{2\rho A_0 a}{\pi} \sum_{i=1}^{\infty} \frac{(-1)^i}{i} \sin \frac{i \pi r}{a} e^{-\frac{D_{AB} (\frac{mr}{a})^2}{t}} \quad (2-22) \]
2.5 Mathematical modeling for the real conditions

2.5.1 Boundary condition

The boundary condition of the parabolic equation of (2-11) is Dirichlet type. It means the boundary on the outer layer is a specific function. This function for the boundary needs to be calculated in this study. Numerical method using MATLAB has been used to find the unknown boundary condition and as a result the numerical solution of the equation.

2.5.2 Dimensionless form

The non-dimensional form of equation is the simplified equation, which reduces the number of parameters. Non-dimensionalized parameters are better to understand and enough simplified to work with. Moreover, by changing the scale, the relative computing quantitative can be acquired. Another advantage of making transport equation dimensionless, is the compatibility to use it for other cases with same boundary conditions because the comparison between the sets of data will be easier.

Defining some dimensionless parameters is required for making the equation dimensionless. Reference values of “\( \rho_{A0} \)” for mass concentration and “a” for radius have been considered. Defined dimensionless forms of parameters are:

\[
\begin{align*}
    u^* &= \frac{u}{a \rho_{A0}} = \frac{r \rho_A}{a \rho_{A0}} \\
\end{align*}
\]

(2-23)
\[ r^* = \frac{r}{a} \]  
\[ t^* = \frac{tD_{AB}}{a^2} \]

(2-24)  
(2-25)

By Substitution of these expressions into the equation of (2-11), the non-dimensional diffusion equation governed as this:

\[ \frac{\partial u^*}{\partial t^*} = \frac{\partial^2 u^*}{\partial r^*^2} \]  
(2-26)

The boundary conditions in dimensionless form has been expressed as:

\[ u^*(r^*, 0) = \frac{r}{a} = r^* \]
\[ u^*(0, t^*) = 0 \]
\[ u^*(1, t^*) = 0 \]

For the convenience, the star has been dropped from the notation for all the following equations. Therefore, all the equations used for the model are non-dimensionalized.

\textbf{2.5.3 Mathematical modeling for coated microparticle}

The mathematical modeling for monolithic system has been explained. The novel method which is developed in the experimental data is to combine monolithic system with a coating layer as it is shown in figure 2-2. In this case, the initial burst decreases
significantly because of the protecting polymer layer. The illustration for mathematical modeling has been developed here:

Figure 2-2. Schematic view of coated microparticle with diffusion coefficient of $D_1$ for inner layer and $D_2$ for outer one.

The equations for inner layer:

$$\frac{\partial \rho_1}{\partial t} = D_1 \frac{\partial}{\partial r} \left( r^2 \frac{\partial \rho_1}{\partial r} \right)$$  \hspace{1cm} (2-27)

Using the transformation of $u_1 = r \rho_1$, it is governed as:

$$\frac{\partial u_1}{\partial t} = D_1 \frac{\partial^2 u_1}{\partial r^2}$$  \hspace{1cm} (2-28)

For the second layer (outer layer), the equation would be:

$$\frac{\partial \rho_2}{\partial t} = D_2 \frac{\partial}{\partial r} \left( r^2 \frac{\partial \rho_2}{\partial r} \right)$$  \hspace{1cm} (2-29)

By transformation of $\rho_2$ to $u_2$ using $u_2 = r \rho_2$, the following equation achieved:

$$\frac{\partial u_2}{\partial t} = D_2 \frac{\partial^2 u_2}{\partial r^2}$$  \hspace{1cm} (2-30)
The process of making the equations dimensionless is based on the parameters of inner part (Sphere 1), because the layer of coating is too thin which is ignorable in comparison to the radius of the monolithic system.

The dimensionless parameters for this system are:

\[ u^* = \frac{u}{a \rho A_0} = \frac{r \rho A}{a \rho A_0} \]  

\[ r^* = \frac{r}{a} \]  

\[ t^* = \frac{t D_1}{a^2} \]  

Based on these defined parameters, the dimensionless forms of equations are achieved. The equation for monolithic system (sphere 1) obtained as:

\[ \frac{\partial u^*}{\partial t^*} = \frac{\partial^2 u^*}{\partial r^*} \]  

And for the outer layer:

\[ \frac{\partial u^*}{\partial t^*} = \frac{D_2}{D_1} \frac{\partial^2 u^*}{\partial r^*} \]  

As the equations for this system are obtained, the next step is to define boundary conditions.

Regarding to the interface of the two layers, the equations have been derived:

\[ -D_1 \frac{\partial \rho_1}{\partial r_1} \bigg|_{r = a} = -D_2 \frac{\partial \rho_2}{\partial r_2} \bigg|_{r = a} \]  

For understanding better, the relations of diffusion coefficients and mass concentrations of both layers need to be illustrated:

\[ G = \frac{D_2}{D_1} \]
\[ \rho_2 = \rho_1 E \]  

As a result, the equation for this boundary is simplified to:

\[ \frac{\partial \rho_1}{\partial r} \bigg|_{r = a} = G \cdot E \cdot \frac{\partial \rho_1}{\partial r} \bigg|_{r = a} \]  

(2-38)

The obtained equation for this boundary would be:

\[ GE = 1 \]  

(2-39)

As it is shown, there is no change by considering this interface equation because it only helps to get the right relation between the parameters and it has not added any other equations. Therefore, the system considered to be a sphere with changing efficient diffusion coefficient as a function of radius as it is shown in figure 2-3. The general equation for this system is considered as:

\[ \frac{\partial u}{\partial t} = G \cdot \frac{\partial^2 u}{\partial x^2} \]  

(2-40)

\[ G = \frac{D_2}{D_1} \quad r^* = 0 \text{ to } \frac{b}{a} \]

\[ G = 1 \quad r^* = 0 \text{ to } 1 \]

**Figure 2-3.** Schematic view of drug diffusion through monolithic and reservoir system considering a sphere with changing efficient diffusion coefficient.
Chapter 3

Numerical method

3.1 Need for numerical methods

Partial differential equations (PDEs) are the multivariable equations which are useful for solving most of the transport problems. Analytical solutions are the most accurate ways to solve the PDE equations. However, they provide solutions for the very simple problems and it is not easy to achieve the analytical solution for a differential equation. Therefore, numerical methods have been used for solving PDE equations.

