MODELING OF DRUG RELEASE KINETICS FROM POROUS CERAMIC DISKS

by

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A thesis submitted to the faculty of
The University of North Carolina at Charlotte
in partial fulfillment of the requirements
for the degree of Master of Science in
Mechanical Engineering

Charlotte

2014

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ABSTRACT

APURVA UPENDRA JOSHI. MODELING OF DRUG RELEASE KINETICS FROM POROUS CERAMIC DISKS.
(Under the direction of DR. HARISH CHERUKURI & DR. AHMED EL-GHANNAM)

The use of biomaterials as drug delivery systems (DDS) eliminates the adverse side effects of systemic drug administration. Silica-based bioceramics have been widely studied as DDS and demonstrated a unique ability for controlled drug release locally that target infected bone tissues. Successful treatment using a DDS requires the release of a therapeutic dose of the drug for a period of time long enough to eradicate the infection. Porosity characteristics and chemistry of the scaffold can significantly control drug binding and release kinetics. In particular, many studies have demonstrated that the porosity percent and pore size distribution dictate the surface area of the material available for drug adsorption and the subsequent release inside the body. The two primary mechanisms governing the drug release from porous, inert bio-ceramic materials are the dissolution of the drug from the outermost surface and diffusion from the inner pores to the physiological solution. The former mechanism leads to a burst release phase while the latter leads to a sustained release phase. The present study uses a combination of experimental and theoretical approaches to study the relative importance of these two mechanisms and the influence of various porosity parameters on them.

In the experimental part of the study, porous α-Cristobalite ceramic discs were prepared using powder metallurgy techniques. The porosity characteristics of the ceramic discs were varied and characterized by mercury porosimetry. The discs (n = 4) were immersed in antibiotic solution (Vancomycin) for either 4 hrs or 24 hrs. The amount of drug adsorbed on the porous ceramic was determined and correlated to

the porosity characteristics of the material. Moreover, the vancomycin release kinetics from porous α-Cristobalite samples into physiological solution was measured and correlated to the porosity characteristics and the initial drug adsorption. Concurrently, Fickian diffusion laws were used to develop the drug desorption and diffusion models from the α-Cristobalite disks. The governing differential equations for drug concentration were solved using the finite element software package `ABAQUS`. The computational results and the experimental data were used to determine the mass transfer coefficient and diffusion coefficient values for different porosities and drug immersion times. The role of drug desorption and diffusion mechanisms in drug release from porous α-Cristobalite was studied. The experimental results show that a higher percent of drug release was achieved for the disks with the highest porosity contributed by micro-size pores. The contribution of nano pores to the total surface area have resulted in lower rates of drug release during diffusion dependent sustained release stage. Lower values of diffusion coefficient indicate that the diffusion of drug through the porous ceramic matrix is very slow and that initial burst release is predominantly due to the dissolution process.

DEDICATION

I dedicate my thesis to my parents, Anagha and Upendra Joshi and my brother Aniket Joshi for their strong and continuous support in all my endeavors.

ACKNOWLEDGMENTS

I thank my advisors, Dr. Harish Cherukuri and Dr. Ahmed El-Ghannam for their valuable guidance with vision and patience. They made this project a great learning experience for me. Without their support, this project would not have been possible. I would like to thank Dr. Harish Cherukuri for being very supportive and encouraging throughout. I would also like to thank Dr. Didier Dréau for his participation in my thesis committee.

I would also like to thank Christopher Trujillo for his help in getting me acquainted with the necessary equipments in lab and constantly sharing his knowledge and working experience.I would like to thank Micromeritics Instrument Corporation to provide me with timely analysis of the samples.

I would like to thank my friends, Akshay Deshpande, Chinmay Avachat, Kshitij Gawande and Swapnil Patil for their help and unique inputs time and again. Lastly I would like to thank all my relatives, roommates and friends for supporting me and for making my stay at UNCC memorable.

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CHAPTER 1: INTRODUCTION

Human health relies on appropriate diet and lifestyle throughout a lifetime. When the homeostasis characteristic of good health is altered, individuals are in a disease state [1]. Diseases can be associated with pain, disturbance in functionality of the body and quality of life. Whenever possible, diseases are treated with medication and surgery. In particular, chemical molecules, i.e., drugs can slow down or reverse the effects of specific disease states, including infection, injury, aging-related imbalances or hormonal imbalances. Accurate diagnosis and appropriate dosage of those drugs are keys to successful treatments of a given disease state. The success of each drug therapy mainly depends on the rate and movement of drug molecules at their target site. As the human body is mainly constituted of water, the factors affecting the rate of drug molecule movement in aqueous solution are essential to drug efficacy. In the present work, we investigated the optimization of drug delivery using a bio-ceramic carrier.

1.1 Literature Review

The purpose of this review is to summarize the current status of the field of drug delivery. Both experimental and mathematical analyses are presented. Previous studies have investigated various localized drug delivery systems especially to achieve sustained drug release rate. Mathematical models have been developed to study the release kinetics of drug in aqueous solutions.

J. Siepmann developed an approach to identify which mathematical model is suitable for particular system [2]. Mathematical modeling helps to identify and develop drug release kinetics and thus is useful in the effective development of drug product limit-

ing both cost and time. The drug delivery systems were characterized on the basis of their geometries like slabs, cylindrical or spherical shapes [2], dosage forms which can be homogeneously dispersed or concentrated at the core of the carrier device, moving or non-moving boundary conditions, the drug concentration higher or lower than the solubility, and type of matrix material [2]. On those bases, mathematical equations for different delivery systems were developed [2].

Y. Zhou and X. Y. Wu applied the finite element method to solve the mathematical equations for diffusion controlled drug release from matrix material. They considered finite element method to simple geometries under perfect sink conditions and with well stirred finite volume to review its efficacy. They validated the finite element solution by comparing with the exact solution for simple cases. So they applied this method to complex geometries such as tablets, hollow cylinders, dough-nut shaped cylinders with different boundary conditions. They also studied the effect of composite structure such as foam/matrix pessaries, multi-layered tablets and membrane coated elastomer rings on release kinetics. Like Siepmann, they also stated the importance of mathematical modeling and its simulation to predict the release kinetics of new device and also the customized devices before their production [3]. Also various experiments are being carried out to study the suitable bio-material to achieve sustained release kinetics.

Ahemad El-ghannam and his colleagues presented the efficacy of using porous silica calcium phosphate nano-composite (SCPC) particles as drug carrier in the delivery system. They were found to get the desired sustained release from these particles which proved their efficacy as therapeutic agents. They also analyzed the effect of surface chemistry on the release kinetics. For the same material SCPC of the carrier but for different surface characteristics like porosity, surface area etc, the release rate changed significantly [4].

1.2 Drug Delivery Systems

"A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body" [5]. It is the mechanism which concerns with both quantity and time duration of drug presence inside a body. This process includes the injection of the therapeutic product inside a body and release of active component from this product. It can be said that drug delivery system is the formulation of the drug's chemical composition, a device used for its delivery inside a body, dosage form and quantity of drug dosage [7].
Targeted drug delivery can be defined as the "method of delivering medication to a patient in a manner that it increases the concentration of the medication in some parts of the body relative to others" [6]. Thus, targeted drug delivery is a way of delivering the required quantity of the drug to the required organ or part of the body which needs to be treated. In this, medication is concentrated on the infected organ or tissue while reducing the concentration of medication in the entire body. This helps reducing the chronic side effects in the body due to unnecessary drug and improves the efficiency of the drug delivery at the site of action. There are a number of ways to design drug delivery systems. One of the most popular ways is to use bio-active materials as drug carrying devices in the form of pellets, particles etc and then engage them to release the therapeutic dose of drug for an extended period of time. Different mechanisms have been applied to make drug delivery systems work efficiently.

1.2.1 Controlled Drug Delivery

With the traditional systemic drug administration method, the concentration of drug actives varies significantly with time (figure 1.1). The fluctuations of the drug level in the body above the toxic level and below the minimum therapeutic dose are not optimal for efficient treatment. Moreover, the long term periodic systemic intake

of drug may cause significant side effects. With the use of biomaterials as carriers of the drug, the drug level is maintained constant between the maximum and minimum therapeutic limits for longer duration. This delivers a drug at the predetermined rate for, locally or systemically for a specified period of time. The control drug delivery system is supposed to maintain a constant drug level in the body for a certain period of time to achieve complete healing. The maintenance of therapeutic drug concentration eliminates the need to take drug dosage frequently. This reduces the side effects on the body and the purpose is served effectively [7]. Figure 1.1 is a schematic demonstrating the drug concentration profile in the body after using systemic injection and a drug delivery system.

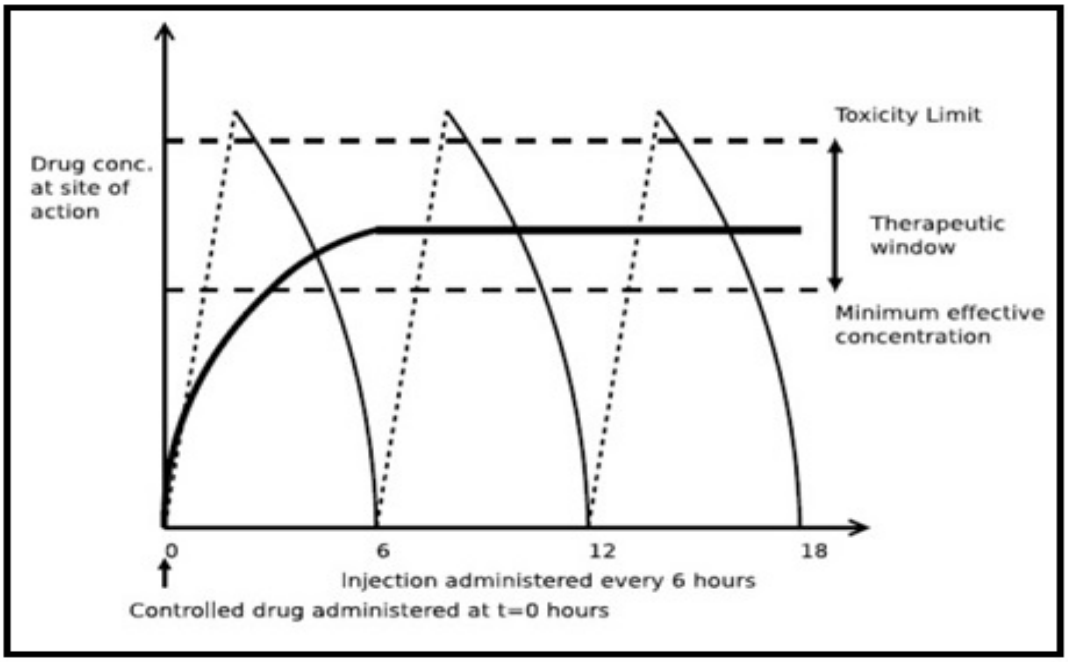

Figure 1.1: Controlled drug release vs conventional drug release.
[7]

1.3 Diffusion Controlled Drug Delivery

Diffusion plays a very important role in controlled drug delivery systems. Diffusion controlled drug delivery system is based on phenomena such as a combination of water diffusion, drug dissolution, drug diffusion from the drug carrier. The rates of drug release from these mechanisms are, in general, different from each other. Thus, the slowest process is the rate limiting step for the entire mass transport sequence.
Diffusion is defined as the movement of the substance/molecules from a region of high concentration to a region of low concentration. Thus, concentration gradient is change in the value of concentration over the distance. Diffusion can be termed as "to spread out" from high concentration to low concentration. Thus, this results in mass transport [9].

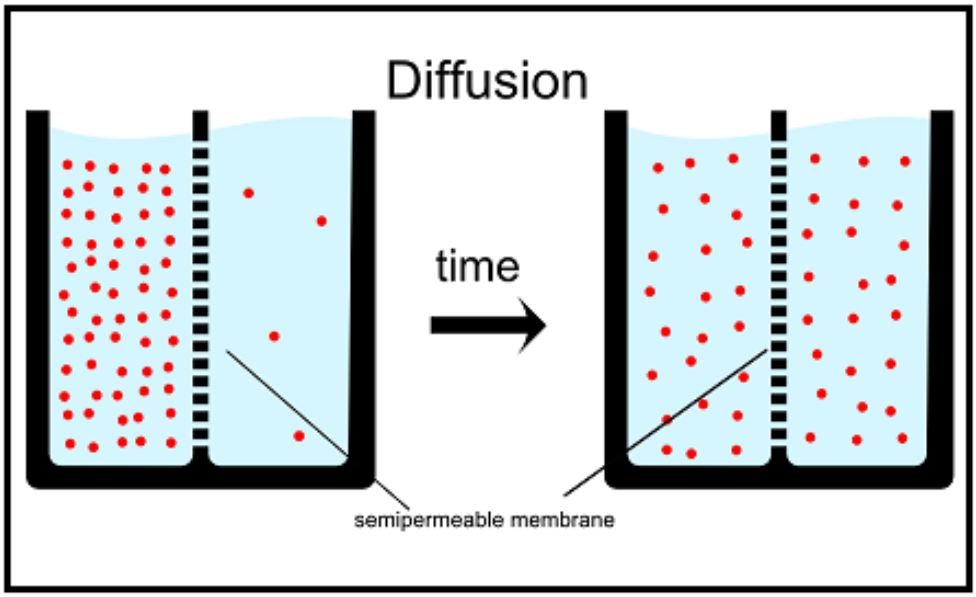

Figure 1.2: Diffusion process.
[11]

1.3.1 Fick's Law and its Application in Diffusion Controlled Release

Adolf Eugen Fick (1829-1901) was the first person to describe the concept of diffusion quantitatively. He observed that mass diffusion is analogous to heat conduction.

In 1855, he published "Uber Diffusion" in "Poggendorffs Annalen der Physik". In this, he defined the basic concept behind the diffusion phenomenon. In simple words it can be said that the solute moves from a region of higher concentration to a region of lower concentration across the concentration gradient assuming steady state condition. Concentration gradient acts as a driving force. "The mathematical equation of diffusion in isotropic substance is based on the hypothesis that the rate of transfer of the diffusing substance through unit area of a section is proportional to the concentration gradient measured normal to the section[9]." Isotropic means the system in which structure and the other diffusion properties at any given point are same relative to all directions [9].

$$J = -D\nabla c \tag{1.1}$$

where,

J = Drug concentration flux

D = Diffusion coefficient or diffusivity

c = Concentration

The negative sign indicates that process of diffusion occurs in the direction opposite to that of higher concentration i.e. diffusion occurs down the concentration gradient. Fick's second law gives the diffusion equation. This equation governs the time rate of change of concentration due to diffusion of the solute within the solvent [2]. Upon combining with the first law given by Equation 1.1, Fick's second law leads to [2].

$$\frac{\partial c}{\partial t} = D\Big(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2}\Big) \tag{1.2}$$

where t is total time and x, y and z spatial coordinates.

Equation 1.2 can be solved for the solute (drug) concentration as a function of time and space by using the initial and boundary conditions. In drug delivery system, the

initial condition typically is the drug concentration just prior to the diffusion process. It is given by the amount of drug distributed in the system before the release process starts. The boundary conditions specify the known drug concentration information at the boundaries such as the sink condition where the drug concentration is known or the "insulated condition" where the concentration flux is zero. Boundary conditions determine conditions for diffusion at boundary of drug delivery system. If the device dimensions don't change with time, then the boundary condition is called as stationary boundary conditions otherwise it is called as moving boundary conditions. Analytical solution for the drug release system as a function of time can be determined by solving equation 1.2.

1.3.2 Types of Diffusion Controlled Systems

Diffusion controlled systems can be classified on the basis of different parameters like the distribution of drug inside the matrix material, initial drug concentration, the geometry of the drug delivery system. Thus, depending on these parameters, drug delivery systems are classified in different categories [10].

Figure 1.3 represents different types of drug delivery systems:

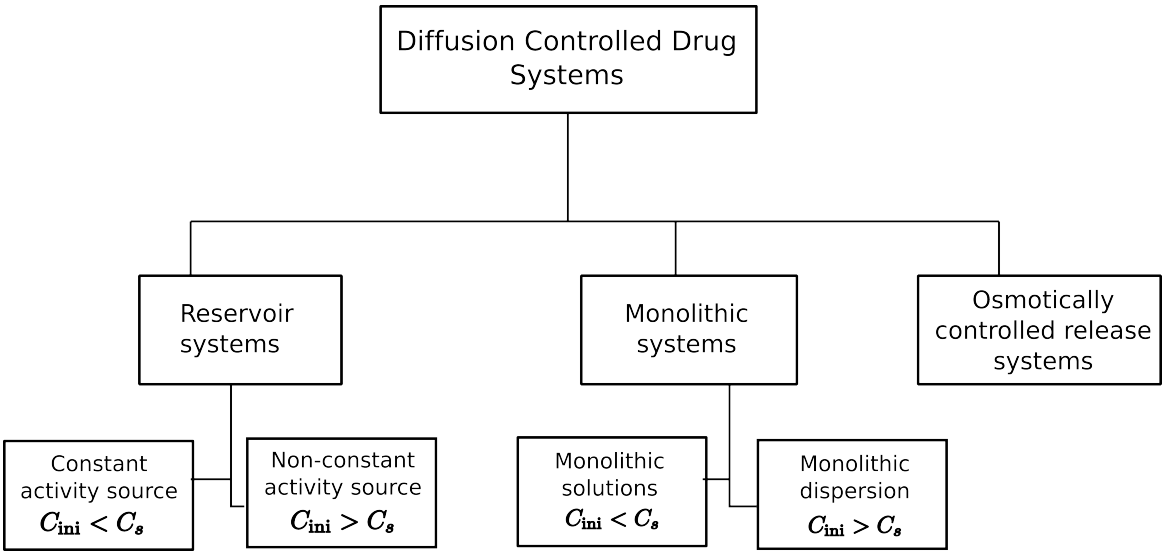

Figure 1.3: Classification of diffusion controlled systems.

1.3.2.1 Reservoir System

The reservoir system consists of a drug layer surrounded by a matrix material. The drug in which drug is completely separated from the barrier material. Therefore, the drug is at the core of the matrix material and is surrounded by a membrane. Since it forms the core-shell structure, this is called as reservoir system. Figure 1.4 describes the reservoir systems in brief.

Reservoir systems can further be classified as "non constant activity source" and "constant activity source" reservoir system. In non-constant activity source system, initial drug concentration is below the drug solubility. Thus, after penetration of the aqueous solution in the system, dug dissolves in the aqueous system and diffuse out through the membrane. However in constant activity source, the initial drug concentration is higher than that of drug solubility. When aqueous solution penetrates, drug dissolves in it and forms saturated drug solution. Thus, when drug diffuses out through the membrane, the released drug molecules are replaced by the remaining drug excess. As a result, drug concentration remains constant at the core. The slowest process is considered as the rate determining process. Since diffusion is much slower than that of dissolution, diffusion is considered to be the rate deciding process.

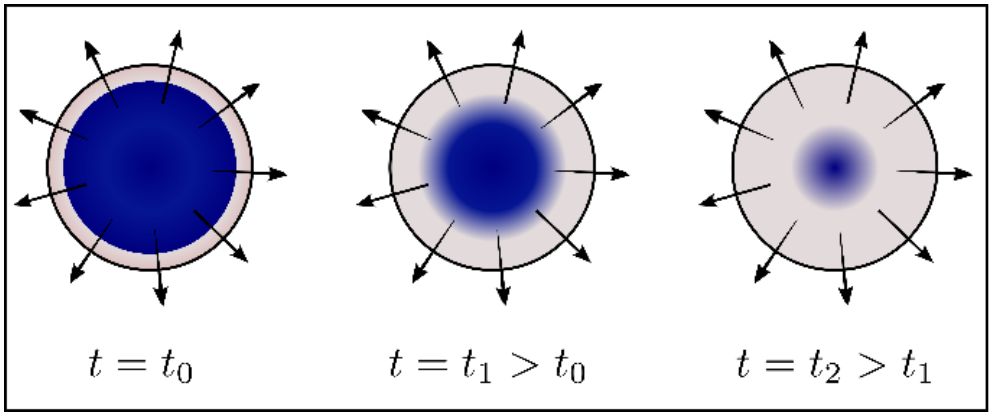

Figure 1.4: Schematic of reservoir system.

1.3.2.2 Monolithic System

In a monolithic system, drug dissolves or disperses in the common solvent and after evaporation of solvent, solid solution or solid dispersion is obtained. This is also called as one structured system since drug molecules are distributed homogeneously throughout the matrix material. This system is called as one-structured system. Figure 1.5 represents the monolithic systems.

If the initial drug concentration is less than that of drug solubility, then this system

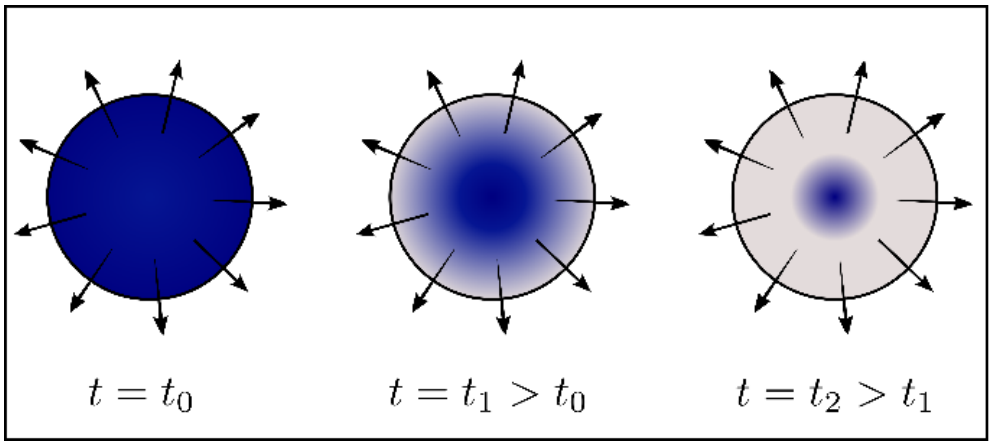

Figure 1.5: Monolithic system.

is called as monolithic solutions. In this system, the rate of release decreases with increase in time. However in the monolithic dispersion system, initial drug concentration is higher than that of drug solubility. In this, the drug completely dissolves into the aqueous solution and diffuses out through a matrix material.

1.3.2.3 Osmotically Controlled System

This is also one of the controlled drug delivery methods. In this method, drug carrying device utilizes osmotic pressure gradient of water to force out the drug particles from the opening of tablet. This tablet has water permeable jacket having small holes through which water penetrates and forces out the drug from tablet. The flow of water is controlled by restricting water flow through a micrometer scale to larger

diameter pores. This is the oral drug delivery system. Though this system is effective for drugs having short half-life.

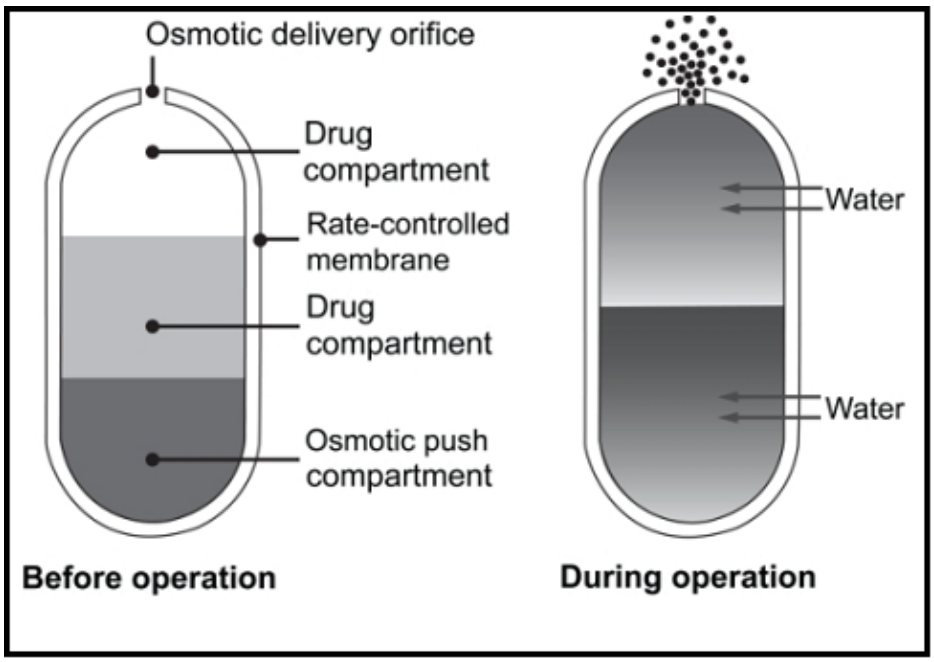

Figure 1.6: Osmotic controlled release system.
[13]

1.4 Objectives

The goal of the present study is to develop and validate the computational model to study the primary mechanisms of dissolution and diffusion, which determine the release rate of the drug from the porous α-Cristobalite disks of different porosities. For the present study, two approaches were implemented which are Experimentations and Computational Analysis. In the experimental part of the study, porous α-Cristobalite ceramic discs were prepared using powder metallurgy techniques. The porosity characteristics of the ceramic discs were varied and characterized by mercury porosimetry. The discs (n = 4) were immersed in antibiotic solution (Vancomycin) for either 4 hrs or 24 hrs. The amount of drug adsorbed on the porous ceramic was determined and correlated to the porosity characteristics of the material. Moreover, the vancomycin release kinetics from porous α-Cristobalite samples into physiological solution was

measured and correlated to the porosity characteristics and the initial drug adsorption. Concurrently, Fickian diffusion laws were used to develop the drug desorption and diffusion models from the α-Cristobalite disks. The governing differential equations for drug concentration were solved using the finite element software package `ABAQUS`. The computational results and the experimental data were used to determine the mass transfer coefficient and diffusion coefficient values for different porosities and drug immersion times. The role of drug desorption and diffusion mechanisms in drug release from porous α-Cristobalite was studied.

CHAPTER 2: CRISTOBALITE DISCS AS DRUG DELIVERY SYSTEM FOR VANCOMYACIN

2.1 Introduction

Drug delivery systems offer the advantage of controlled release of drug in targeted manner with the minimal side effect. In the present study the therapeutic efficacy of a porous α-Cristobalite disks as a new delivery system was evaluated in vitro. There are number of experiments were done showing the significant differences in loading and release capacities of drug delivery system from different drugs and their carriers.

For the present study, the α-Cristobalite particles of size 90 μm-150 μm were used. Cristobalite is a high-temperature polymorph of silica. It has the same chemical formula as that of silica but has different crystal structure. Polyethylene glycol (PEG) is polyether compound having many applications in medical industry. This polymer is a biodegradable. So difficulties in achieving complete excretion would be very easy. For drug delivery systems, polymer is used with silica to make the porous scaffold. The Drug is reserved by this polymer matrix and it travels to the targeted area through the tortuous pathways to exit the device.

A drug that is used in this study is called as Vancomycin. This is an antibiotic useful to treat bacterial infections. This falls in class of medications called glycopeptide antibiotics. Vancomycin is poorly absorbed from the intestine. Hence it must be given intravenously for systemic administration. This may cause the severe adverse effects. Thus several attempts have been made for treatment of disease using Vancomycin drug carrier devices.

Figure 2.1: Carver press die.

2.2 Materials and Methods

2.2.1 Material Preparation

Porous α-Cristobalite disks were synthesized by mixing α-Cristobalite particles of size 90 μm-150 μm with different amounts of PEG to obtain different porous structures of the disks. For each disks 500mg of mixture was pressed using Carver Press-Die Hydraulic Jack. The pressure applied to press the disks was 283 MPa. The following table shows the characteristics of the disks preparation. After pressing the disks, they were heat treated to let burn out the PEG and thus the porous structure was formed. The heat treatment given is tabulated below. These disks were further used for drug loading and release study. Also these samples were tested to analyze the

Table 2.1: Characteristics of disks preparation.

Characteristics	Sample 1 (Cris 50)	Sample 2 (Cris 15)	Sample 3 (Cris 0)
PEG% by weight	50	15	0
Amt. of water added μl	0	50	50

Table 2.2: Heat treatment to prepare the disks.

Remove Water-100°C for 1hr	Burn PEG-350°C for 24hrs	Sinter-900°C for 1hr
200°C for 1Hhr	1100°C for 12hrs	

surface properties and porosity.

Figure 2.2: Porous ceramic disks with different porosities.

2.2.2 Drug Loading

Vancomycin drug was added to Phosphate Buffer Saline (PBS) solution of pH 7.4, to make drug solution of concentration 8 mg/mL. The mixture was well stirred till all the drug completely dissolved. Each disks was immersed in a separate pallet containing 2 mL of this drug solution. After immersing the disks for 4 hours, they were taken out and let them dry overnight. The solution was stored in the vial to measure how much drug adsorbed by each disks. The dried disks were further used for

drug release. The other set of experiment was also carried out. For this, everything was kept same except the immersing time of disks into drug solution was changed to 24 hrs.

2.2.3 Drug Release

After drying all the disks, each disks was separately immersed in 2 mL of PBS solution of pH 7.4 in each pallet. After certain time interval 1 mL of the immersing solution was taken out and stored in the vial. Whenever the immersing solution was taken out, the same amount of fresh PBS was added to the pallet to maintain the constant volume. These pallets were put on the orbital shaker at 120 rpm at 37°C. The time points of 1 hr,4 hrs, 8 hrs, 24 hrs, 2 Days, 3 Days, 10 Days, 15 Days, 22 Days and 30 Days were chosen to take out the solution. The stored solution samples were further used for HPLC test to analyze how much drug was released. In other set of experiment same procedure was repeated and collected the samples.

2.3 HPLC Analysis

High Performance Liquid Chromatography (HPLC) is the improved form of column chromatography. This is used in analytical chemistry to identify and quantify each component of the sample. Very high pressurized liquid solvent containing sample mixture to be analyzed is passed through a column. This column contains solid adsorbent material. The different components of sample mixture reacts differently with the adsorbent material. Therefore there causes a different flow rates for different material which leads to separation of component while flowing out.

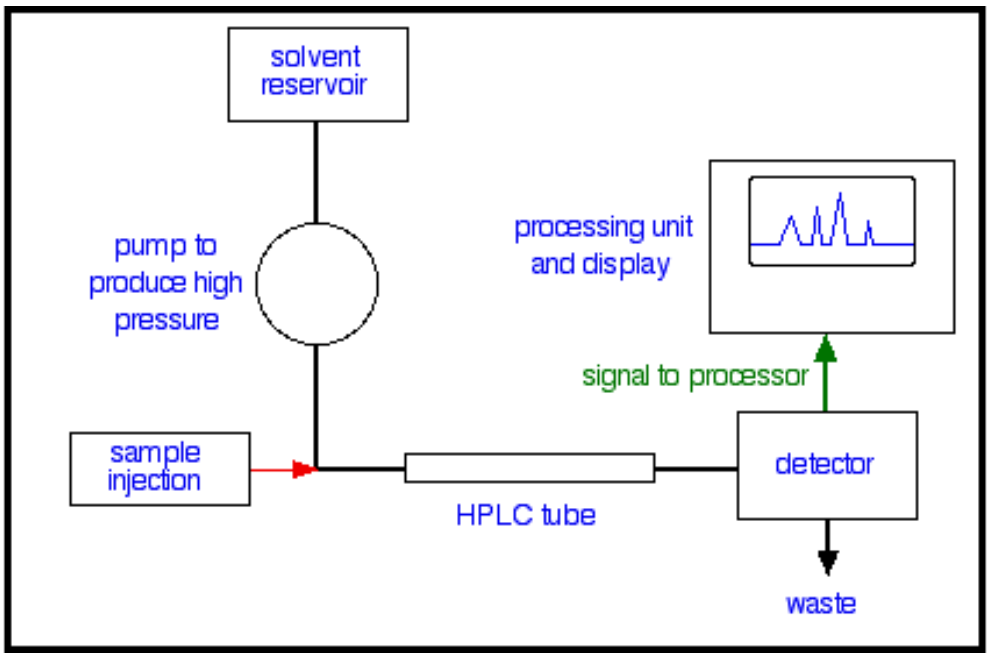

Figure 2.3: Schematic of HPLC.
[15]

2.3.1 Working of HPLC

2.3.1.1 Injection of the Sample

Injection of the sample is completely automated process. It injects the predefined volume of the sample and let it pass through the detector column [15].

2.3.1.2 Retention Time

The total time of traveling of a compound through a detector column is called as retention time which is measured from the time sample is injected to time at which it displays the maximum peak. This time depends on pressure, stationary phase, solvent's composition and temperature of the column [15].

2.3.1.3 The Detector Column

UV lights of various wavelengths are passed through a detector column. Particular compound absorbs UV light of particular wavelength. The amount of UV light

absorbed by the compound depends on the quantity of a compound passing through that beam of UV light [15].

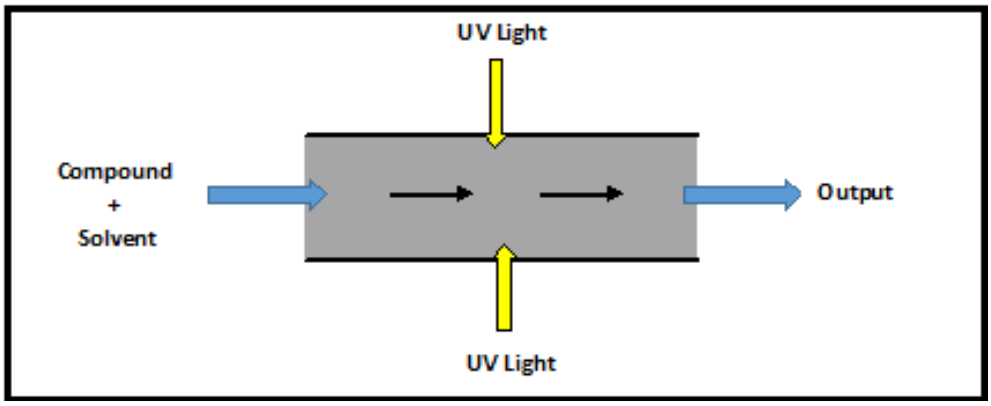

Figure 2.4: Detector column.

2.3.1.4 Interpreting Output

The output will be recorded as a series of peaks. If the known amount of compound is passed through a column then for that known value, a peak is plotted. Then from this value of peak, the unknown quantity of the same compound can be calculated by simple mathematical calculations[15].