3.2 Numerical methods for differential equations

Finite difference method, finite element method, and finite volume method are some of the common methods which have been used for transport problems. For solving one dimensional problems of drug delivery, there are two numerical methods: Finite difference method and method of lines. Method of lines (MOL) is a method which has been used to solve the diffusion equation numerically.
In this method, the time derivative is considered continuous as follows: \( ^{18}\)

\[
\frac{dc}{dt} = D\left[\frac{C(x_{m+1}, t) - 2C(x_m, t) + C(x_{m-1}, t)}{(\Delta x)^2}\right]
\]

(3-1)

However, the finite difference method is more popular than this method. In the proposed research, the finite difference method is selected to solve the diffusion equation. Therefore, the following part describes more details for it.

### 3.3 Finite difference method

Discretization is the basic idea of numerical methods. A discrete number of points in the domain provides us the solution for the PDE equation. These points are called nodes or grid points in the numerical methods. Forming of the grids are by dividing the domain in the desired direction of the problem. It means nodes are in the intersection of subdivided regions.

The number of grid points should be large enough to get accurate solution close to the exact solution of original differential equation. Uniform and non-uniform grids are different kinds of these divisions. In the proposed research, uniform meshes (or grids) have been used.

The process of achieving the diffusion equation from the set of grid point equations is called discretization process and the method which is applied to do this conversion is called discretization method. Local profile assumptions have been considered for the discretization process as it is important to know how the concentration is changing in the
surrounded local neighborhood of the grid points. As a result, derivation of the set of algebraic equations and a method for their solution have been provided by numerical methods.

One of the methods for changing the transport equation to a set of discrete equations is the finite difference method. The finite difference method is the most efficient method in comparison with the other mesh-based discretization methods such as finite volume and finite element. Finite difference method is often used to achieve numerical solution of the equations with specified initial and boundary conditions.16

Finite difference method suggests an approximation solution using finite set of difference equations. In this case, time and space are divided into equal dimensions of $\Delta t$ and $\Delta x$. They are defined as

$$t_n = t_0 + n\Delta t$$  \hspace{1cm} (3-2)

$$x_m = x_0 + m\Delta x$$ \hspace{1cm} (3-3)

The one dimensional mesh in this process is as follows:

![Figure 3-1. One dimensional mesh for space](image)

There are three different techniques in finite difference methods for generating finite difference equations in space which are written based on the first derivatives:
1. Forward difference method: \[
\frac{\partial u}{\partial x} = \frac{u_{i+1} - u_i}{\Delta x}
\] (3-4)

2. Backward difference method \[
\frac{\partial u}{\partial x} = \frac{u_i - u_{i-1}}{\Delta x}
\] (3-5)

3. Central difference method: \[
\frac{\partial u}{\partial x} = \frac{u_{i+1} - u_{i-1}}{2\Delta x}
\] (3-6)

The needed equation for the problem of this research is second derivative which is approximated by central difference method:

\[
\frac{\partial^2 u}{\partial x^2} = \frac{u_{i+1} - 2u_i + u_{i-1}}{(\Delta x)^2}
\] (3-7)

Time derivative term can be replaced by these numerical schemes:

1. Implicit method:

\[
\frac{\partial u}{\partial t} = \frac{u_{i,j} - u_{i,j-1}}{\Delta t}
\] (3-8)

2. Explicit method:

\[
\frac{\partial u}{\partial t} = \frac{u_{i,j+1} - u_{i,j}}{\Delta t}
\] (3-9)

The implicit scheme has been used in the proposed research. The approximation solution has been achieved by replacing finite difference grids using implicit method for time and central difference for space:
\[ \frac{C(x_m, t_n) - C(x_m, t_{n-1})}{\Delta t} = D\left[ \frac{C(x_{m+1}, t_n) - 2C(x_m, t_n) + C(x_{m-1}, t_n)}{(\Delta x)^2} \right] \] (3-10)

Based on the equation (3-10), this calculation can be done by information of the previous time steps. Therefore, the results are achievable by provided data of initial and boundary conditions.

### 3.3 Solution to the problem using Finite difference method

As it was mentioned in the last part, using finite difference method results in a set of difference equations which are as substitute for the PDE equation. The governed difference equations are written at each of the nodes. Hence, solving these equations simultaneously brings about approximate values at each node and helps to solve the original PDE equation. The finite difference method for the dimensionless equation of

\[ \frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} \] using implicit method for time and central method for space is as follows:

\[ \frac{u_{i,j} - u_{i,j-1}}{\Delta t} = \frac{u_{i+1,j} - 2u_{i,j} + u_{i-1,j}}{(\Delta x)^2} \] (3-11)

If it is assumed to have m number of grid points in space, there are m-1 finite difference equations.
\[ u_{i,j} - \left( 2 + \frac{\Delta x^2}{\Delta t} \right) u_{i,j} + u_{i-1,j} = -\frac{\Delta x^2}{\Delta t} u_{i,j-1} \]

\[ i=1 \quad u_{2,j} - \left( 2 + \frac{\Delta x^2}{\Delta t} \right) u_{1,j} + u_{0,j} = -\frac{\Delta x^2}{\Delta t} u_{1,j-1} \]

\[ \vdots \]

\[ i=m-1 \quad u_{m,j} - \left( 2 + \frac{\Delta x^2}{\Delta t} \right) u_{m-1,j} + u_{m-2,j} = -\frac{\Delta x^2}{\Delta t} u_{m-1,j-1} \]

In order to use MATLAB software to solve these equations, first the equation has to be converted to a matrix. The following page presents the equations into matrix form:
\[
\begin{bmatrix}
- \left(2 + \frac{\Delta x^2}{\Delta t}\right) & 1 & 0 & 0 \\
1 & - \left(2 + \frac{\Delta x^2}{\Delta t}\right) & 1 & 0 \\
0 & 1 & - \left(2 + \frac{\Delta x^2}{\Delta t}\right) & 1 \\
0 & 0 & 1 & - \left(2 + \frac{\Delta x^2}{\Delta t}\right)
\end{bmatrix}
\begin{bmatrix}
u_{1,j} \\
u_{2,j} \\
u_{m-2,j} \\
u_{m-1,j}
\end{bmatrix}
= - \frac{\Delta x^2}{\Delta t}
\begin{bmatrix}
u_{1,j-1} \\
u_{2,j-1} \\
u_{m-2,j-1} \\
u_{m-1,j-1}
\end{bmatrix}
\begin{bmatrix}
u_{0,j} \\
u_{m,j}
\end{bmatrix}

(3-12)
\]
First matrix is called ‘A’ matrix with the size of m-1×m-1 which consists of known coefficients of unknown variables of u (i) in ‘j’ time step. Matrix “U” is the one for unknown variables at time step of j which are the desired to be solved by these finite difference equations. ‘B’ matrix includes variables of time step ‘j-1’ and ‘C’ matrix includes both of the boundary conditions in time step j. The product of right side of the equation considered to be ‘H’ matrix.

It is required to solve the discrete equations in order to solve the original differential equation. Direct method is one of the ways to achieve this aim. The equation for this method is:

\[ AU = H \]  

(3-13)

In the above equation, A and H are the known matrices from the discrete equations and U will be known using the direct method of inversion.

\[ U = A^{-1}H \]  

(3-14)

However, the matrix ‘C’ has to be found in order to get the H matrix and solve the equation.

### 3.3.1 Real boundary condition

Boundary condition is the necessary factor to solve the equation. Hence, the focus of this part is to find appropriate boundary condition for the target equation.

The boundary condition for r=0, is zero at any time regarding to the transformation which has been done. As the radius of this boundary is zero, the product of it would be zero.
\[ u(r,t) = r \rho(r,t) = 0 \quad (3-15) \]

As it mentioned before, the zero boundary condition at \( r=a \) can be assumed to be zero only for simplification approach and only if the high velocity of fluid in the environment removes all the diffused drug. However, the goal of this research is to model the real problem. Therefore, it is important to govern the real boundary condition. This boundary has been identified as \( u_m \) in the matrix of finite difference equations.

To find out the boundary condition at \( m (u_m) \), the mass concentration has to be written for the \( r=a \). Here is the procedure to find the boundary condition at \( r=a \).

By writing the mass flux at \( r=a \),

\[ n_{Ar} = -D_{AB} \frac{\partial \rho_A}{\partial r} \bigg|_{r=a} \quad (3-16) \]

And considering the area for the transport, the mass transport rate is achieved.

Mass transport rate\( = 4\pi a^2 n_{Ar} \bigg|_{r=a} \quad (3-17) \)

Integration of mass transport over the time, would result in total mass for time \( t \).

Total mass for time \( t = 4\pi a^2 \int_0^t n_{Ar} \bigg|_{r=a} \ dt \quad (3-18) \)

Considering the volume of environment which the drug diffuses out, the mass concentration over time at boundary condition of \( m \) would be:

\[ \rho \bigg|_{r=a} = \frac{-4\pi a^2 D_{AB} \int_0^t \frac{\partial \rho_A}{\partial r} \big|_{r=a} \ dt}{V} \quad (3-19) \]
This is the real equation for the outer boundary condition which has been implemented in the model.

3.3.2 Numerical solution for coated microparticle

The numerical solution for the coated chitosan particle has been done by the same numerical approach using implicit method for time and central method. However, the different efficient diffusion coefficients change the equations. Here are the equations for coated microparticle:

\[
\frac{\partial u}{\partial t} = G \frac{\partial^2 u}{\partial x^2}
\]

\[G = \frac{D_2}{D_1} \quad r^* = 1 \text{ to } \frac{b}{a}\]

The thickness of coating layer is too small that is ignorable. Hence, one sphere with varying diffusion coefficient has been considered for the numerical method. However, the changing point in space has been implied in the code.

Implicit scheme for time and central method for space have been applied for the numerical method of coated microparticle transport equation:

\[
\frac{u_{i,j} - u_{i,j-1}}{\Delta t} = G \frac{u_{i+1,j} - 2u_{i,j} + u_{i-1,j}}{\Delta x^2}
\]
The equation of (3-21) is the general equation of coated microparticle. Replacing i index by the numbers from 1 to m-1 (interval numbers) would give the discrete equations to solve the transport equation numerically.

\[ u_{i+1,j} - \left( \frac{\Delta x^2}{G \Delta t} + 2 \right) u_{i,j} + u_{i-1,j} = -\frac{\Delta x^2}{G \Delta t} u_{i,j-1} \] (3-22)

For \( x=0 \) to \( a = \Rightarrow G=1 \quad r^* = 0 \) to 1

\[ x=a \) to \( b = \Rightarrow G = \frac{D_2}{D_1} \quad r^* = 0 \) to \( \frac{b}{a} \)

Since the thickness of outer layer is too small, it would be negligible and the ratio of the dimensionless radius of inner and outer layer could be considered as one. However, in the numerical method, some points considered to be in the region of outer layer.