2.3.2 HPLC Test Setup

A ZORBAX Eclipse Luna C8 HPLC column (4.6 X 100 mm; 5μm; Phenomenex, Torrance, CA) was used to separate Vancomycin. The samples were detected by ultraviolet absorbence at 280nm since compounds of Vancomycin can absorb most of UV light at this wavelength. The injection volume used for was 300μL. The solvent was extracted at flow rate of 1.5 ml/min at pressure of 200 bar with the following gradient conditions: The mobile phase of a mixture of A % 5mM KH2PO4, pH 2.8, and mobile phase B % acetonitrile. At 0 and 1.5 min: 97% A, 3% B at 10 and 13.5 min: 80% A, 20% B and at 14.5 and 16.5 min: 97% A, 3% B. Known Vancomycin solution standards over the range of 8.0-0.0071825 mg/mLwere used to plot the calibration

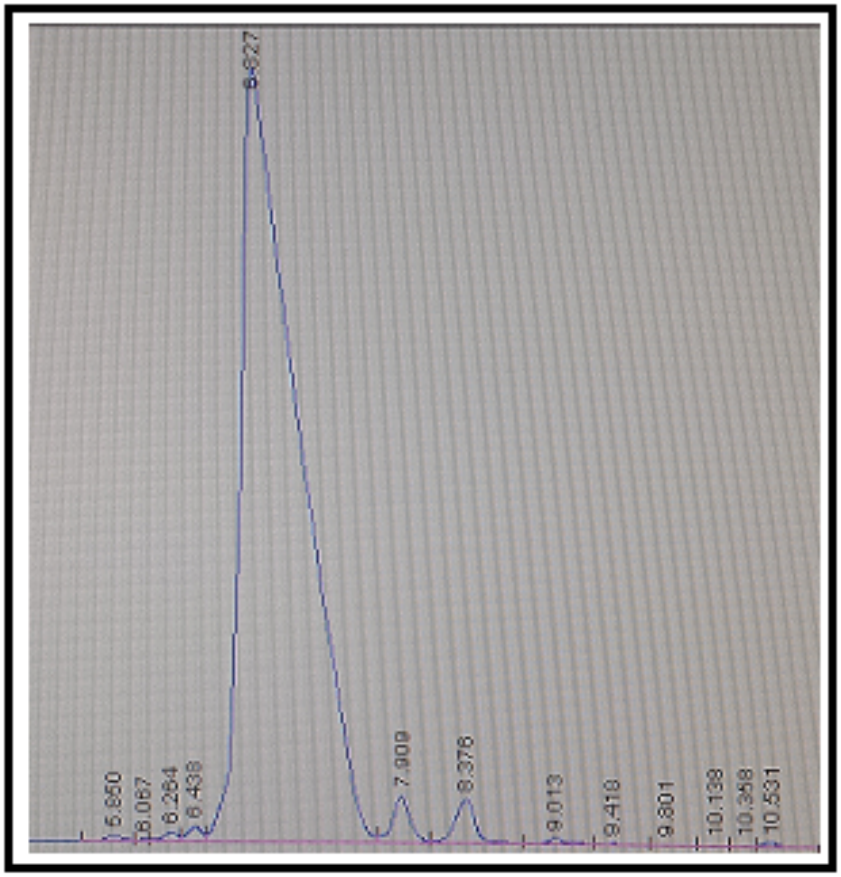

Figure 2.5: Area under curve detected by detector column.

curve. The stored samples diluted in 1:1 proportion with PBS and loaded on HPLC to analyze how much drug was adsorbed and released over the selected time period.

2.3.3 Surface Characteristics

The porosity, pore size distribution and the surface area of the disks were analyzed using Mercury intrusion porosimetry and BET (Micromeritics, Norcoss,GA)). Porosimetry is useful in understanding the formation and structure of the material. There are different sizes of pores occur which decide the porosity of the material. Distribution of the pore sizes plays an important role in adsorption of the drug molecules. Also surface area plays major role in release kinetics. Thus some of the characteristics and phenomenon which was considered in the present study is explained in the

Figure 2.6: Test setup for HPLC.

following sections.

2.3.3.1 Porosity

Porosity is defined as the measure of void spaces in material. It is fraction of the volume of voids over the total volume given as a percentage between 0 to 100%. Percent porosity can be defined by following equation 2.1 [16]

$$Percent \;\; Porosity = \left(1 - \frac{\rho_{se}}{\rho_{sa}}\right) 100 \tag{2.1}$$

Where ρ_{se} is envelope density which is calculated by including pore spaces within material particles while calculating total volume. ρ_{sa} is called as absolute density which determined by excluding void spaces between the particles and the pores of sample while measuring its volume.

2.3.3.2 Pore Size and Volume

The shape of the pores is assumed to be cylindrical. With this assumption, pore size is determined in terms of diameter of the opening or the width of the slit. The pore diameter less that 2 nm are considered to be micropores. Pore diameter greater than 2 nm are called as macropores. Whereas pore volume is determined by subtracting material's volume from total volume. Thus it can be defined as material's air volume less from material's total volume [16].

2.3.3.3 Surface Area

The total area of pores available for the drug molecules to get adsorbed is the total surface area m^2/g. Higher the surface area, faster is the drug release.

2.3.4 Mercury Porosimetry

To determine characteristics of material's porous nature, a technique called Porosimetry is used. This technique involves intrusion of non-wetting liquid into the material at high pressure with the help of device called as porosimeter.

This technique is based on the capillary law governing liquid penetration in small pores. For mercury which is non-wetting liquid, this law is expressed by the Washburn equation2.2 [16].

$$D = \frac{1}{P} 4\gamma \cos\phi \tag{2.2}$$

where,

D = Pore diameter

P = Applied pressure

γ = Surface tension of mercury

ϕ = Contact angle between mercury and sample.

While performing mercury porosimetry, it is assumed that pores are cylindrical in

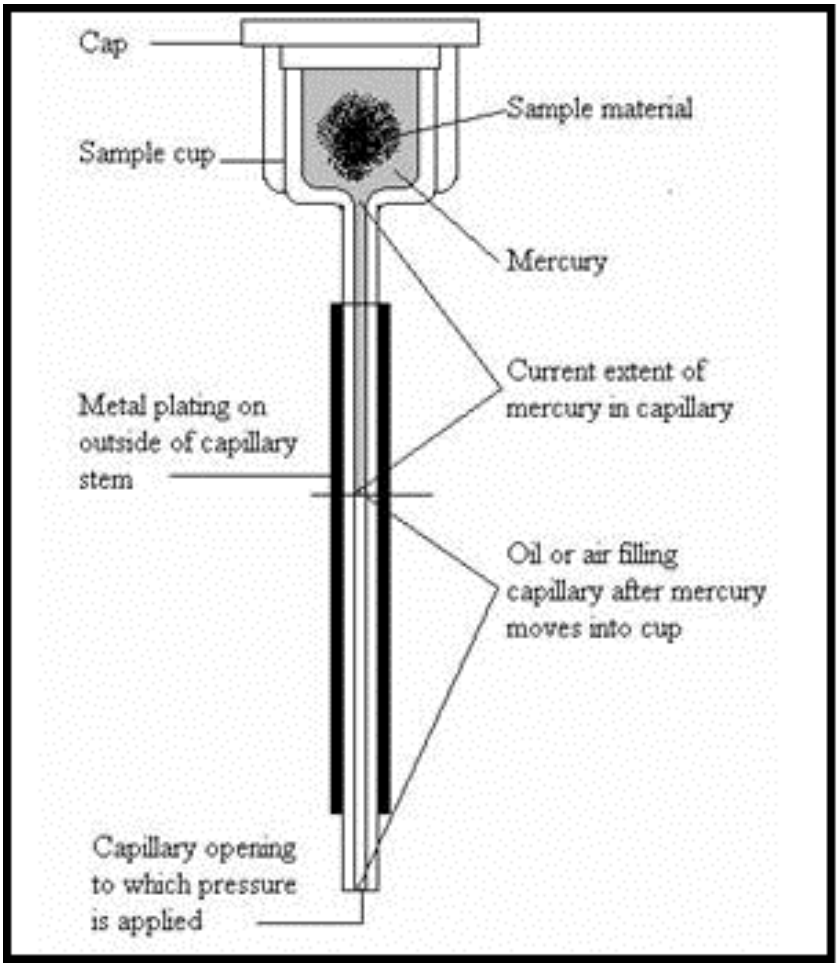

Figure 2.7: Mercury intrusion porosimetry.
[16]

shape. Since mercury is non wetting liquid, it doesn't get penetrated easily into the pores. Some external pressure needs to apply. For the large pores, required external pressure is lower than that of required for small pores. The volume of pores can be determined by measuring how much volume of mercury penetrates into material with different pressures [16].

2.3.5 Surface Characteristics Analysis

Micromeritics did the mercury porosimetry and BET tests to measure the porosity, pore size distribution, pore diameter and surface area of the samples. All the derived results are stated in table below.

The Cris 50 samples were expected to have higher porosity since they had the max-

Table 2.3: Characteristics of the α-Cristobalite disks.

Characteristics	Cris 50	Cris 15	Cris 0
Sample Weight (g)	0.2269	0.3803	0.5209
Porosity (%)	72.4247	59.2928	58.6087
Total pore area (m^2/g)	2.271	2.307	2.262
Avg. pore diameter (μm)	2.0554	1.0427	1.1056

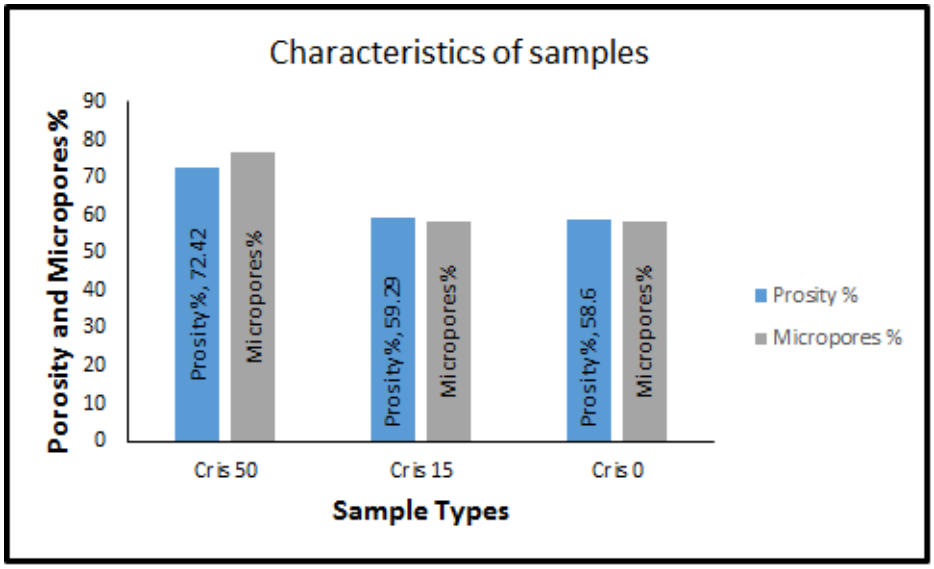

Figure 2.8: Comparison of porosity and micropores percentage for Cris 50, Cris 15 and Cris 0.

imum amount of PEG in it than those of Cris 15 and Cris 0 samples. Also, there is no significant difference in porosity for Cris 15 and Cris 0 samples. The surface areas of all the three samples were comparable. As per the graph of Cumulative Intrusion Volume and Incremental Intrusion Volume vs pore diameter, Cris0, Cris15 and Cris50 have the pores in the size range 3nm to 0.99 nm contributing 41.93 %, 43.33% and 23.27% of the total pore volume respectively. Thus figure 2.8 gives the comparison of micropores percentage in all the three samples. Cris 50 has the highest percentage of micropores present in it. However, Cris 15 and Cris 0 have comparable percentage of micropores. Figure 2.9 is basic plot from mercury intrusion analysis and it gives

an estimation of how porosity is distributed in the sample. With the help of data from incremental intrusion volume, at what diameter the pore volume is concentrated and the distribution characteristics were analyzed and given by figure 2.10. Therefore, samples of Cris 50 had the least amount of nanopores samples contributing to drug release, however the samples Cris 15 and Cris 0 had a comparable size range of nanopores contributing to drug release.

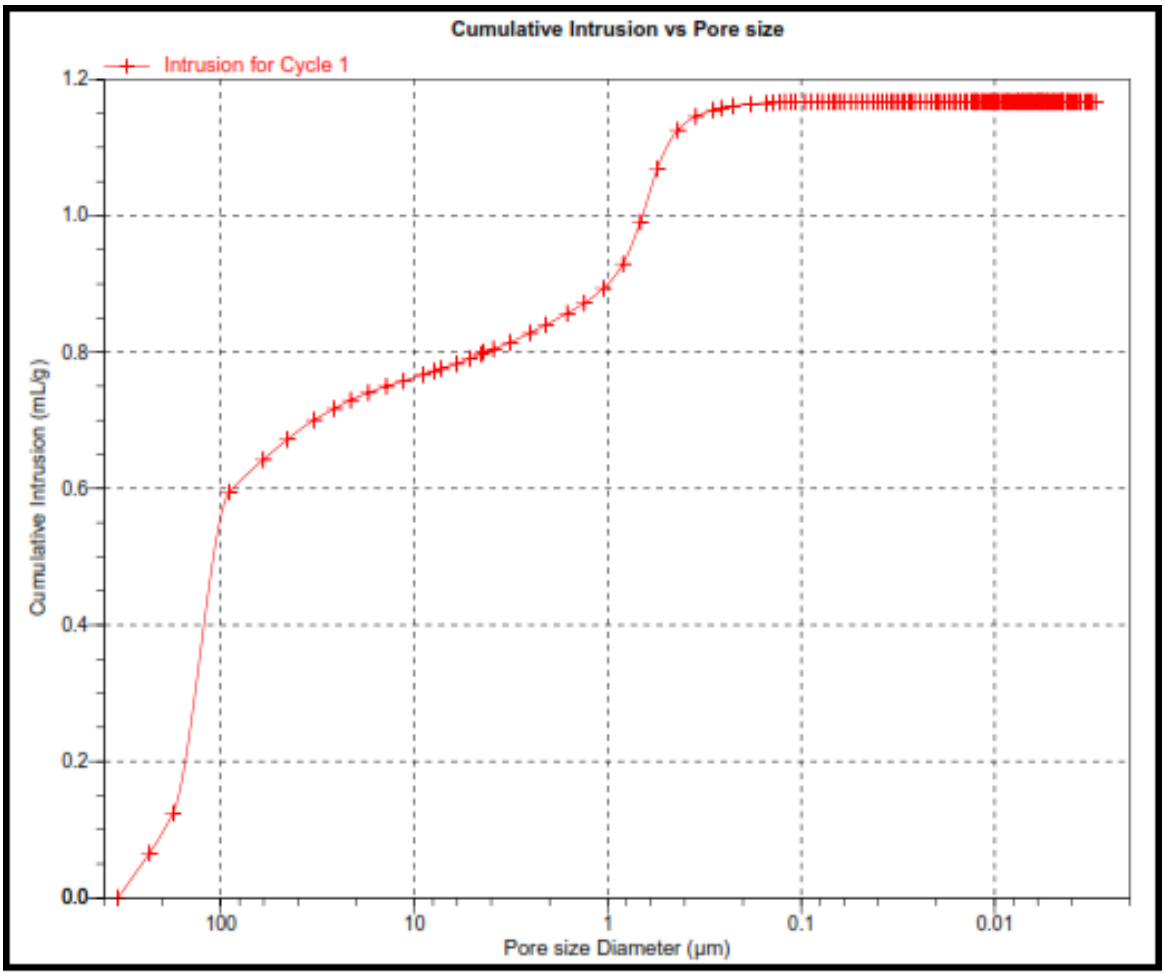

Figure 2.9: Cumulative intrusion volume vs pore diameter: Cris 50.

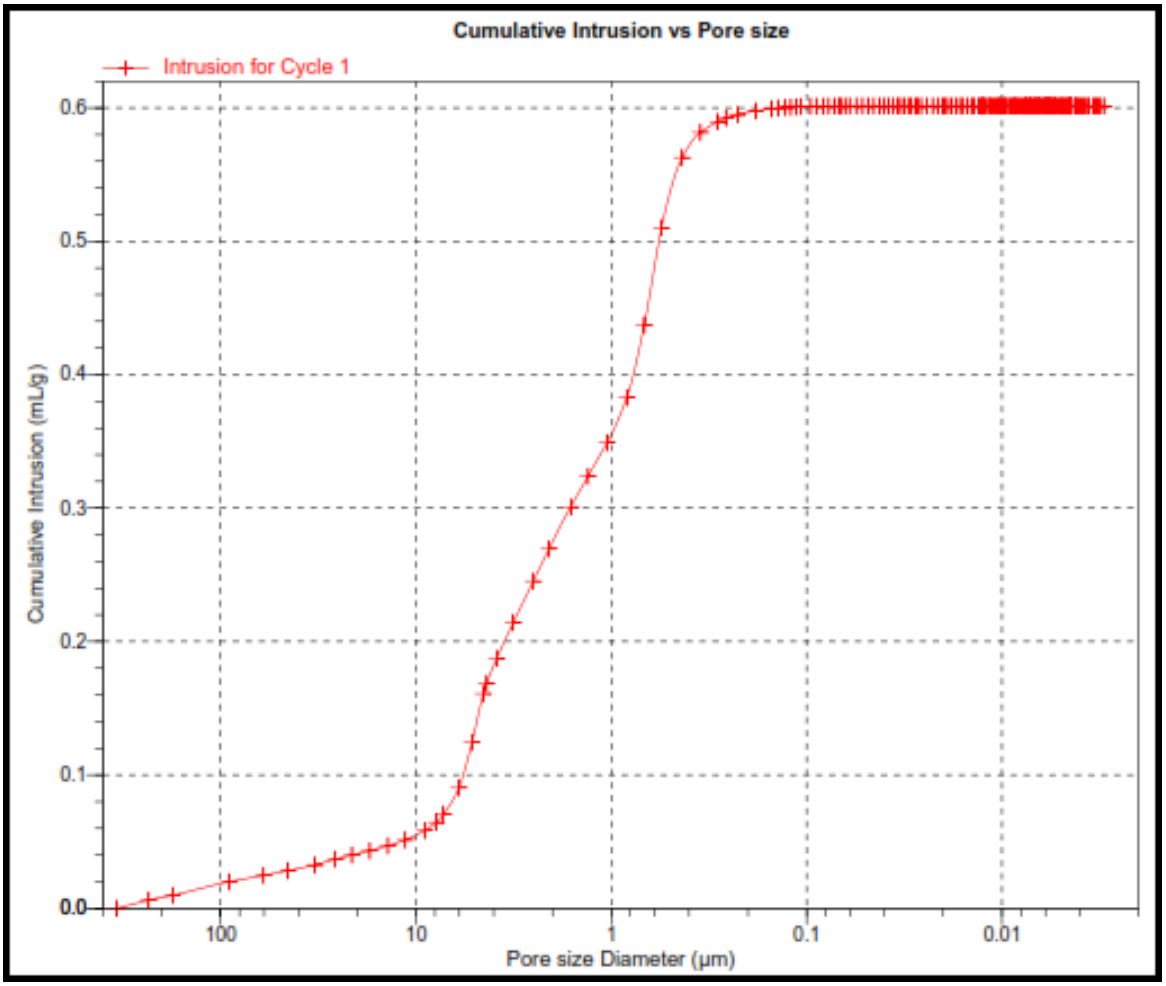

Figure 2.9 (Continued): Cumulative intrusion volume vs pore diameter: Cris 15.