The next page shows the matrix for the finite difference equations:
\[
\begin{pmatrix}
- \left(2 + \frac{\Delta x^2}{G\Delta t}\right) & 1 & 0 & 0 \\
1 & - \left(2 + \frac{\Delta x^2}{G\Delta t}\right) & 1 & 0 \\
0 & 1 & - \left(2 + \frac{\Delta x^2}{G\Delta t}\right) & 1 \\
0 & 0 & 1 & - \left(2 + \frac{\Delta x^2}{G\Delta t}\right)
\end{pmatrix} \begin{pmatrix}
[\mathbf{u}_{1,j} \\
\mathbf{u}_{2,j} \\
\mathbf{u}_{m-2,j} \\
\mathbf{u}_{m-1,j}
\end{pmatrix} = \frac{\Delta x^2}{G\Delta t} \begin{pmatrix}
[\mathbf{u}_{1,j-1} \\
\mathbf{u}_{2,j-1} \\
\mathbf{u}_{m-2,j-1} \\
\mathbf{u}_{m-1,j-1}
\end{pmatrix} - \begin{pmatrix}
\mathbf{u}_{0,j} \\
\mathbf{u}_{m,j}
\end{pmatrix}
\]

(3-23)
3.4 Validation of results

3.4.1 Stability

Stability is one of the numerical challenges. A finite difference method needs to be stable in order to achieve a converged solution. In a Stable numerical method, none of the errors grow from step to step of the numerical proceeding. In other words, a stable method is the one which iterating the solution does not affect the growing of the small deviation from the correct solution.\(^\text{20}\)

Large time and space intervals are two of the challenges of instability. Large time and space intervals usually decrease the chance of getting convergence code. On the other hand, too small intervals cause some oscillations in the code. Therefore, finding an optimum range of time and space intervals is important. For this reason, both of the time and space intervals have been optimized in this study. With respect to this, different parameters have been tried to get the convergence code.

3.4.2 Comparison with analytical solution

Analytical solution was developed for the simple boundary condition in chapter 2. In order to verify the numerical results, a comparison with the analytical solution have been done. For this reason, both of the boundary conditions were considered to be zero and dimensionless forms of mass concentration and space were used. The figure of 3-2 shows this comparison.
Figure 3-2. Comparison between profile of mass concentration using numerical method and analytical solution. Dashed red line is analytical and solid black line is numerical method.

As it can be seen in the figure, the numerical solution almost fitted to the analytical solution. This would evaluate that the numerical method is correct and by modifying the boundary conditions, the real problem can be solved. In the next chapter, the promising results of the numerical model is shown.
Chapter 4

Results and discussion

In order to solve the issued problem, the simulation was done using the finite difference method incorporated in a MATLAB code. The first aim of simulation was to model the monolithic system without any coating. As it was illustrated in numerical method chapter, the matrices have been defined in the software using the assumed parameters. Iterative loops and matrix inverse were some of the techniques which have been applied in this code.

4.1 Effective parameters

Several factors affect the system and consequently the simulation. Each of these parameters are assumed in the model logically. Diffusion coefficient and porosity are two of the effective parameters in the system. The product of these parameters results in the efficient diffusion coefficient. Therefore, the role of efficient diffusion coefficient is important in the model.
The volume of the solution, which the drug diffuses in it, is another parameter which was modified to get the best results. The volume of solution is effective in the model because it shows up in the real boundary condition which illustrated in equation 3-19. The other factor is the radius of microsphere which is explained in detail in this section. All these parameters are considered to be important in the model and were optimized to fit the experimental data.

4.1.1 Efficient diffusion coefficient

In porous hydrogels, porosity and tortuosity of the hydrogels affect the diffusion coefficient. This will happen when pores are very larger than molecular size of the drug. One of the main purposes of this research is to show the importance of efficient diffusion coefficient factor. Hence, the aim is to choose the optimized efficient diffusion coefficient to achieve the desired results, which would match the reality of the process. Finding the optimum efficient diffusion factor helps to get the best results in modeling method. Efficient diffusion coefficient of chitosan hydrogel was approximately considered to be $10^{-9}$ cm$^2$/s. It is necessary to mention that the microparticle is considered homogenous because of the high porosity, so the diffusion occurs all over the sphere.
4.1.2 The radius of microparticle

The average radius of all chitosan particles has been considered as the radius of the modeled chitosan particle. The average radius of experiment has been calculated using scanning electron microscopy (SEM) and ImageJ software. However, in the modeling, the average radius has been calculated in different way as follows.

Mass of diffusion for each particle would be:

\[ m_i^t = 4\pi a_i^2 \int_0^t n_{Ar} \left| r = a_i \right. \, dt \]  

(4-1)

The average mass over the time is governed by this equation:

\[ m_{average}^t = \frac{4\pi \sum_{i=1}^b a_i^2 \int_0^t n_{Ar} | r = a_i \, dt}{b} \]  

(4-2)

By Replacing \( n_{Ar} = -D_{AB} \frac{\partial \rho_A}{\partial r} \), the average diffused mass is achieved:

\[ m_{ave.}^t = -\frac{4\pi D_{AB}}{b} \sum_{i=1}^b \int_0^t a_i^2 \left. \left( \frac{\partial \rho_A}{\partial r} \right) \right|_{r = a_i} \, dt \]  

(4-3)

Implementing the sigma inside the integral results in:

\[ m_{ave.}^t = -\frac{4\pi D_{AB}}{b} \int_0^t \left( a_1^2 \left( \frac{\partial \rho_A}{\partial r} \right) \right|_{r = a_1} + a_2^2 \left( \frac{\partial \rho_A}{\partial r} \right) \right|_{r = a_2} + \cdots + a_b^2 \left( \frac{\partial \rho_A}{\partial r} \right) \right|_{r = a_b} \, dt \]  

(4-4)

Term of \( \left( \frac{\partial \rho_A}{\partial r} \right) \right|_{r = a_i} \) achieved by the previous time step terms. They are known because of the defined initial condition. The same approach has been done to write the modeled code.

\[ \int_0^{t_{n-1}} \left. \frac{\partial \rho_A}{\partial r} \right|_{r = a} \, dt = \frac{\partial \rho_A}{\partial r}(a, t_{n-1}) \Delta t + \rho_A(a, t_{n-1}) \]  

(4-5)

As a result, the equation is turned to this:
\begin{align*}
m_{ave}^t |_{a_i, t_n} &= - \frac{4\pi D_{AB}}{b} \left( \rho_A(a_1, t_{n-1}) \frac{\partial \rho_A}{\partial r} \Delta t + \rho_A(a_1, t_{n-1}) \right) + a_2^2 \left( \frac{\partial \rho_A}{\partial r} \Delta t + \rho_A(a_2, t_{n-1}) \right) + \cdots + a_b^2 \left( \frac{\partial \rho_A}{\partial r} \Delta t + \rho_A(a_b, t_{n-1}) \right) \\
\rho_A(a_2, t_{n-1}) &= \cdots + \rho_A(a_b, t_{n-1}) \quad (4-6)
\end{align*}

Based on the analytical solution, the $\rho_A$ would be:

\begin{equation}
\rho_A(r, t) = - \frac{2\rho_A_0 a}{\pi r} \sum_{j=1}^{\infty} \frac{(-1)^j}{j} \sin \frac{j\pi r}{a} e^{-D_{AB} \left( \frac{j\pi}{a} \right)^2 t} \quad (4-7)
\end{equation}

Which the derivative of it would be:

\begin{equation}
\frac{\partial \rho_A(r, t)}{\partial r} = - \frac{2\rho_A_0 a}{\pi r} \sum_{j=1}^{\infty} \frac{(-1)^j}{j} \cos \frac{j\pi r}{a} e^{-D_{AB} \left( \frac{j\pi}{a} \right)^2 t} \quad (4-8)
\end{equation}

For radius of $a_i$ and time of $t_{n-1}$,

\begin{equation}
\frac{\partial \rho_A(a_i, t_{n-1})}{\partial r} = -2\rho_A_0 \sum_{j=1}^{\infty} \frac{e^{-D_{AB} \left( \frac{j\pi}{a_i} \right)^2 t_{n-1}}}{a_i} \quad (4-9)
\end{equation}

By replacing these terms into the equation, the governed equation is:

\begin{align*}
m_{ave}^t |_{a_i, t_n} &= - \frac{4\pi D_{AB}}{b} \left( \rho_A(a_1, t_{n-1}) \frac{\partial \rho_A}{\partial r} \Delta t + \rho_A(a_1, t_{n-1}) \right) + a_2^2 \left( \frac{\partial \rho_A}{\partial r} \Delta t + \rho_A(a_2, t_{n-1}) \right) + \cdots + a_b^2 \left( \frac{\partial \rho_A}{\partial r} \Delta t + \rho_A(a_b, t_{n-1}) \right) \\
\rho_A(a_2, t_{n-1}) &= \cdots + \rho_A(a_b, t_{n-1}) \\
\frac{\partial \rho_A(a_i, t_{n-1})}{\partial r} &= -2\rho_A_0 \sum_{j=1}^{\infty} \frac{e^{-D_{AB} \left( \frac{j\pi}{a_i} \right)^2 t_{n-1}}}{a_i} \\
(4-10)
\end{align*}

Or

\begin{equation}
m_{ave}^t |_{a_i, t_n} = \frac{8\pi \rho_A_0 D_{AB}}{b} \sum_{i=1}^{b} a_i \left( \sum_{j=1}^{\infty} e^{-D_{AB} \left( \frac{j\pi}{a_i} \right)^2 t_{n-1}} \right) \Delta t \quad (4-11)
\end{equation}

Therefore, the diffused mass equation for multiple parameters have been governed. In order to get the average radius of the particles, it can be assumed that the diffused mass of these b particles is the same as a particle with their average average radius.
In this case, there is a need to find the average diffused mass equation for one particle.

Based on the analytical solution, the derivative of $\rho_A$ regarding to $r$ is defined.

$$\frac{\partial \rho_A}{\partial r} \bigg|_{r=a} = -2\rho_A \sum_{j=1}^{\infty} e^{-\frac{D_{AB}}{a^2} \left(\frac{j\pi}{a}\right)^2 t}$$ (4-12)

The total mass would be achieved by

$$Total\ mass = -4\pi a^2 D_{AB} \int_0^t \frac{-2\rho_A}{a} \sum_{j=1}^{\infty} e^{-\frac{D_{AB}}{a^2} \left(\frac{j\pi}{a}\right)^2 t} \ dt$$ (4-13)

So the simplified total mass by considering the constants would be:

$$Total\ mass = 8\pi \rho_A D_{AB} \int_0^t \sum_{j=1}^{\infty} e^{-\frac{D_{AB}}{a^2} \left(\frac{j\pi}{a}\right)^2 t} \ dt$$ (4-14)

Implementing the integration into the sigma, the equation would be:

$$Total\ mass = 8\pi \rho_A D_{AB} \left( \sum_{j=1}^{\infty} \frac{1}{-\frac{D_{AB}}{a^2} \left(\frac{j\pi}{a}\right)^2 t} e^{-\frac{D_{AB}}{a^2} \left(\frac{j\pi}{a}\right)^2 t} \right) \bigg|_0^t$$ (4-15)

Finally, the total mass for one particle would be:

$$Total\ mass = \frac{8a^3 \rho_A}{\pi} \sum_{j=1}^{\infty} \left( \frac{1-e^{-\frac{D_{AB}}{a^2} \left(\frac{j\pi}{a}\right)^2 t}}{j^2} \right)$$ (4-16)

Finding the term of “a” in a way that makes the (4-16) equation equals to the total diffused mass of multiple particles (4-11) is the aim. This approach achieved by MATLAB software and the result is 6 micrometers in comparison to the experimental average radius of 10 micrometers. This difference would be for some reasons such as the simplifying assumptions and different methods of calculation, which have been used.
4.1.3 Specific effective parameters for coated microparticle

The ratio of efficient diffusion coefficient of coating to the efficient diffusion coefficient of microsphere (G) and the thickness of coating are the two specific parameters which affect the coated system. In this section, the effect of them on the modeling is illustrated.