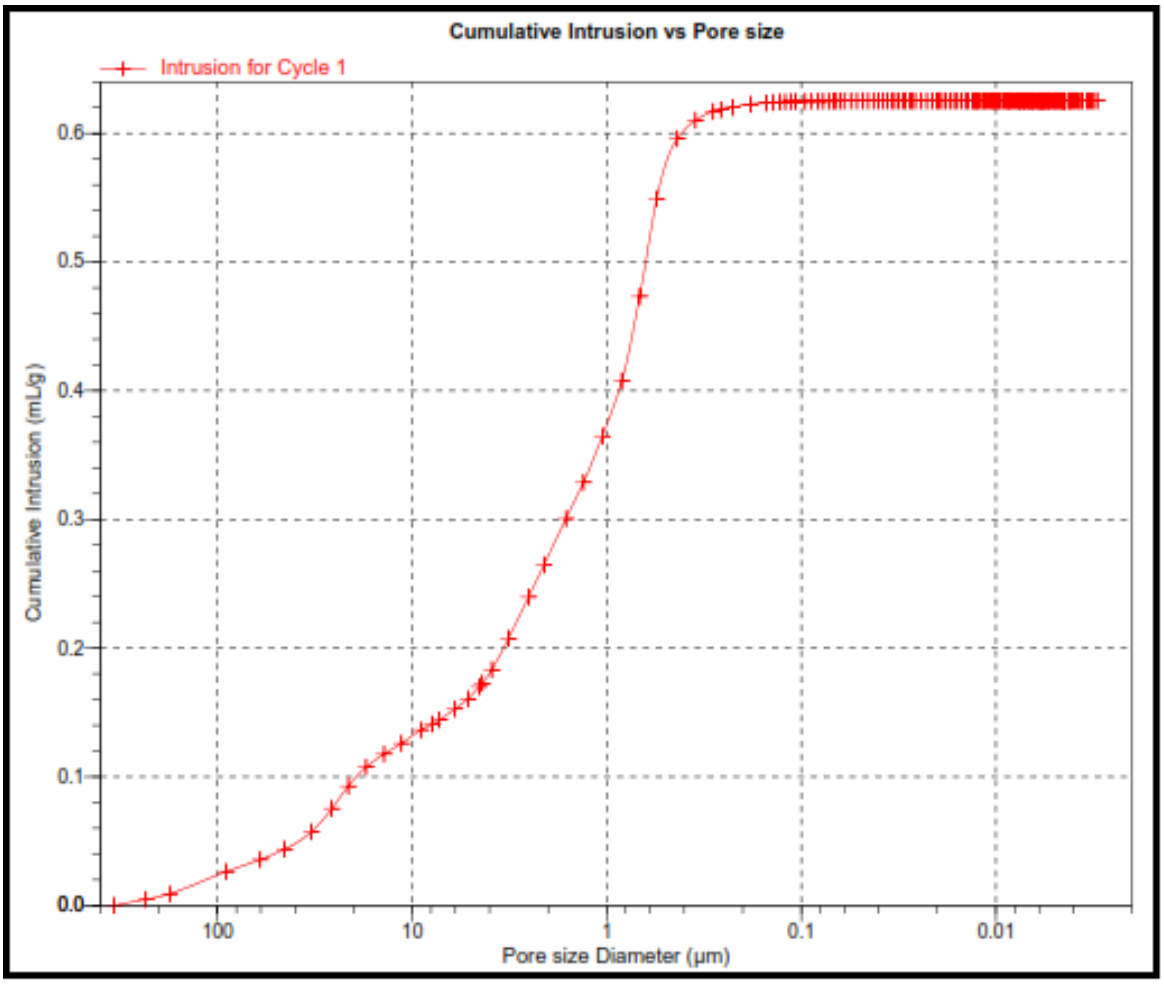

Figure 2.9 (Continued): Cumulative intrusion volume vs pore diameter: Cris 0.

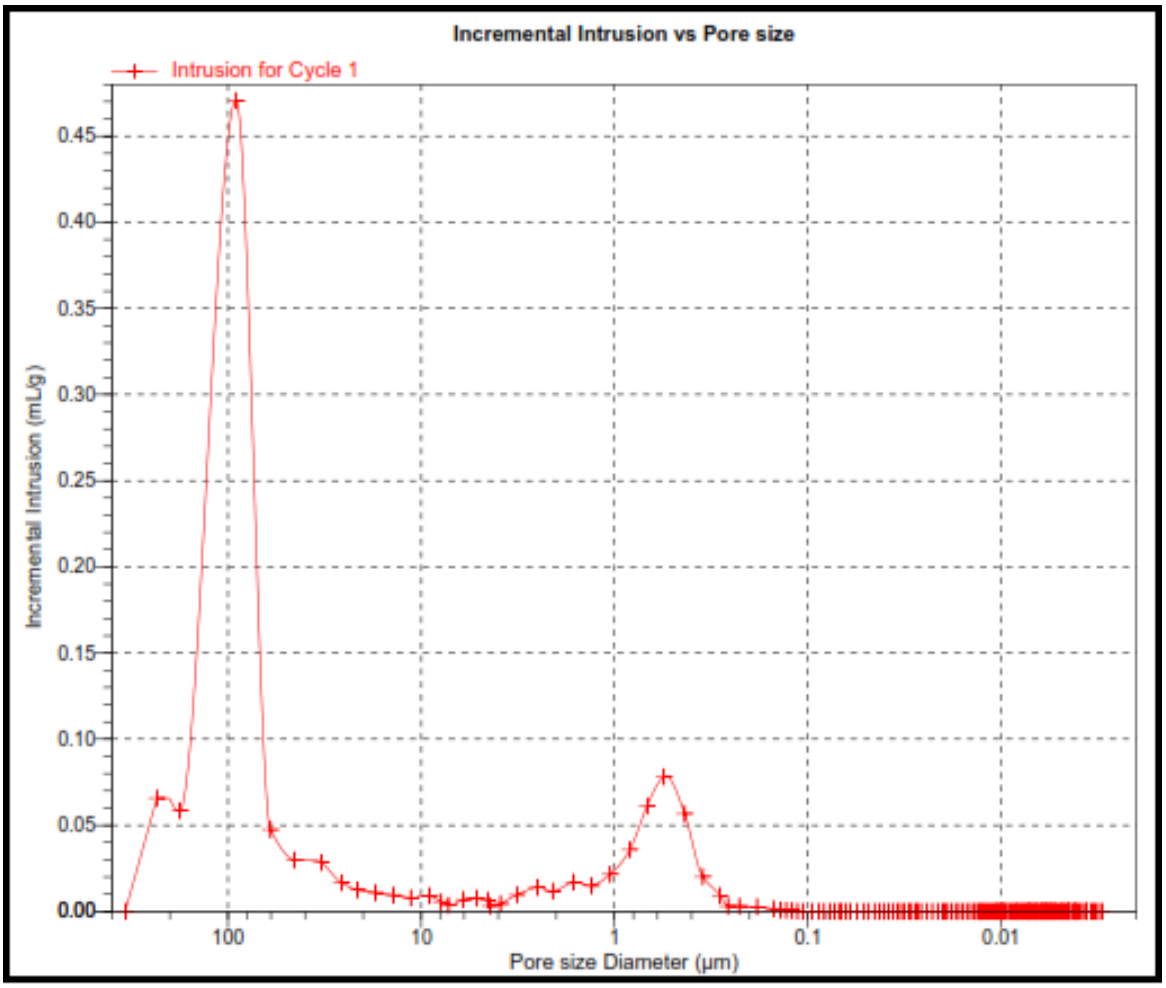

Figure 2.10: Incremental intrusion volume vs pore diameter: Cris 50.

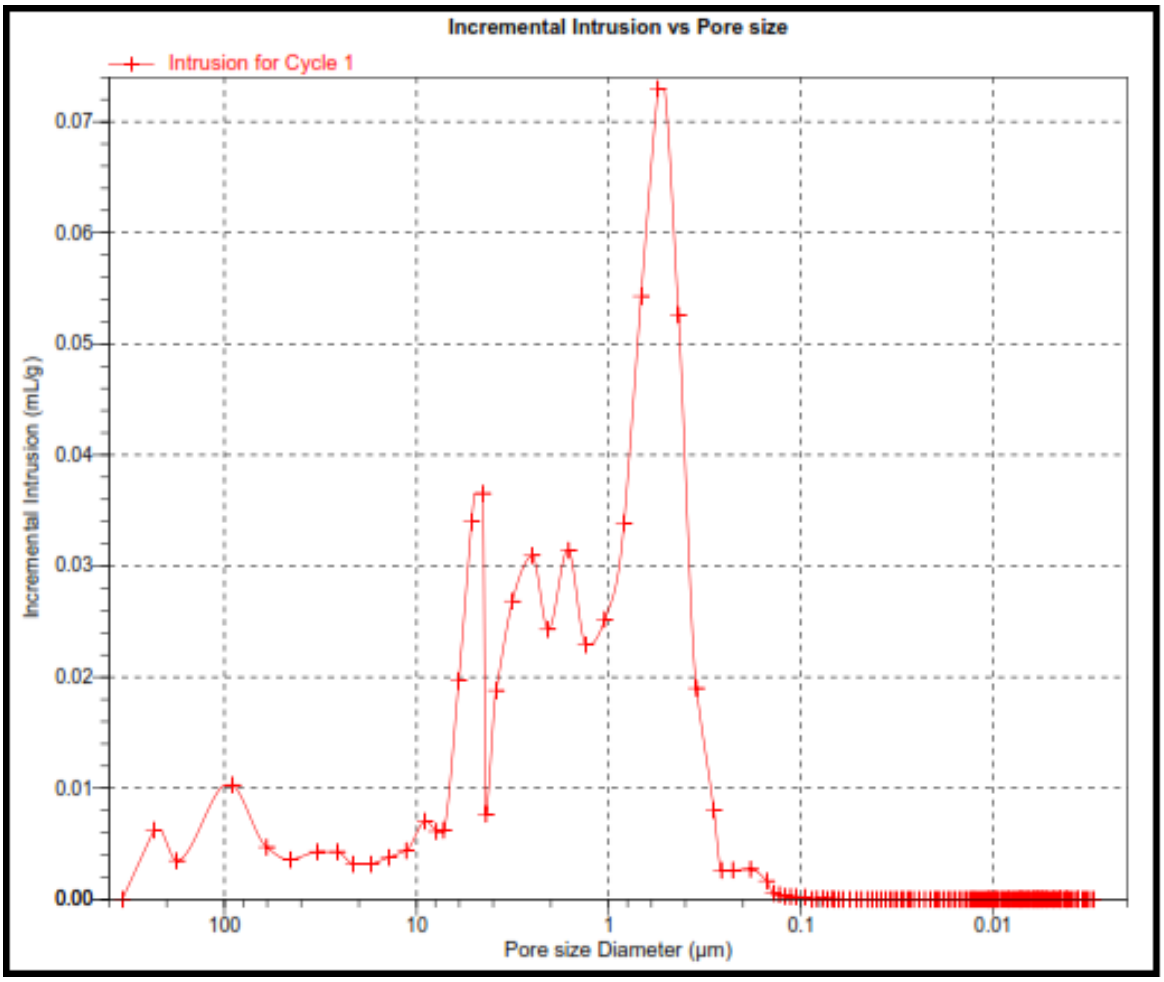

Figure 2.10 (Continued): Incremental intrusion volume vs pore diameter: Cris 15.

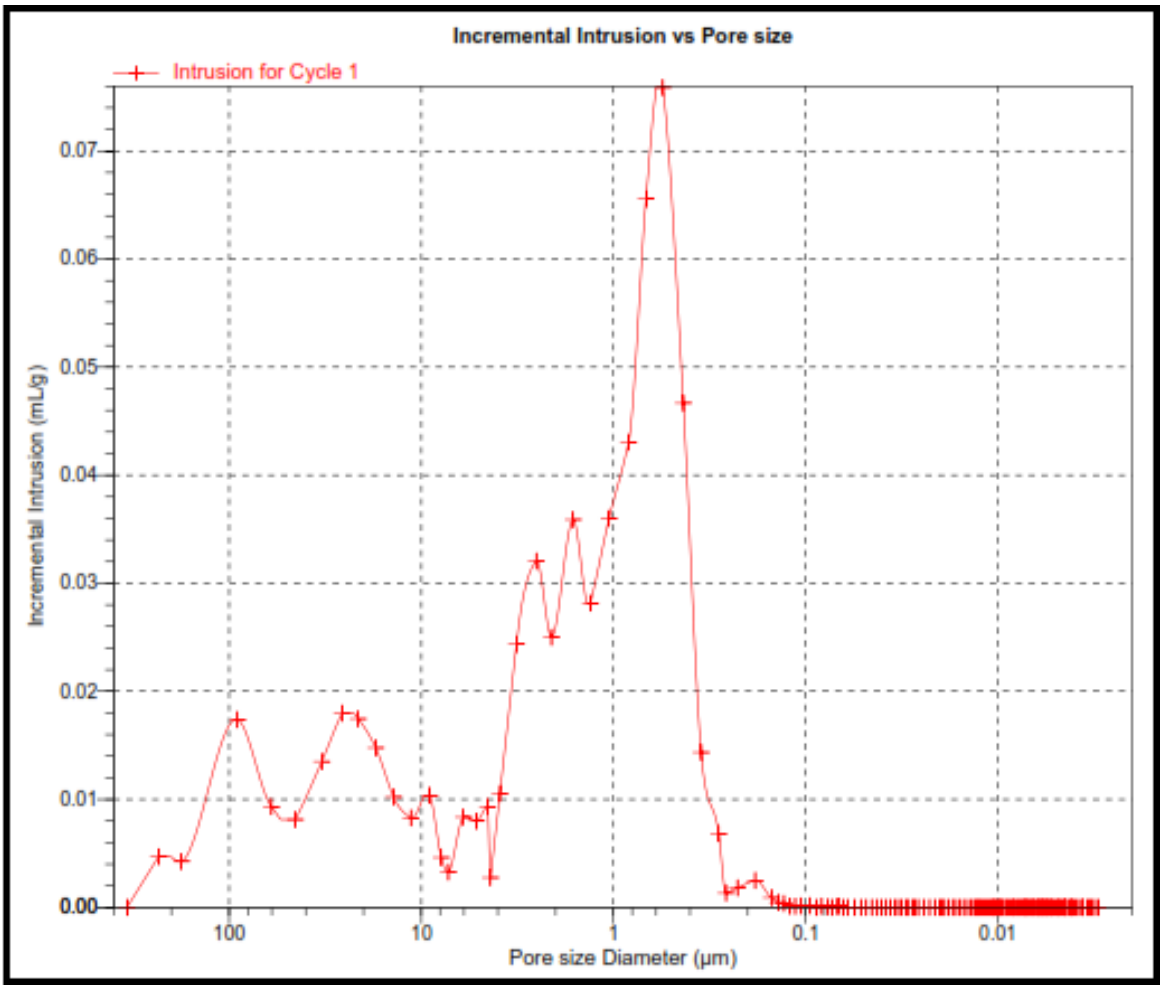

Figure 2.10 (Continued): Incremental intrusion volume vs pore diameter: Cris 0.

CHAPTER 3: COMPUTATIONAL MODEL

3.1 Assumptions

Monolithic system was the best suited for the problem statement in the present study. For the present study, some assumptions were made to calculate total amount of drug released from the drug delivery system. The assumptions are discussed below.

1. Geometry selected for the present study is considered as a perfect cylinder.
2. Drug release is uniform in angular direction.
3. For the inert Cristobalite disks, the two main mechanism of drug release are diffusion and dissolution (desorption).
4. Diffusion process is assumed to be significantly slower than dissolution process.
5. The concentration flux at the outer radius is zero.
6. There was no significant erosion or swelling of the matrix material. Therefore geometry of the disk does not undergo any deformation.

With these assumptions, one-dimensional and two-dimensional axisymmetric models were sufficient to study drug release from α-Cristobalite drug carrier. With this, the computational time was reduced to calculate the total drug concentration from 3-D geometry. A finite element model of the drug delivery system was developed in `ABAQUS`. The diffusion process modeled in two stages. The initial burst release phase was modeled considering only the PBS and the subsequent diffusion dominated stage was modeled considering both the disk and the PBS. The mass transfer coefficient K_c

for burst release phase/dissolution and the Diffusion coefficient D in the Cristobalite were determined for the three different porous samples using results of finite element method in combination with the experimental results.