4.1.3.1 Effect of G parameter

As the ratio of the efficient diffusion coefficient of coating to the efficient diffusion coefficient of microsphere decreases the cumulative concentration of released drug in the outer boundary decreases as well. The reason is that by decreasing the G parameter and considering the efficient diffusion coefficient of microsphere as constant, the amount of $D_2$, the efficient diffusion coefficient of coating decreases. As a result, the coating would prevent more from the highly drug release. The comparison between the effect of higher G and less G on the system is shown in the figure 4-1.
Figure 4-1. Effect of $G$ value on cumulative drug release. $G$ is 0.8 for black solid line and 0.1 for blue solid line.

Based on this trend, the optimized $G$ is considered for the final results to fit the experimental data.

**4.1.3.2 Effect of coating thickness**

The thickness of coating is another effective parameter for coated system but the effect of it is not as much as $G$ parameter. Increasing the thickness affects the drug release in a way that it decreases the amount of cumulative drug concentration. The changes is illustrated by comparison between different thicknesses in figure 4-2.
Figure 4-2. Effect of thickness on cumulative drug release. In the model, the thickness of shown grey line is 10 grid points and for blue line is 100 grid points.

The thickness in the model is considered close to the approximate thickness from the experimental data and assumed to be a thin layer.

4.2 Results

4.2.1 Modeling and experimental results

4.2.1.1 Modeling for non-coated microparticle

The modeling results have been evaluated by experimental results. The comparison between the modeled and experimental data for the percentage of cumulative drug release versus time in the outer boundary of monolithic system is shown below:
Figure 4-3. Graph of cumulative drug release from non-coated microparticle. Comparison between experimental and modeling data. Solid line is modeling and points are experimental data.

The initial burst is not as much as traditional drugs but still needs to be worked on it to achieve lower amount of dose dumping of drug.

The experimental data which has been done by Dr. Rodriguez\textsuperscript{1} shows that the combination of monolithic and reservoir system gives promising results regarding to decrease the initial burst and get better controlled drug delivery. As it is mentioned in the previous chapters, the system contains a drug-dispersed microsphere which coated with another polymer layer. In this study, the simulation for this system has been done using finite difference method incorporated in a MATLAB code.
4.2.1.2 Modeling for coated microparticles:

In the model for coated microparticle, it has been considered that there is a sphere with changing diffusion coefficient and porosity, and as a result changing efficient diffusion coefficient. In this set of modeling, two parameters are added to the system which are coating thickness and coating porosity. Coating thickness is considered in the model based on the experimental findings and implemented in the code. The thickness of coating helps to find the place of changing porosity and efficient diffusion coefficient. Coating porosity as the other factor, affects the efficient diffusion coefficient of coated part.

The experimental data are based on three different coatings: PLA, PLGA 50:50 and PLGA 85:15. The experimental data and modeling data for all the coatings are provided here:
Figure 4-4. Graph of cumulative drug release from PLGA 50:50 coated microparticle. Comparison between experimental and modeling data. Experimental data in dark blue points and modeling data in light blue solid line.

Figure 4-5. Graph of cumulative drug release from PLGA 85:15 coated microparticle. Comparison between experimental and modeling data. Experimental data in dark blue points and modeling data in light blue solid line.
Figure 4-6. Graph of cumulative drug release from PLA coated microparticle. Comparison between experimental and modeling data. Experimental data in dark blue points and modeling data in light blue solid line.

Optimization of two parameters helped to get better fit for each experimental data. First, the ratio of efficient diffusion coefficient of coating to the efficient diffusion coefficient of inner microsphere was optimized. Second, the volume of solution which affects the constant in outer boundary condition has been modified to get best fit.

As it is observed in the shown figures, both of the experimental and modeling results illustrates the same trend of cumulative drug release percentage over time. They describe the importance of efficient diffusion coefficient in the drug release process. Hence, adding a low porous coating to the monolithic system of drug delivery advanced the process.
4.2.2 Comparison of Coated and non-coated results

To have a better idea regarding the effect of coating on the drug release system, the comparison between results of non-coated with coated system in both experimental and modeling set of data is shown in the figures 4-7, 4-8 and 4-9:

Figure 4-7. Graph of cumulative drug release from PLGA 50:50 coated microparticle in comparison with non-coated one. Solid line is modeling and points are experimental data. Non-coated in red and coated in blue.
Figure 4-8. Graph of cumulative drug release from PLGA 85:15 coated microparticle in comparison with non-coated one. Solid line is modeling and points are experimental data. Non-coated in red and coated in blue.

Figure 4-9. Graph of cumulative drug release from PLA coated microparticle in comparison with non-coated one. Solid line is modeling and points are experimental data. Non-coated in red and coated in blue.
The source of modeling deviations from experimental data are the assumptions which were made for writing the model. One of these deviations could be from the uniform thickness assumption. In the experiment, the thickness of coating in some part of the microsphere could be higher and it would cause less initial burst. However, the uniform thickness is assumed in the model. In this case, the modeling results show higher initial burst than the experimental data. Another possible error source would be the uniform diffusion assumption which could cause deviation from experimental data.