3.2 Modeling Approach

The actual assembly of the disk and the PBS is given by the figures 3.1 and 3.2 below. The computational model was divided into two steps which are shown in

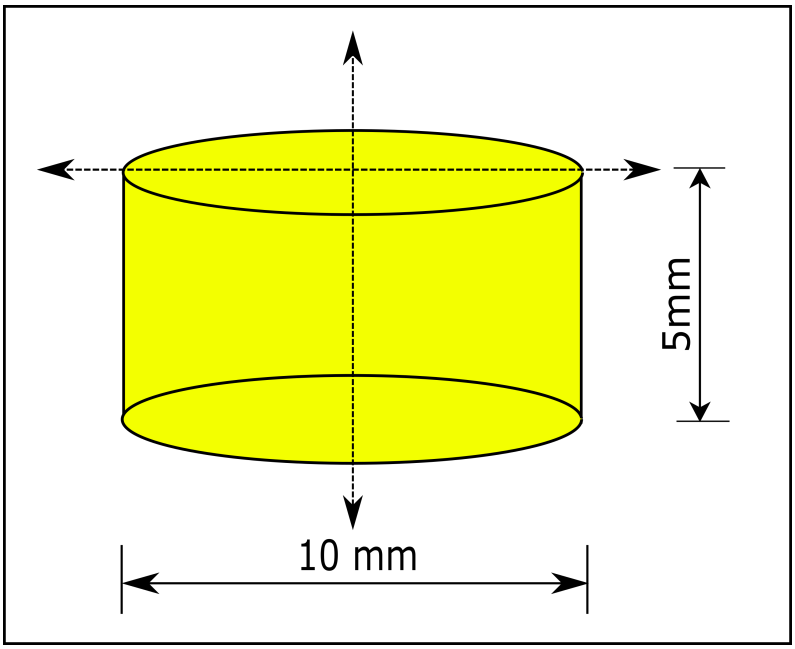

Figure 3.1: Disk Geometry.

figure 3.3.

The first the step is dissolution of the adsorbed drug in PBS. In this step, the stack of drug layers formed on the uppermost surface of the disk. Loosely bound drug dissolves in PBS immediately after immersing the disk in PBS. This process results in the burst release phase. Maximum amount of drug is released in this process. The drug release into PBS from the adsorbed drug on the surface of the mass matrix is modeled as a diffusion process with an associated mass transfer coefficient at the interface between the adsorbed drug layer and the PBS solution.

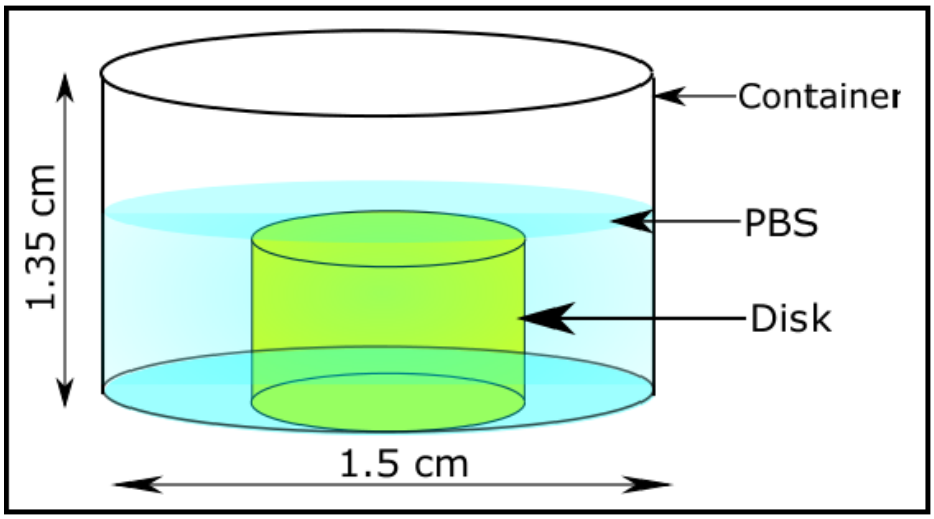

Figure 3.2: Assembly of disk and PBS.

The second step is the diffusion of drug from the ceramic matrix to its surface and then it dissolves in PBS. Thus drug molecules which are deep inside the matrix material, diffuse out through the pores of the disk to the surface and then dissolve into PBS. This is significantly slower process than dissolution process. Diffusion coefficient determines the rate of diffusion of drug through porous material.

By matching the results of total amount of drug released in both burst and sustained release stage with finite elements results, the mass transfer coefficient and diffusion coefficient were determined for Cris 50, Cris 15 and Cris 0.

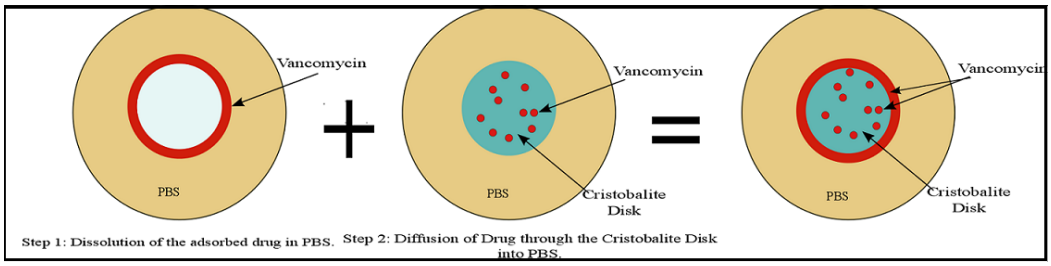

Figure 3.3: Computational modeling approach.

3.3 Governing Equations

Based on the assumptions discussed in the above section the drug concentration $c(t)$ in PBS is found using `ABAQUS`. The domain occupied by PBS is discretized into n_{el}

elements consisting of n nodes per element. The governing equation for drug release into PBS is the same as the transient diffusion equation. Thus, the nodal values of drug concentration in the PBS are obtained by treating the problem as a transient heat conduction equation. The nodal values are then used to find the total amount of drug released into PBS as follows [17]. The total amount of drug released into PBS at any time t is given by

$$M(t) = \int_{\Omega} c(t) d\Omega \tag{3.1}$$

where Ω is the region occupied by PBS. Let Ω^e represent an element e. Then, $M(t)$ can be written as

$$M(t) = \sum_{e=1}^{n_{\mathbf{el}}} \int_{\Omega^e} c(t) d\Omega^e = \sum_{e=1}^{n_{\mathbf{el}}} M^e(t) \tag{3.2}$$

where

$$M^e(t) := \int_{\Omega^e} c(t) d\Omega^e \tag{3.3}$$

Here, Ω^e is the region occupied by the element e. Clearly, $M^e(t)$ is the cumulative drug released into element e. In the following, we derive finite element approximations to $M^e(t)$ for one-dimensional and two-dimensional axisymmetric elements.

3.4 One-Dimensional Axisymmetric Elements

On each element, the drug concentration $c(t)$ is given by the approximation

$$c(t) = \sum_{a=1}^{n} N_a(r) c_a(t) \tag{3.4}$$

where, $c_a(t)$ and $N_a(r)$ are the concentration and shape function at node a. r is the radial coordinate for the one-dimensional axisymmetric problem. For axisymmetric

one-dimensional, linear elements, $n = 2$. Then, $M^e(t)$ given by equation (3.3) can be written as

$$M^e(t) = \sum_{a=1}^{n} c_a(t) \int_{\Omega^e} N_a(r) d\Omega^e = 2\pi h \sum_{a=1}^{n} c_a(t) \int_{r_1}^{r_2} r N_a(r) dr. \tag{3.5}$$

Here, h is the height of the disk, r_a is the radial co-ordinate of node a with $a = 1, 2$. Upon changing the integration domain to the master element with the co-ordinate ξ, the above becomes

$$M^e(t) = \pi h l_e \sum_{a=1}^{2} c_a(t) \int_{-1}^{1} r(\xi) N_a(\xi) d\xi. \tag{3.6}$$

with l_e being the length of the element e. For isoparametric formulation, $r(\xi) = r_1 N_1(\xi) + r_2 N_2(\xi)$. Then, the cumulative drug released into element e (equation (3.6)) becomes

$$M^e(t) = \pi h l_e \sum_{a=1}^{2} c_a(t) \int_{-1}^{1} \left[r_1 N_1(\xi) + r_2 N_2(\xi) \right] N_a(\xi) d\xi. \tag{3.7}$$

Since $N_1(\xi) = \frac{1}{2}(1 - \xi)$ and $N_2(\xi) = \frac{1}{2}(1 + \xi)$, equation (3.7) becomes

$$M^e(t) = \pi h l_e \left(c1 \left(\frac{2}{3} r1 + \frac{1}{3} r2 \right) + c2 \left(\frac{1}{3} r1 + \frac{2}{3} r2 \right) \right) \tag{3.8}$$

where $c1$ and $c2$ are the concentrations at node 1 and node 2. Thus total amount of drug released by one-dimensional axisymmetric model was calculated by adding the $M^e(t)$ over the number of elements.

3.4.1 `MATLAB` Program for One-dimensional Axisymmetric Model

```
clear all;
clc;
```

```
TotEle = load('DiskpbsEle.dat');
TotTemp =  load('Exp2DiskPbsNT0.dat');
H = 0.5;
he = 0.0005;
%Read number of elements
s1=size(TotEle);
s2=s1(:,1); % No of elements

% Read nodes corresponding to elements
for i=1:s2
    for j=1:2
        nodes(i,j)=TotEle(i,j+1);
    end
end



%Calculating total amount at different 10 time steps
for t=1:7
    %Calculating amount of drug at a time step for no.
    of elements.
    %s2 is number of elements.
    %Me is amount of drug at a time step for each element.

    for m=1:s2

        n1=nodes(m,1);
        n2=nodes(m,2);
```

```
        r1=TotTemp(n1,2);
        r2=TotTemp(n2,2);
        c1=TotTemp(n1,t+2);
        c2=TotTemp(n2,t+2);

        Me(m,t)=pi*H*he*(c1*(2/3*r1+1/3*r2)+c2*(1/3*r1+2/3*r2));
    end

    %MeTot is total amount of drug at a time step from number
    of elements.
    %So total drug released at a time step.
    %and then calculated at different timesteps.
    MeTot(t,1)=sum(Me(:,t));
end
```

3.5 Two-Dimensional Axisymmetric Elements

On the similar lines of derivation of total drug released with one-dimensional axisymmtric modeling, the same can be calculated for two-dimensional axisymmetric model. For each element, the approximate drug concentration is given by

$$c(t) = \sum_{a=1}^{n} N_a(r) c_a(t) \tag{3.9}$$

where, $c_a(t)$ and $N_a(\xi, \eta)$ are the concentration and shape function at node a. r is the radial coordinate, z is the coordinate in Cartesian z axis for the two-dimensional axisymmetric problem. For axisymmetric two-dimensional rectangular elements $n =$

4. $M^e(t)$ given by (3.3) can be written as

$$M^e(t) = \int_{\Omega^e} c(rd\theta)drdz = 2\pi \int_{\Omega^e} cr(drdz) \tag{3.10}$$

The coordinate of node a is (r, z).

After changing the integration domain to master element with the coordinates η and ξ, the above equation becomes

$$M^e(t) = \frac{\pi A_{\Omega^e}}{2} \int_{-1}^{1} c(\xi, \eta)\ r(\xi, \eta)\ d\xi d\eta \tag{3.11}$$

$$M^e(t) = \frac{\pi A_{\Omega^e}}{2} \int_{-1}^{1} \left[\sum_{a=1}^{4} c_a N_a(\xi, \eta)\right] \left[\sum_{a=1}^{4} r_a N_a(\xi, \eta)\right] d\xi d\eta \tag{3.12}$$

With A_{Ω^e} being the area of the element. Thus above can be written with dummy variable P_a as

$$M^e(t) = \frac{\pi A_{\Omega^e}}{2} \sum_{a=1}^{4} c_a P_a \tag{3.13}$$

$$P_a = \left[\sum_{a=1}^{4} r_a N_a(\xi, \eta)\right] \tag{3.14}$$

For isoparametric formulation,

$$r = \frac{1}{2}r1 - \frac{1}{2}r1\xi + \frac{1}{2}r2 + \frac{1}{2}r2\xi \tag{3.15}$$

Since, for rectangular element $r1 = r3$ and $r2 = r4$, also the height of the element is

constant throughout,

$$p_1 = \frac{2}{3}r1 + \frac{1}{3}r2 \tag{3.16}$$

$$p_2 = \frac{1}{3}r1 + \frac{2}{3}r2 \tag{3.17}$$

$$p_3 = \frac{1}{3}r1 + \frac{2}{3}r2 \tag{3.18}$$

$$p_4 = \frac{2}{3}r1 + \frac{1}{3}r2 \tag{3.19}$$

Thus equation (3.14) becomes as given below. This is the cumulative released into element e

$$M^e(t) = \pi\frac{A_e}{2}\left[\left(\frac{2}{3}c1 + \frac{1}{3}c2 + \frac{1}{3}c3 + \frac{2}{3}c4\right)r1 + \left(\frac{1}{3}c1 + \frac{2}{3}c2 + \frac{2}{3}c3 + \frac{1}{3}c4\right)r2\right] \tag{3.20}$$

Summing over the number of elements would give the total amount of drug released in the given volume of the solution.

3.5.1 MATLAB Program for Two-dimensional Axisymmetric Model

Thus the MATLAB code to calculate total amount of drug released with two-dimensional axisymmetric modeling is given by:

```
clear all;
clc;

nodeNum = 1;
H = 0.0125;
he = 0.0125;
```

```
ntNodes= load('Exp2_PBS0.dat');
S1=size(ntNodes);
s2 = ntNodes(:,1);
TotLines = S1(:,1);
TotColumn = S1(1,2);
TotNodes = max(s2);

for i=1:TotLines
    if (ntNodes(i,1) == nodeNum)
        tempNode(nodeNum,1) = ntNodes(i,1);

    for j=2:TotColumn
            tempNode(nodeNum,j) = ntNodes(i,j);
    end
    nodeNum = nodeNum+1;

    end
end

ntFinal= load('exp12PbsCords.dat');

for L=2:TotColumn
    for k=1:TotNodes
        ntFinal(k,L+1) = tempNode(k,L);
    end
end
```

```
allEle = load('exp12dPbsEle.dat');
e1 = size(allEle);
e2 = e1(:,1);

for a=1:e2
    for b=1:4
        nodes(a,b)=allEle(a,b+1);
    end
end

for t=1:3
    for m =1:e2
       n1=nodes(m,1);
       n2=nodes(m,2);
       n3=nodes(m,3);
       n4=nodes(m,4);
       r1=ntFinal(n1,2);
       r2=ntFinal(n2,2);
       c1=ntFinal(n1,t+2);
       c2=ntFinal(n2,t+2);
       c3=ntFinal(n3,t+2);
       c4=ntFinal(n4,t+2);

Me(m,t)=pi*0.5*H*he*{(r1*(2/3*c1+1/3*c2+1/3*c3+2/3*c4) +
r2*(1/3*c1+2/3*c2+2/3*c3+1/3*c4))};

    end
```

```
    MeTot(t,1)=sum(Me(:,t));

end
```

3.6 Modeling of Drug Release as an Axisymmetric One-Dimensional Problem

3.6.1 Model Geometry

As discussed above, the problem was modeled in two stages. For the initial phase of burst release/dissolution, only the PBS was considered. The geometry to model the PBS consist of only the line which is equal to outer boundary of the disk to the end tip of the PBS container. The next stage was modeled for diffusion dominant phase in which both the disk and the PBS were considered. The geometry of the total system is given by figure 3.4.

3.6.2 Material

The density and specific heat of PBS are considered as unit value. The diffusion coefficient in PBS was assumed to be equal to that of in water. Hence the diffusion coefficient was considered as 2.3 x 10^{-5} cm^2/sec. The diffusion coefficient in the Cristobalite was determined by matching experimental value of the total amount released in the PBS after given time interval of 24 hrs and 7 days. The density and specific heat values were considered to be unit [19].

3.6.3 Boundary Conditions and Load

The stack of loosely bound drug layers over each other gets washed out in dissolution phase. Concentration of these drug layers was assumed equal to the density of the drug which is equal to 1.7 g/cm^3 [18]. It was given as sink temperature in the

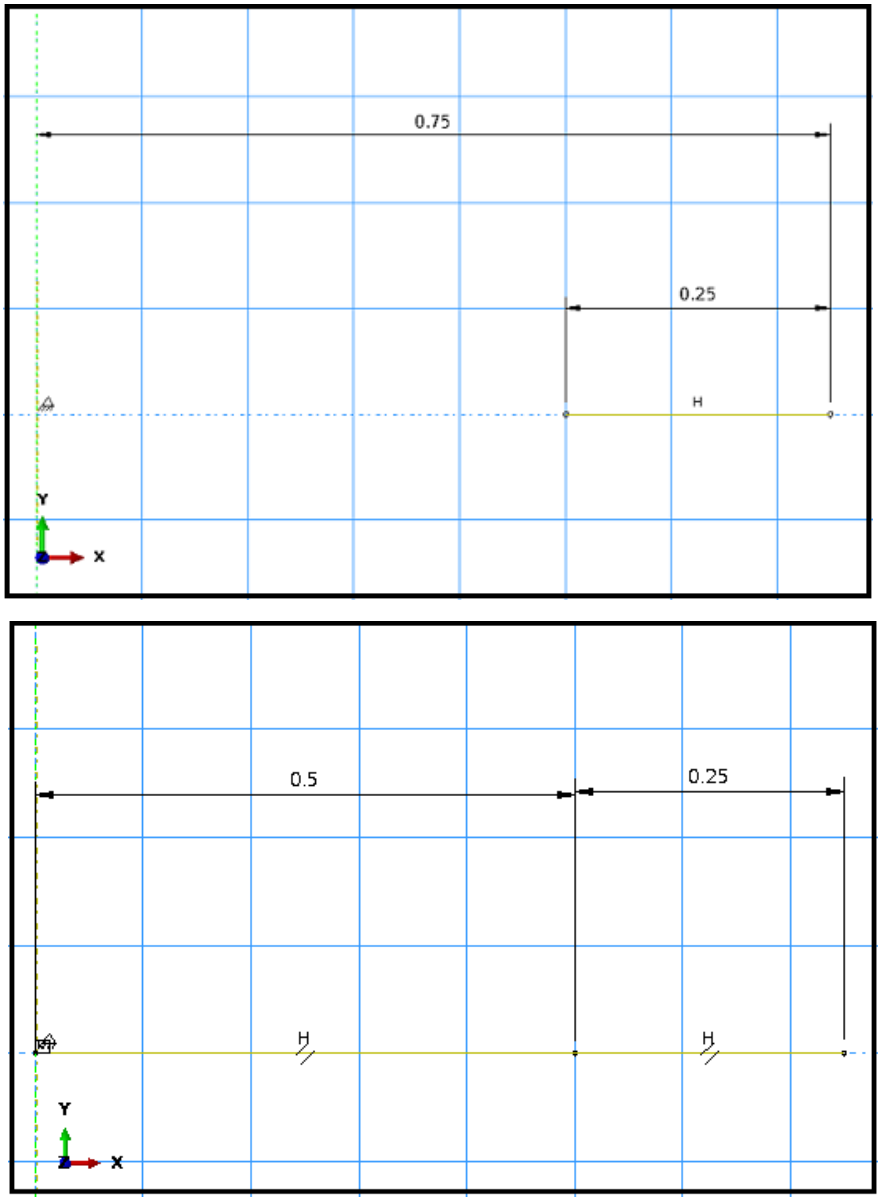

Figure 3.4: 1-D Geometry of the PBS and disk and PBS for burst release and diffusion phase respectively.

concentrated film condition type of interaction module. The initial concentration in the PBS solution was assumed to be zero before the drug release started. Eventually the concentration of drug molecules in the PBS increase at the end of the burst release phase. The mass transfer coefficient was determined by matching experimental value of amount of drug released in the PBS at the end of burst release phase which was of 1 Hour. For the diffusion dominant phase output of initial burst release phase was used

to define the initial conditions of the complete system. The disk was given the initial concentration as the amount of drug loaded on the disk per unit volume (mg/cm^3). This is shown in figure 3.5

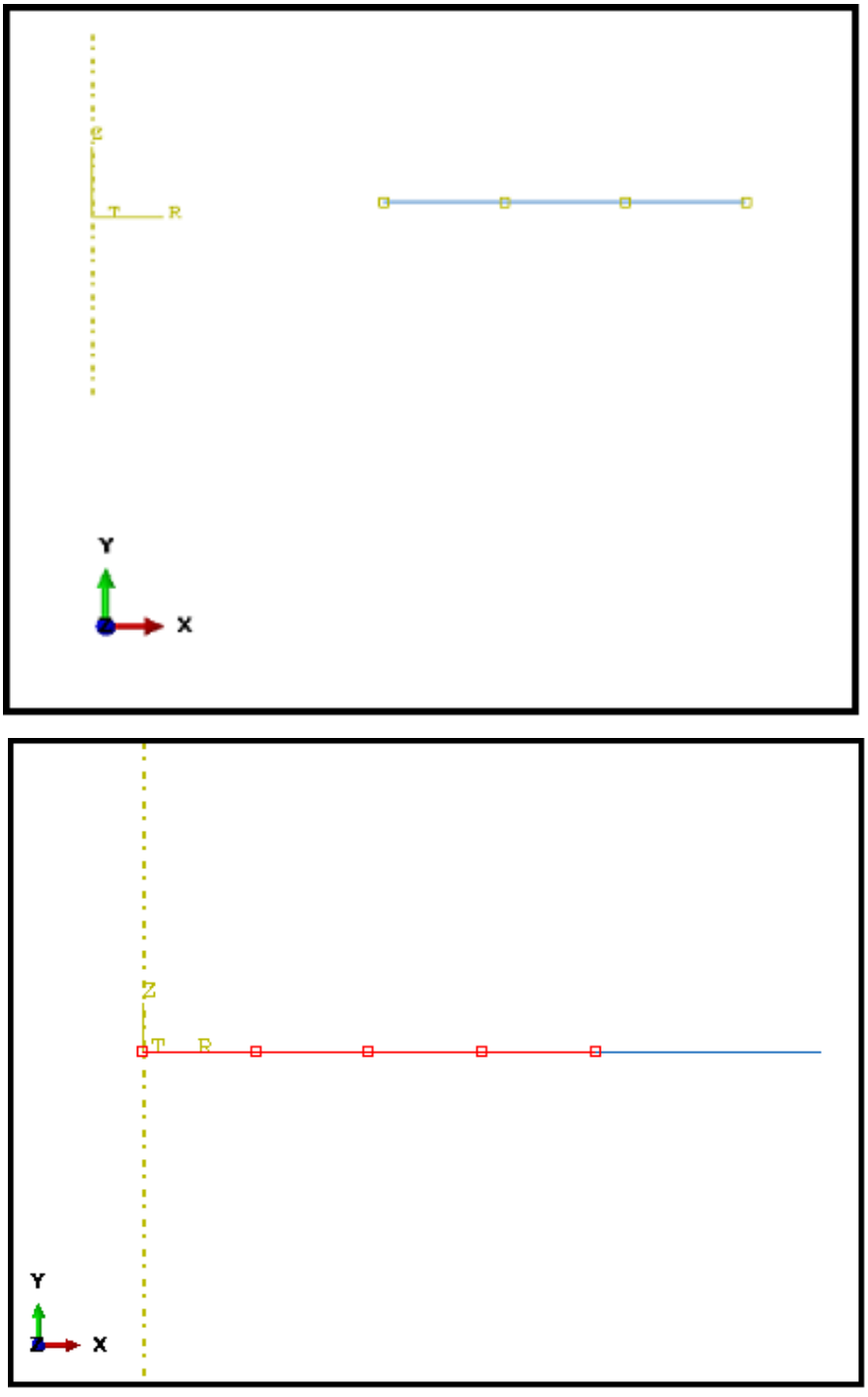

Figure 3.5: Initial and boundary conditions for 1-D model.

3.6.4 Element Type and Meshing

For the present model, the DCCAX2 element type was used which is 2-node axisymmetric linear line type forced convection/diffusion element. Total number of 500 elements created for PBS model and 1500 elements for the whole drug delivery system with the mesh size of 0.0005 cm [17].

3.6.5 Output

The concentration of each node of each element was requested through field output and then operated by `MATLAB` code with equation (3.8) to calculate total concentration of drug released in the PBS after total release time of 24 hrs and 7 days. The same procedure was repeated for each type of porosity of the samples.

3.7 Modeling of Drug Release as an Axisymmetric Two-Dimensional Problem

3.7.1 Model Geometry

As described in the section above similar model was built using two-dimensional axisymmetry. In this model, the drug release was assumed to happen in both radial and axial direction along z-axis. The model geometries are given in figure 3.6.

3.7.2 Material

The same values of density and specific heat were used to build a 2-D model. The diffusion coefficient remains constant in PBS solution. The mass transfer coefficient for the burst release phase and diffusion coefficient for the burst release phase were determined using the same procedure explained in the above section for different porosities samples.

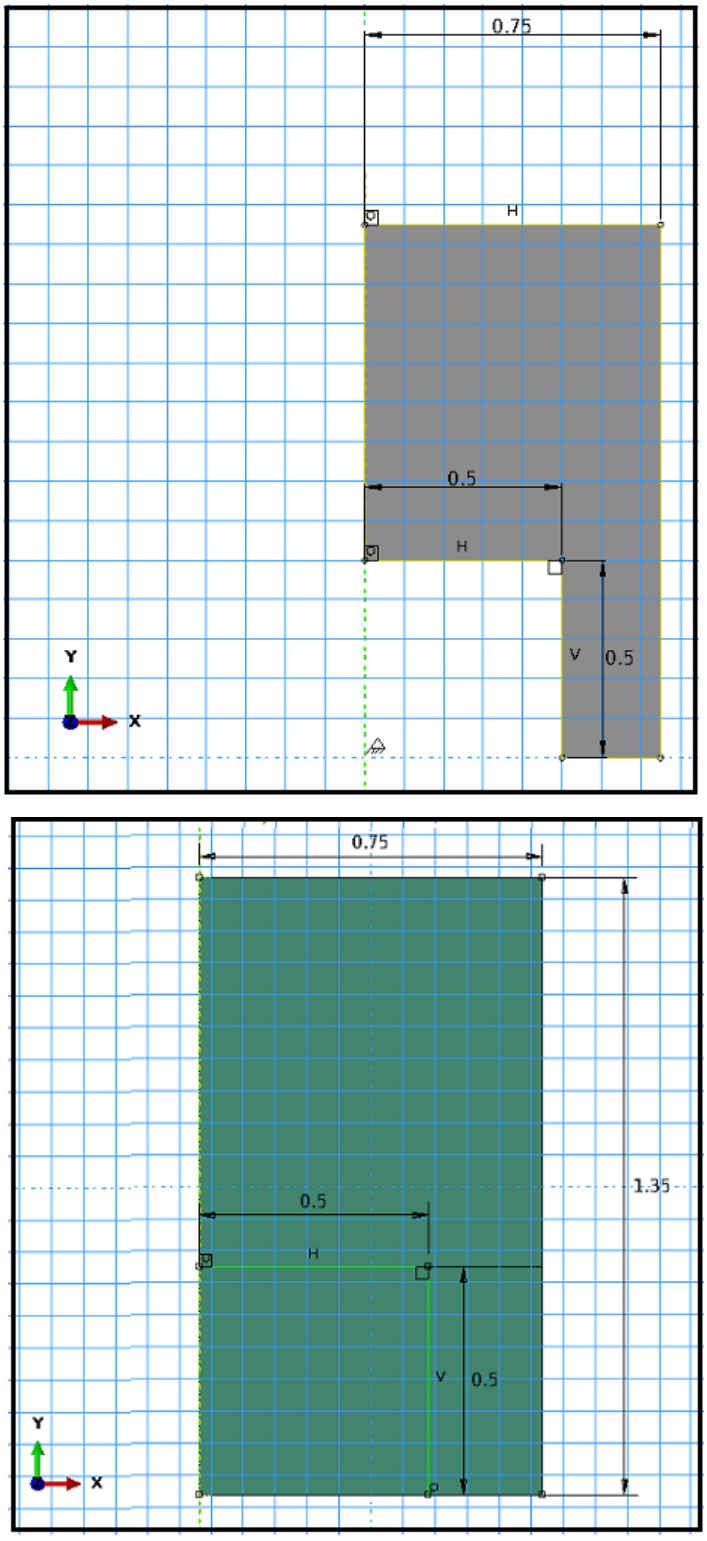

Figure 3.6: 2-D Geometry of the PBS and disk and PBS for burst release and diffusion phase respectively.

3.7.3 Boundary Conditions and Load

The same boundary conditions as one-dimensional model were applied in two-dimensional modeling. This is shown in figure 3.7.

3.7.4 Element Type and Meshing

For two-dimensional axisymmetric model, DCCAX4 element type was used which is 4-node forced convection/diffusion element. The element size used was 0.0125cm. 4880 element for PBS model and 6480 elements for the entire system were created and shown in figure 3.8 [17].

3.7.5 Output

The concentration of each node of each element was requested through field output and then operated by `MATLAB` code with equation (3.20) to calculate total concentration of drug released in the PBS after total release time of 24 hrs and 7 days. The same procedure was repeated for each type of porosity of the samples.

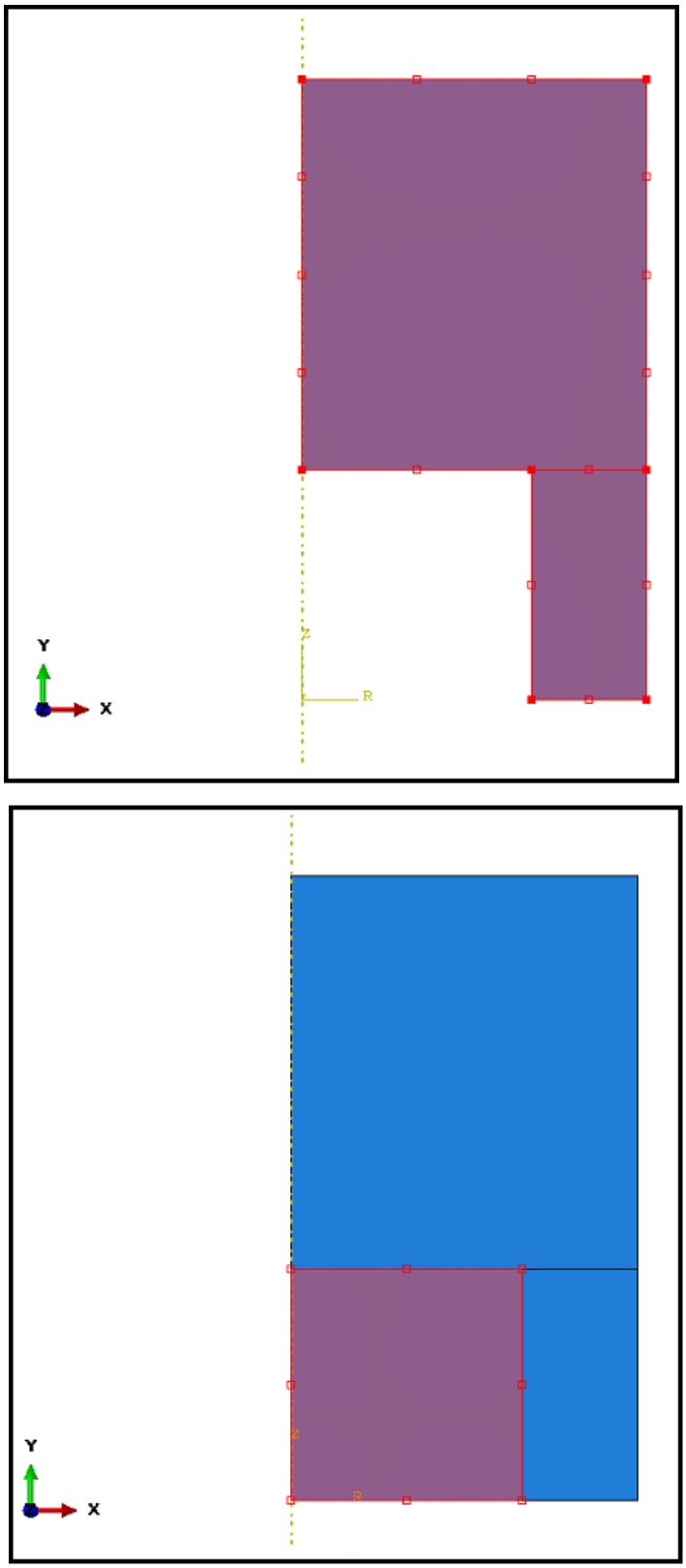

Figure 3.7: Initial and boundary conditions for 2-D model.

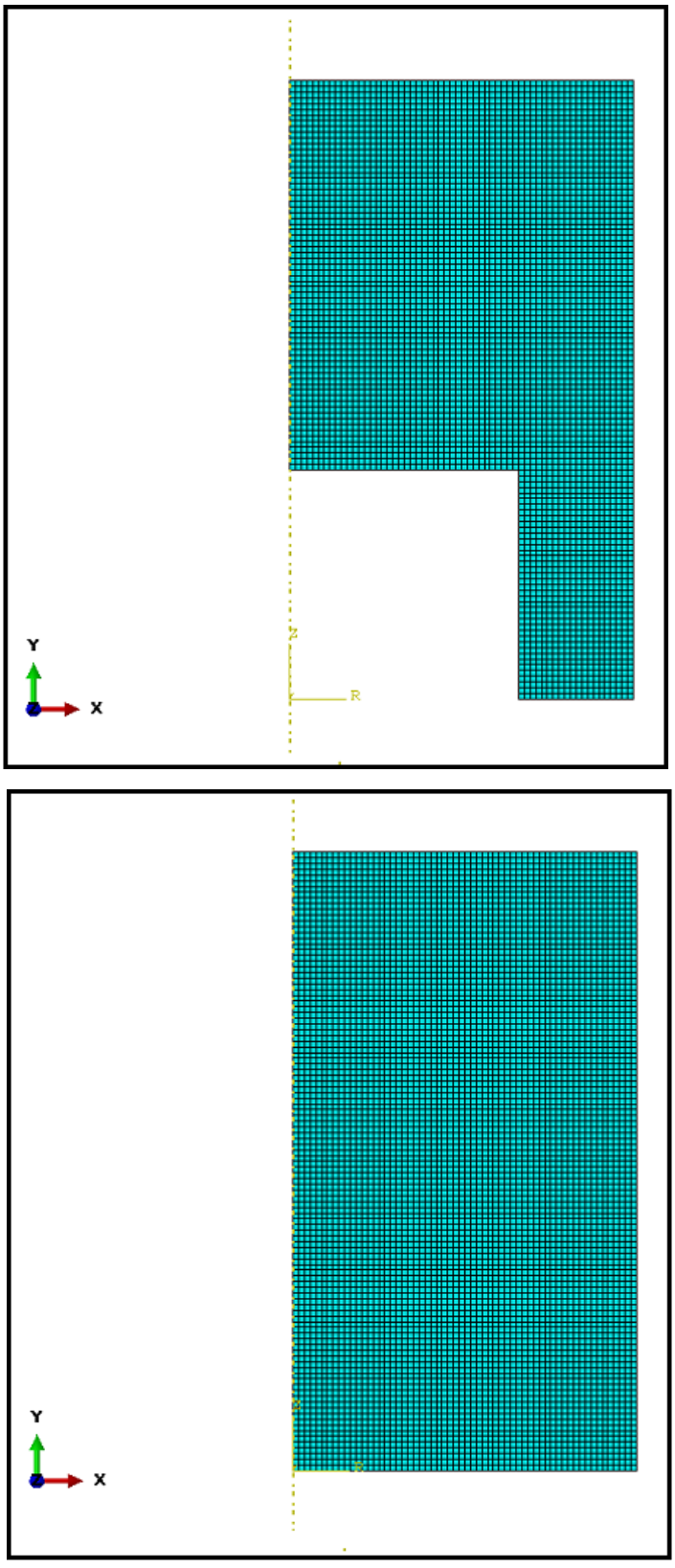

Figure 3.8: Meshing for 2-D model.