4.5 Summary

The modeled system considered as diffusion controlled system. Many of the pharmaceutical studies in this area believes that this model is related to non-degraded polymer and the swelling and erosion of polymer have to be considered. However, in reality the diffusion is the key factor and it is proved in this study that diffusion is the rate limiting.

In conclusion, drug diffusion is the most important process in the drug delivery system. The focus should be on enhancing the diffusion coefficient and porosity to get better controlled drug delivery systems. As it is illustrated in both experimental and modeling results, adding a layer of coating with lower efficient diffusion coefficient would improve the drug release. Initial burst which is the challenge of drug delivery systems would decrease by the achieved results.
Chapter 5

Conclusion and future work

Experimental and numerical modeling illustrated that diffusion is the main factor in controlling the drug release. As a result, defining porosity and diffusion coefficient in an optimized way, has to be in the prior list of designing controlled drug delivery system. Experimental results have sufficient information to show the diffusion-based drug release process and its improvement by adding the coating layer. However, it is essential to prove it theoretically, using mathematical modeling.

Finite difference method helps to solve the mathematical modeling to get the solution for the partial differential equation. The implementation of numerical method in MATLAB software provided the solution. However, there are some deviations from the experimental data which are caused by modeling assumptions.

One of the assumptions which has been made for the model is that the diffusion occurs all over the sphere because it is highly porous. It is not completely true in experiment. In addition, size of all particles were considered to be the same and equals to the average radius of all of them. However, the size distribution of the particles is known in the experimental data. Another simplifying assumption is the consideration of uniform thickness for all the coatings. This would not happen in experiments. As a result this
assumption is another source of errors. Last but not least, the assumption, illustrated that there is no interface boundary between microsphere and coating, would be a source of the deviations. The reason is that the equilibrium is not that much fast to make the no boundary assumption completely reasonable.

Although the mentioned sources of deviation cause some errors, the fitting of the modeling and experimental data is enough to show the improvement by the coating layer. Furthermore, the model has sufficient information to show the drug release process and proving the importance of diffusion in controlled drug delivery devices. Based on both experimental and modeling results, initial burst would be decreased by controlling the diffusion of drug. Adding a layer to protect the drug diffusion system is the successful approach for this reason.

For future work, finding a generalized method for systems with more coating layers could be one of the interesting works to be done. In addition, by investigating a technique to measure the thickness of coating experimentally, the modeling results would be more accurate. As the porosity and diffusion coefficient are the important parameters in this method, having sufficient experimental data for these parameters would help to have better fitting. Considering the interface boundary between the microsphere and coating would be another future work to develop the model which may decrease the deviation from the experimental data. Based on the proposed model, the number of future experiments will decrease because changing the parameters in the model, would give sufficient information to optimize the experiment condition.
References


Appendix A

Modeling for non-coated microparticle

clear all
clc

% number of space grids
m=274;

% number of time grids
n=200;

% This parameter helps the MATLAB to identify the space grids in order to plot the graph
X=1:m;

% This parameter helps the MATLAB to identify the time grids in order to plot the graph
T=1:n;

% Size of space interval:
Dx=0.38;

% Size of time interval
Dt=0.1;

% Matrix of known coefficients of variables:
A=zeros(m-1,m-1);

% Matrix of unknown variables in time step of j:
B=zeros(m-1,1);

% Matrix of unknown variables in time step of (j-1):
u_i=zeros(m-1,1);

% Matrix of unknown variables at in the boundary, space of m in time step of j:
u_im=zeros(n);

% Mass concentration matrix:
U=zeros(m,1);

% Mass concentration matrix at boundary of m:
Um=zeros(n,1);

A(1,1)=-(2+Dx^2/Dt);
A(1,2)=1;
A(m-1,m-1)=-(2+Dx^2/Dt);
A(m-1,m-2)=1;
for x=2:m-2;
    A(x,x)=-(2+Dx^2/Dt);
    A(x,x-1)=1;
    A(x,x+1)=1;
end

A;

for j=1
    for i=1:m-1

\[ B(i) = \frac{-(i)*(Dx)^3}{Dt}; \]

\[ u_i = A \backslash B; \]

\[ u_im(1) = 0; \]

\[ \text{for } j=2:n \]
\[ \text{for } i=1:m-1 \]
\[ B(i) = \frac{-(Dx^2)/Dt)*(u_i(i));} \]
\[ \text{end} \]
\[ u_im(j) = 2* u_i(m-1) - u_i(m-2); \]
\[ \sigma = u_im(j) - (0.014)*((u_im(j) - u_i(m-1))/Dx - u_im(j))*(Dt); \]
\[ B(m-1) = B(m-1) - \sigma; \]
\[ u_i = A \backslash B; \]
\[ \text{end} \]
\[ \text{for } i=1:m-1 \]
\[ U(i) = u_i(i)/(i)*Dx; \]
\[ \text{end} \]
\[ \text{for } j=1:n \]
\[ Um(j) = u_im(j)/(m*Dx); \]
\[ \text{end} \]
\[ U(m) = (2*u_i(m-1) - u_i(m-2))/(m*Dx); \]
\[ \text{plot}(X,U) \]
\[ \text{axis}([1 274 0.3 1.2]) \]

66
title('Diffusion/Space')
xlabel('X')
ylabel('U')
figure
plot(T,Um,'r')
title('Diffusion/Time at m')
xlabel('T')
ylabel('Um')
Appendix B

Modeling for coated microparticle

clear all
clc

% number of space grids
m=274;

% number of time grids
n=200;

% This parameter helps the MATLAB to identify the space grids in order to plot the graph
X=1:m;

% This parameter helps the MATLAB to identify the time grids in order to plot the graph
T=1:n;

% Size of space interval:
Dx=0.38;

% Size of time interval
Dt=0.1;