CHAPTER 4: RESULTS AND CONCLUSIONS

4.1 Experimental Results

Different tests were done by Micromeritics to analyze surface characteristics. These characteristics govern the drug adsorption and release from matrix material. After running the HPLC test, the unknown concentrations were found out using the calibration curves. The effects of surface properties on drug loading and drug release are discussed in the following section.

4.1.1 Drug Loading

The two different experimental data sets were analyzed. In the first set, disks were immersed for 4 hrs in the vancomycin drug solution and for the second set, the disks were immersed for 24 hrs. The total amount of drug that got adsorbed on the disks was calculated using the HPLC test results. For the experiment with 4 hrs immersion, the average amount of drug adsorbed on Cris 50 was 4.73 mg on total volume of disk. Similarly, for disks Cris 15 and disks Cris 0, the average amount of drug adsorbed was 4.90 mg and 4.90 mg respectively.

For the 2nd set of experiment with 24 hrs of immersion, it was found that, average amounts of drug adsorbed on the disks were 6.25 mg, 6.51 mg and 6.86 mg for the disk types Cris 50, Cris 15 and Cris 0 respectively. Therefore it was observed that as the immersion time increased, the average amount of drug adsorbed on the disks was higher. There was increase of almost 25%-30% increase in drug loading amount of disks due to increased immersion time.

the amount of drug loaded on the disk depends on the total surface area available for

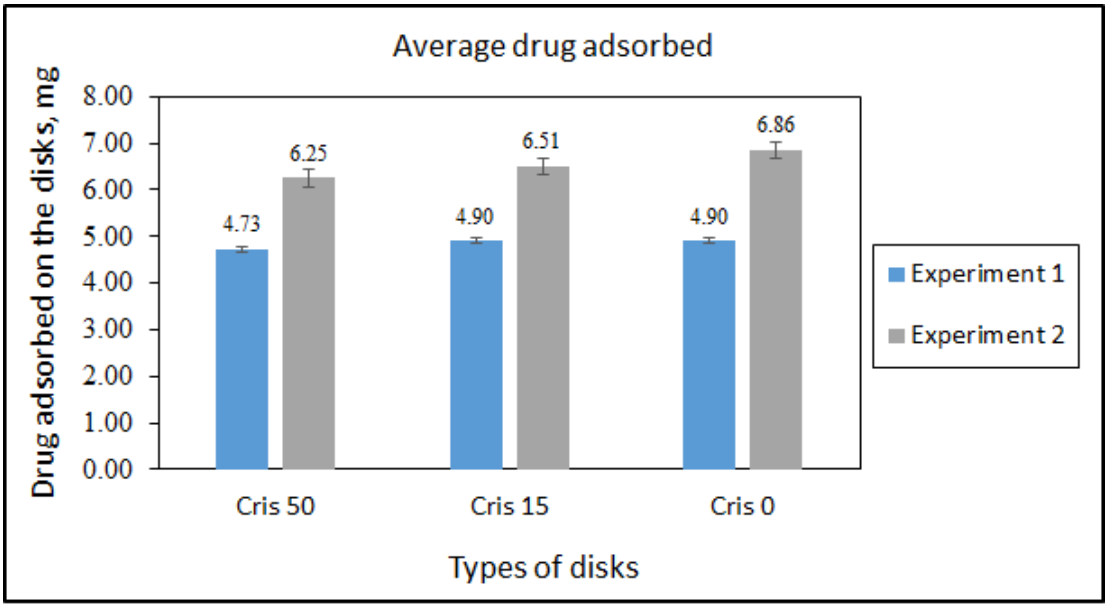

Figure 4.1: Drug adsorbed on the disks.

drug adsorption. From the porosimetry analysis it was found that the total surface area was comparable for disks Cris 50, Cris 15 and Cris 0. Comparable drug binding was in conjunction with the almost same surface areas of Cris 50, Cris 15 and Cris 0.

4.1.2 Drug Release

For the 1st experimental data set with immersion time of 4 hrs, the 3 replicas of each type of disk were considered for drug release. The samples from drug released solution were taken at different time points and tested with HPLC. After each time point, cumulative drug released in total volume was calculated for all the types of disks. Same procedure was repeated for experiment 2 with immersion time of 24 hrs. The graphs were plotted for cumulative release from each replica of the every disk types against total time of drug release from the disks in the solution. Figures 4.2 4.3 and 4.4 give cumulative release from each type of disk for every replica. The drug release for each replica of the different sample types was analyzed. There was no significant difference in the drug release from each replica and confirmed by student t-test and statistical analysis. Also the average cumulative release from Cris 50, Cris

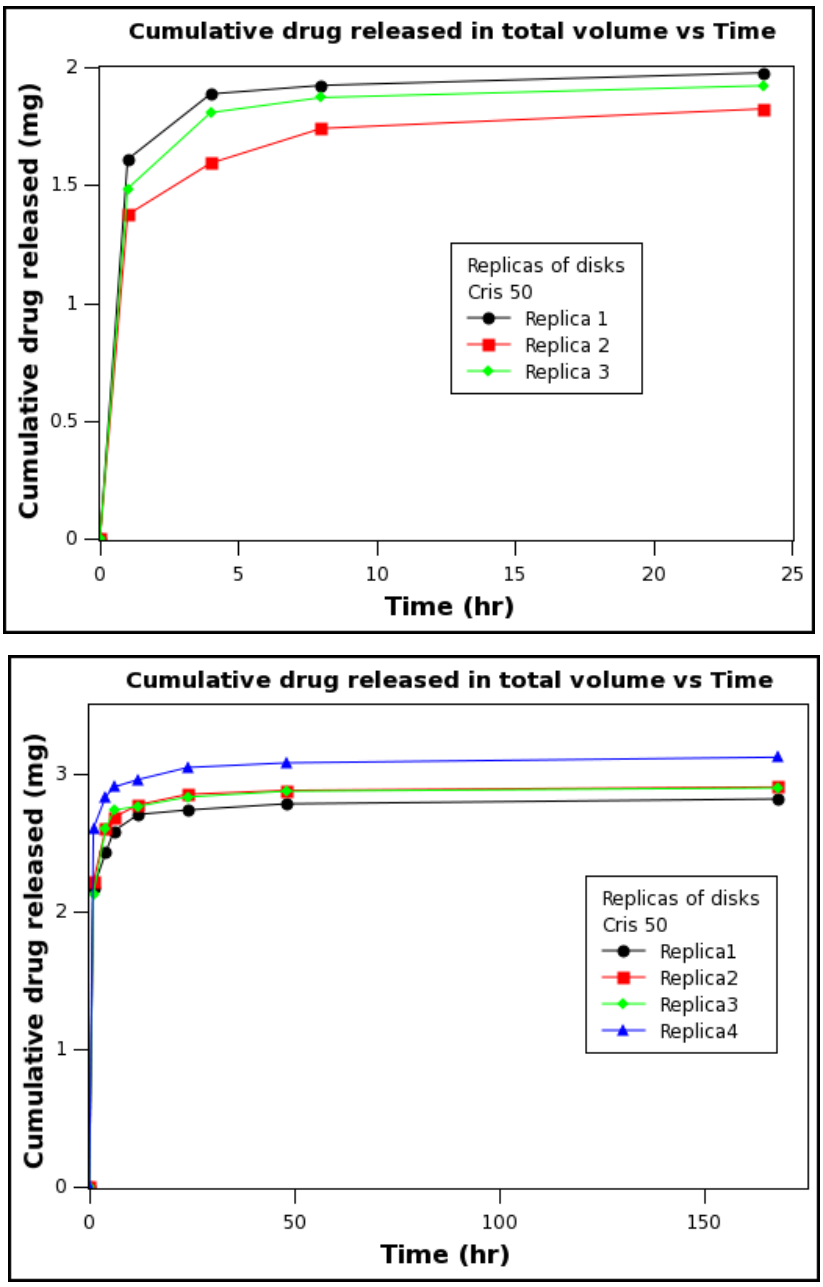

Figure 4.2: Cumulative drug release for Cris 50 samples from experiments 1 and 2 respectively.

15 and Cris 0 was plotted against total time to compare the release kinetics with the change in porosities and pore size distribution. Figures 4.5 show the release profiles for disks. For experiment with immersion time 4 hrs, less drug amount was bound on the disks compared to total amount of drug bound when immersion period was 24 hrs.

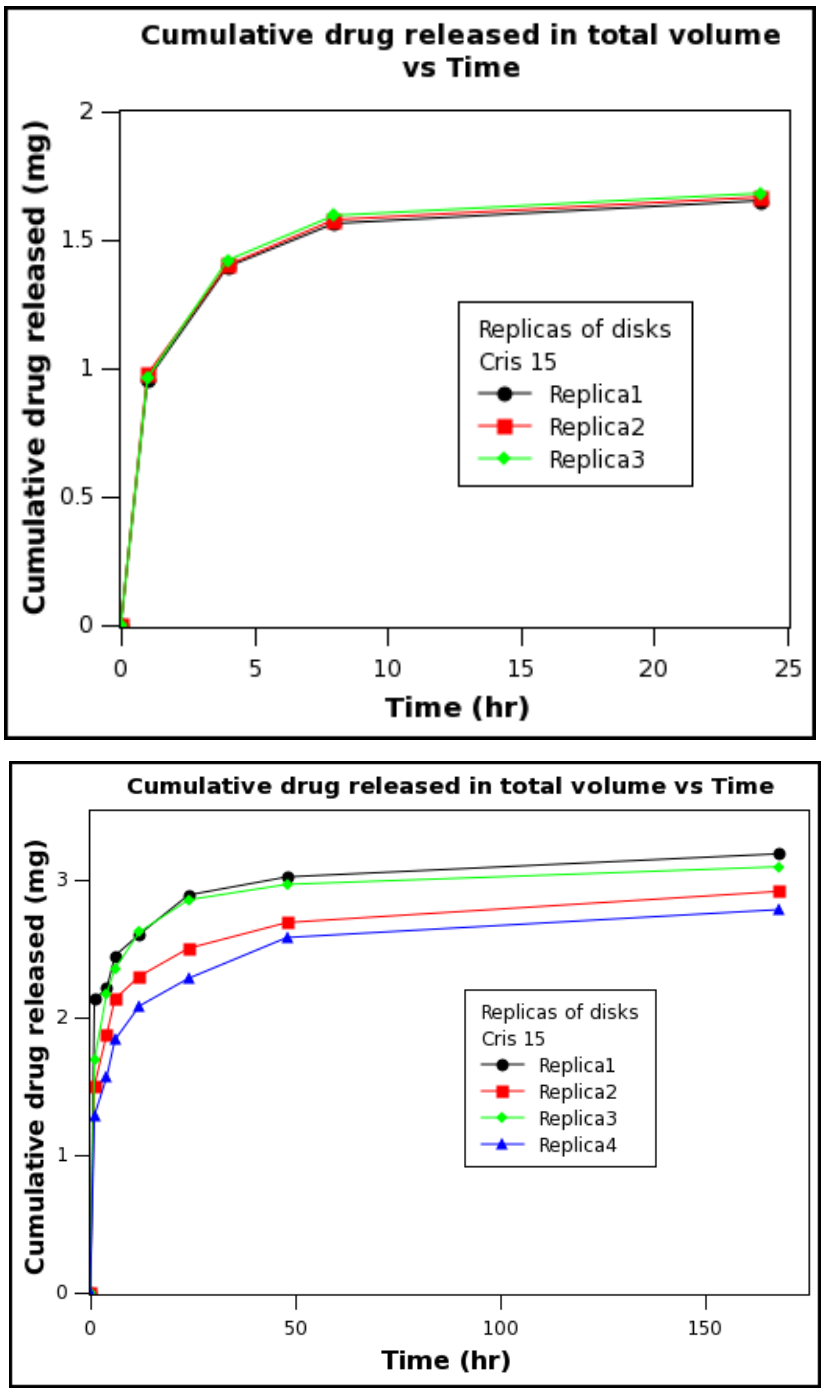

Figure 4.3: Cumulative drug release for Cris 15 samples from experiments 1 and 2 respectively.

Thus time duration of release was significantly increased with increase in immersion time. For the 1st set of experiment with time 4 hrs, it was observed that drug was released up-to 24 hrs and after that the drug amount was undetectable. However in

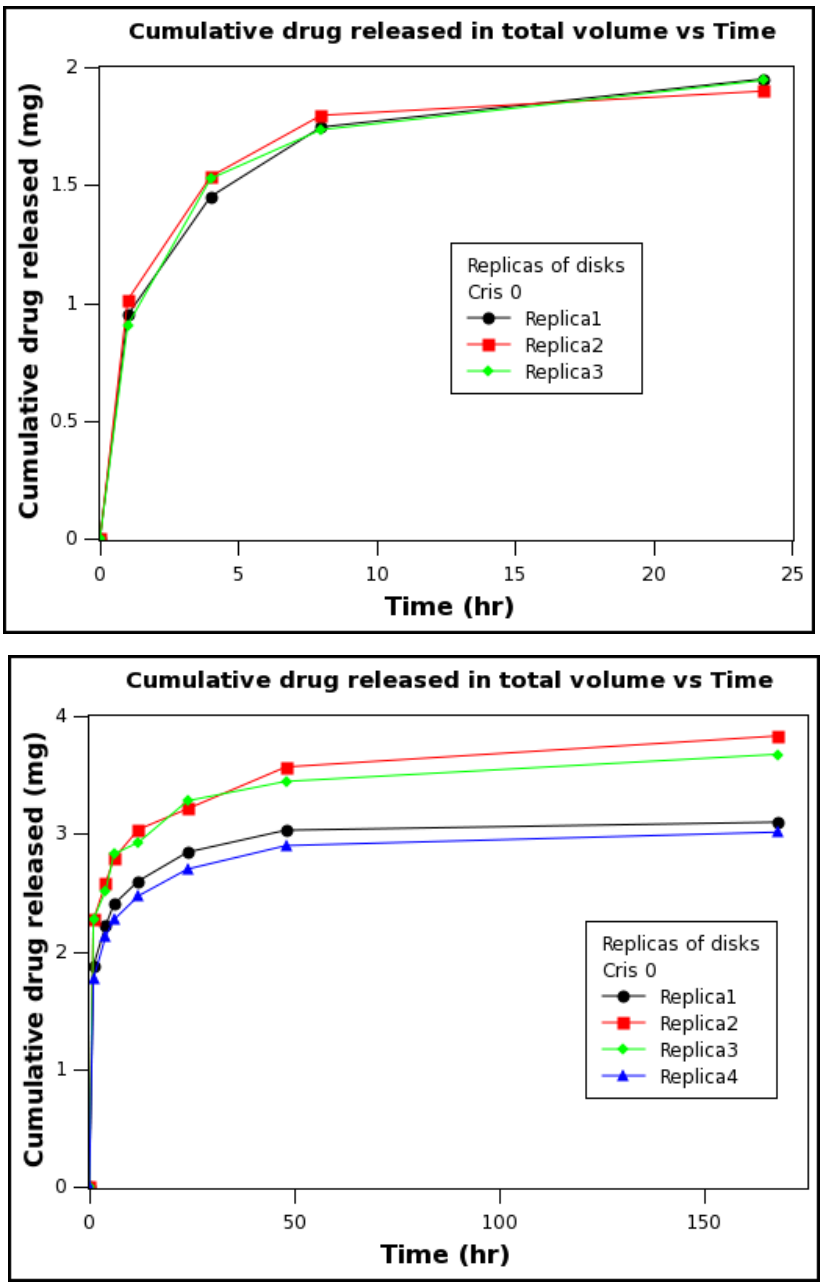

Figure 4.4: Cumulative drug release for Cris 0 samples from experiments 1 and 2 respectively.

the experiment 2 with immersion time 24 hrs, the release took place for about 7 days after which the traces of drug remained undetected. The amount of drug released in 1st experiment was almost the double of that of released in experiment 2. For Cris 50 disks, significantly higher amount of drug was released in the burst release phase

compared to Cris 15 and Cris 0. Since Cris 50 samples have the high percentage of micro-pores, higher amount of drug released in the PBS compared to Cris 15 and Cris 0. In conjunction with the differences in porosities and percent of pore volume contributed by the micropores, the rate of release of drug in burst release phase was increased in the order Cris15 < Cris0 < Cris50 for both the experiments. This phase is a result of dissolution of drug from surface of the disks into PBS.