% Matrix of known coefficients of variables:
A=zeros(m-1,m-1);

% Matrix of unknown variables in time step of j:

B=zeros(m-1,1);

% Matrix of unknown variables in time step of (j-1):

u_i=zeros(m-1,1);

% Matrix of unknown variables at in the boundary, space of m in time step of j:

u_im=zeros(n);

% Mass concentration matrix:

U=zeros(m,1);

% Mass concentration matrix at boundary of m:

Um=zeros(n,1);

% G defines the relation between the efficient diffusion coefficient of the outer part (Coating) to inner part (monolithic system)

G=zeros(m-1,n);

for j=1:n
    for i=1:m-10
        G(i,j)=1;
    end
end

G1=G(i,j)

for j=1:n
    for i=m-9:m-1
        G(i,j)=0.3;
    end
end
G2=G(i,j)
A(1,1)=-(2+Dx^2/Dt*G1);
A(1,2)=1;
A(m-1,m-1)=-(2+Dx^2/Dt*G2);
A(m-1,m-2)=1;
for x=2:m-2;
  A(x,x)=-(2+Dx^2/Dt*G(x,j));
  A(x,x-1)=1;
  A(x,x+1)=1;
end
A;
for j=1
  for i=1:m-1
    B(i)=-(i*(Dx)^3)/Dt*G(i,j);
  end
  u_i=A\B;
end
u_im(1)=0;
for j=2:n
  for i=1:m-1
    B(i)=-(Dx^2/Dt*G(i,j))*(u_i(i));
end

\[ u_{im}(j) = 2u_{i}(m-1) - u_{i}(m-2); \]

\[ \sigma = u_{im}(j) - (0.014)*\left(\frac{(u_{im}(j) - u_{i}(m-1))}{Dx} - u_{im}(j)\right)*Dt; \]

\[ B(m-1) = B(m-1) - \sigma; \]

\[ u_{i} = A\backslash B; \]

end

for \( i = 1:m-1 \)

\[ U(i) = \frac{u_{i}(i)}{(i)*Dx}; \]

end

for \( j = 1:n \)

\[ U_{m}(j) = \frac{u_{im}(j)}{(m*Dx)}; \]

end

\[ U(m) = \frac{(2u_{i}(m-1) - u_{i}(m-2))}{(m*Dx)}; \]

plot(X, U)

axis([1 274 0.3 1.2])

title('Diffusion/Space')
xlabel('X')
ylabel('U')

figure

plot(T, U_{m}, 'r')

title('Diffusion/Time at m')
xlabel('T')
ylabel('U_{m}')
Appendix C

Modeling for average radius

cle

clear

b=100; % b=number of particles
D=10^-12*60; %[cm^2/min]
p=40; %[mg/cubic cm]
c=(8*pi*p*D)/b;
tf=19908/60; %[min]
t=0:tf;
dt=60;
a=linspace(5*(10^-5),0.003,b); %[cm] range of d is from 1 to 60 micrometer
x=0.003;
h=0;
k2=0;
for i=1:b
    syms j;
g=eval(symsum ( exp(-D*((j*pi)/(a(i)))^2)*tf), j , 1 , 100))
h = h + a(i) * g * dt;

z = a(i)

end

l = h * c

for t = 0:dt:tf

syms j;

k = eval(symsum(((1 - exp(-D * ((j * pi) / (x))^2) * t)) / (j^2)), j, 1, 100))

k2 = k2 + k

w = t

end

f = @(x) k2 * ((8 * (x^3) * p) / pi) - l

Y = fzero(f, 1)
Appendix D

Comparison between analytical and numerical solution

clear all
clc

% number of space grids
m=274;

% number of time grids
n=200;

% This parameter helps the MATLAB to identify the space grids in order to plot the graph
X=1:m;

% This parameter helps the MATLAB to identify the time grids in order to plot the graph
T=1:n;

% Size of space interval:
Dx=0.38;

% Size of time interval
Dt=0.1;

% Matrix of known coefficients of variables:
A=zeros(m-1,m-1);

% Matrix of unknown variables in time step of j:
B=zeros(m-1,1);

% Matrix of unknown variables in time step of (j-1):
u_i=zeros(m-1,1);

% Matrix of unknown variables in the boundary, space of m in time step of j:
u_im=zeros(n);

% Mass concentration matrix:
U=zeros(m,1);
U(1)=0;
A(1,1)=-(2+Dx^2/Dt);
A(1,2)=1;
A(m-1,m-1)=-(2+Dx^2/Dt);
A(m-1,m-2)=1;
for x=2:m-2;
    A(x,x)=-(2+Dx^2/Dt);
    A(x,x-1)=1;
    A(x,x+1)=1;
end
A;

for j=1
    for i=1:m-1
        B(i)=-(i)*(Dx)^3/Dt;
    end
end
end
u_i=A\B;
end
for j=2:n
for i=1:m-1
    B(i)=-(Dx^2)/Dt*(u_i(i));
end
u_im(j)=0;
sigma=0;
B(m-1)=B(m-1)-sigma;
u_i=A\B;
end
for i=1:m-1
    U(i)=u_i(i)/((i)*Dx);
end
x=linspace(0,1,274);
figure(1)
plot(x,U)
title('Diffusion/Space')
xlabel('x')
ylabel('U')

r=linspace(0,1,274);
U_temp = cell(1,length(r));

for a = r
    for i = 1:100
        b = find(r==a);
        U_temp{b}(i) = ((-1)^i)/i*(sin(i*pi*a))*exp(-(i*pi)^2*0.001);
    end
end

U_analytic = zeros(1,length(r));

for i = 1:length(r)
    U_analytic(i) = ((-2/pi)*sum(U_temp{i}))/r(i);
end

figure(2);
plot(r,U_analytic)
title('Analytical Diffusion/Space')
xlabel('r')
ylabel('U')