The rate of release was significantly decreased after initial burst release phase. Such slow release rate was maintained for the rest of release duration. This phase is called sustained release phase. Sustained release phase occurs due to diffusion of drug molecules through porous Cristobalite disks. The rate of diffusion depends on the porous structure of the disks which is determined by diffusion coefficient. For Cris 50, Cris 15 and Cris 0 comparable amount of drug released was observed after the sustained release stage. The plot in figures 4.5 gives the average cumulative release profiles for each type of the disk. Also, total percentage of drug released was calculated and plotted against time. This plot gives amount of drug released as a percentage of total drug adsorbed in given time interval. From the plot below, it can be observed that in both the experiments, the total percentage of drug released for each type was comparable in accordance with total amount of drug adsorbed. Though the percentage amount of total drug released is significantly closer, the actual amount of drug released was different. From the graph below 4.6, almost the same percent of drug was released in different time intervals in two experiments. For the disks with 24 hrs immersion time, it can be hypothesized that drug molecules got to diffuse more in the matrix material with the longer loading time. However the drug molecules didn't get enough scope to diffuse deeply inside the pores of matrix material with shorter loading time of 4 hrs. If the therapeutic effect of the drug considered then the drug released amount in the sustained release phase is significantly important. This plot is given by figures 4.6. With the increase in immersion time, the percentage of cumulative release

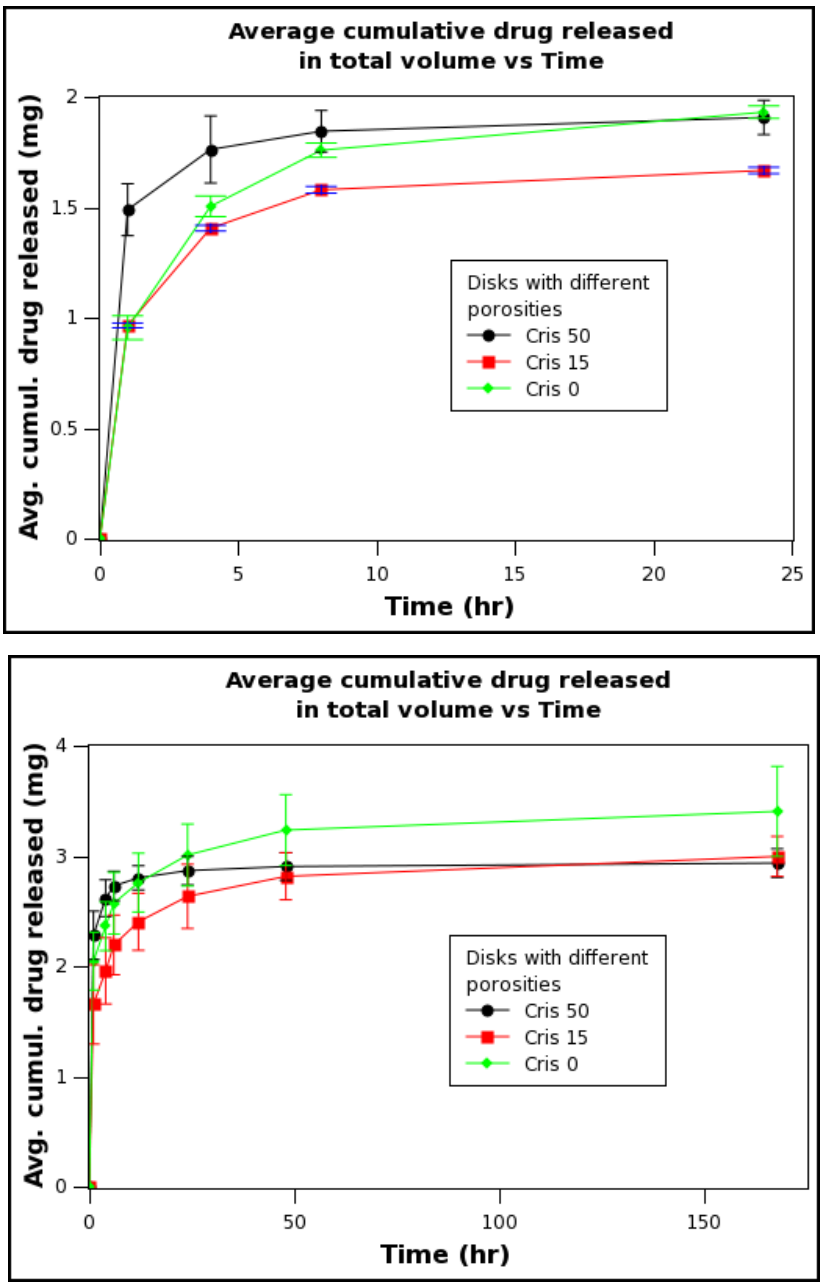

Figure 4.5: Average of cumulative release for Cris 50, Cris 15 and Cris 0 from experiments 1 and 2.

was increase significantly.

4.2 Computational Simulation Results

The finite elements results used in combination with 1st experimental data to determine mass transfer coefficient for the burst release/dissolution phase and diffusion

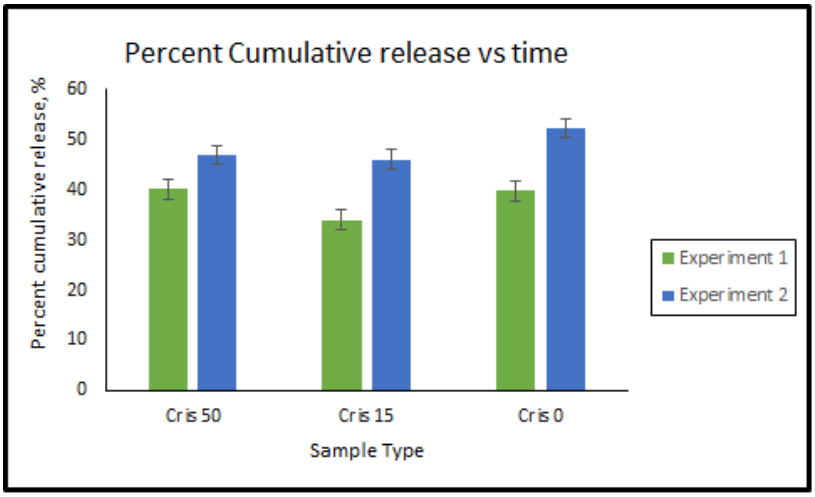

Figure 4.6: Percent cumulative release for Cris 50, Cris 15 and Cris 0 from experiment 1 and 2 respectively.

coefficient for the diffusion dominant phase. The obtained coefficients were validated to calculate total amount of drug released and the results were matched with experiment 2 results where immersion time was 24 hrs.

The difference in one dimensional and two dimensional models was the assumption of release of drug in the axial z-direction. In one dimension axisymmetric model, it was assumed that the release occurs in radial direction only. However in two-dimesional axisymmetric model, drug release in both axial and radial directions was calculated. Though two-dimensional model took longer computational time than that of one-dimensional, the values of coefficients determined by this model were more accurate than that of one-dimensional model.

The contour plots were plotted separately for burst release phase and sustained release phase for Cris 50, Cris 15 and Cris 0. Also the comparison of release profiles obtained from both computational modeling and experiments for Cris 50, Cris 15 and Cris 0.

4.2.1 One-dimension Axisymmetric Model

The contour plots for both burst release phase and sustained release phase were plotted and using the nodal concentration values, total amount of drug release was

calculated. The obtained results matched with 1st experimental data sets and mass transfer coefficient and diffusion coefficient were determined. The following table 4.1 gives the averaged values for these coefficient for each porosity type. The figures be-

Table 4.1: Coefficients determined from one-dimensional axisymmetric model for experiments 1 and 2.

Sample Types	Experiment 1		Experiment 2	
	K_c (cm/sec)	D (cm^2/sec)	K_c (cm/sec)	D (cm^2/sec)
Cris 50	5 x 10^{-7}	5 x 10^{-10}	7 x 10^{-7}	5.2 x 10^{-10}
Cris 15	4 x 10^{-7}	4 x 10^{-10}	5.6 x 10^{-7}	4 x 10^{-10}
Cris 0	4.7 x 10^{-7}	4.6 x 10^{-10}	6.5 x 10^{-7}	4.7 x 10^{-10}

low 4.7 and 4.8 show the contour plots for one-dimensional axisymmetric model in dissolution and diffusion processes respectively for Cris 50, Cris 15 and Cris 0. For one-dimensional axisymmtric model, obtained mass transfer and diffusion coefficients for 1st experimental data, were used to calculate total drug release in experiment 2 with immersion time 24 hrs, and matched the finite element results with experimental results. The release profile was plotted to compare the results. It was found that the obtained results were in good agreement with experimental data. Thus the coefficients were validated for one-dimensional axisymmetric model. Figures 4.9 give the comparison of release profiles for both experimental and computational methods.

4.2.2 Two-dimension Axisymmetric Model

The contour plots for both burst release phase and sustained release phase were plotted and using the nodal concentration values, total amount of drug release was calculated. The obtained results matched with 1st experimental data sets and mass transfer coefficient and diffusion coefficient were determined. The following table **??** gives the averaged values for these coefficient for each porosity type. The figures below 4.7fig:2ddisph and 4.11 show the contour plots for two-dimensional axisymmetric model in dissolution and diffusion processes respectively for Cris 50, Cris 15 and

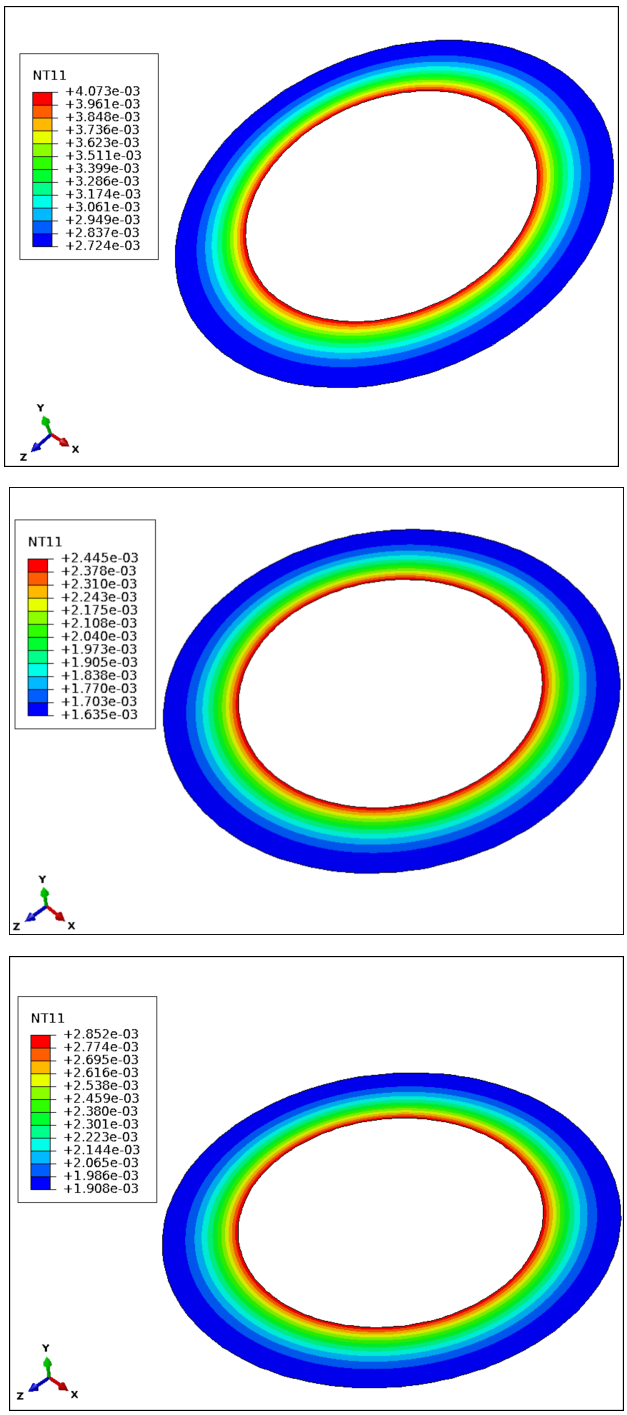

Figure 4.7: Contour plots for one-dimensional model of step 1-dissolution phase for Cris 50, Cris 15 and Cris 0 respectively.

Cris 0. For two-dimensional axisymmtric model, obtained mass transfer and diffusion coefficients for 1st experimental data, were used to calculate total drug release

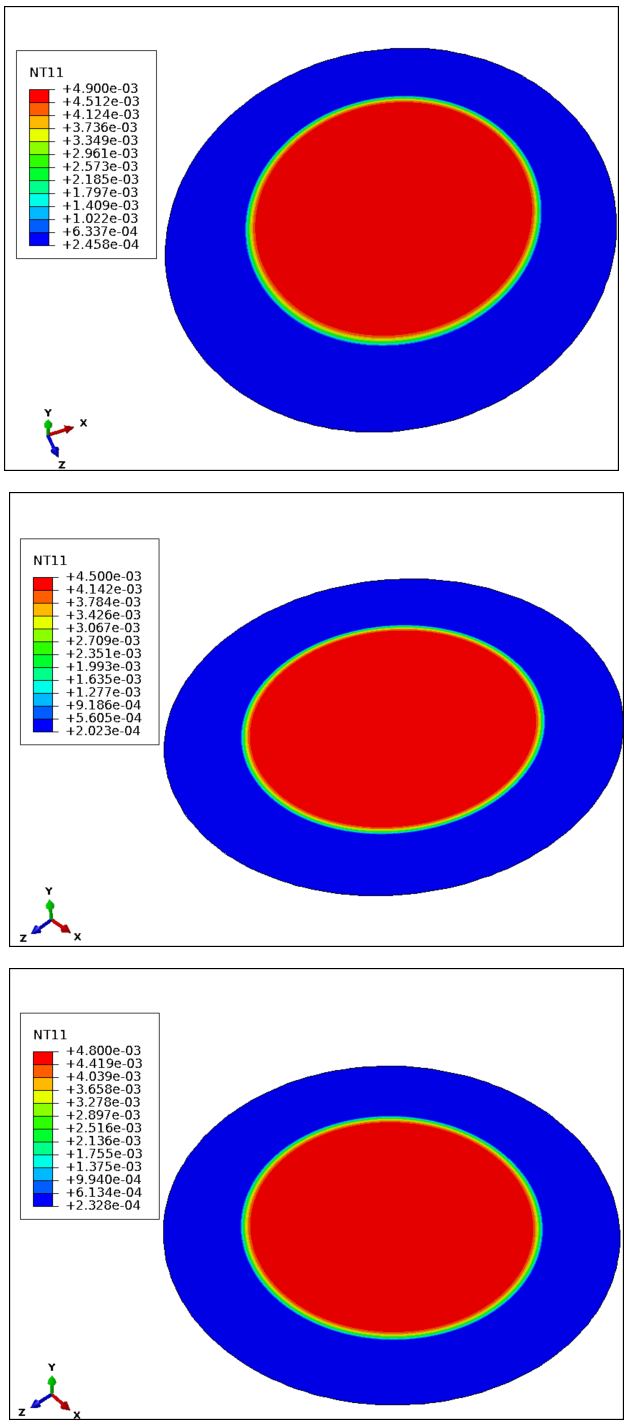

Figure 4.8: Contour plots for one-dimensional model of step 2-diffusion phase for Cris 50, Cris 15 and Cris 0 respectively.

in experiment 2 with immersion time 24 hrs, and matched the finite element results with experimental results. The release profile was plotted to compare the results. It

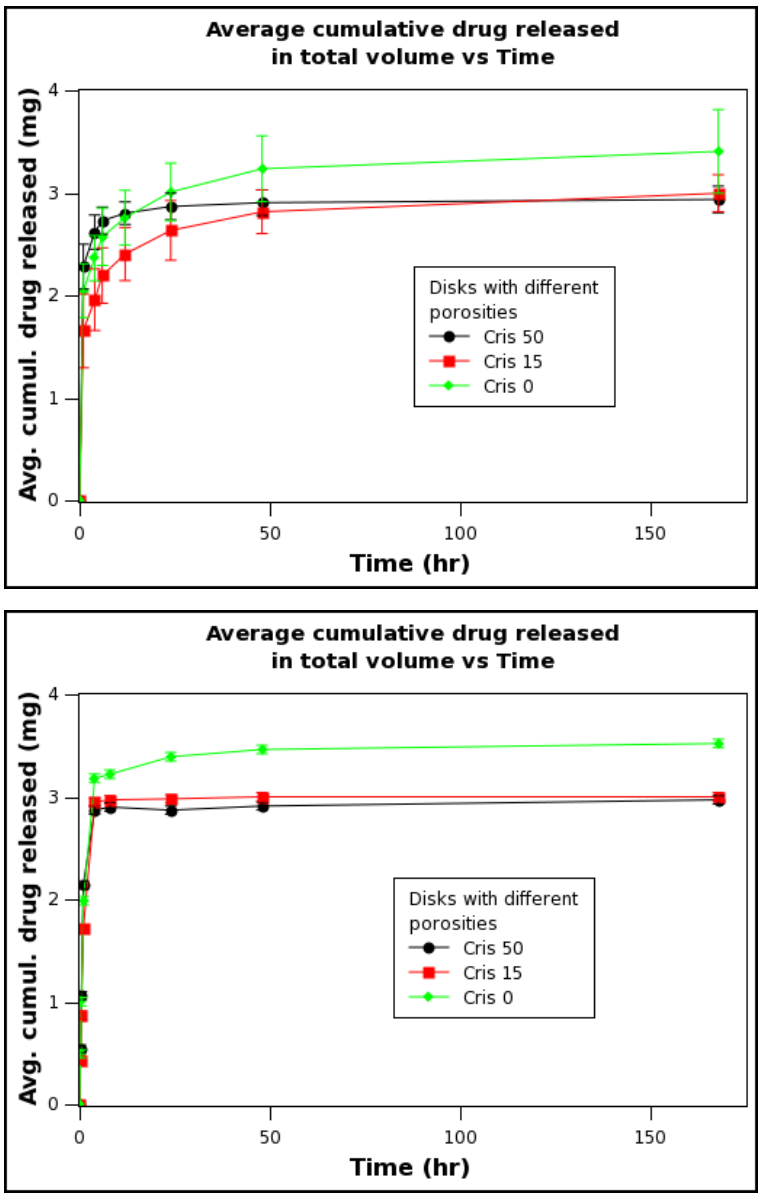

Figure 4.9: Average cumulative release for one-dimensional model in experiment 2 for experimental and computational model.

was found that the obtained results were in good agreement with experimental data. Thus the coefficients were validated for two-dimensional axisymmetric model. Figures 4.12 give the comparison of release profiles for both experimental and computational methods. The above tables **??** and 4.2 give the values of mass transfer coefficient and diffusion coefficient for different porosities samples. It can be observed that, significantly different mass transfer coefficients were obtained for experiment 1 and 2.

Table 4.2: Coefficients determined from two-dimensional axisymmetric model for experiments 1 and 2.

Sample Types	Experiment 1		Experiment 2	
	K_c (cm/sec)	D (cm)	K_c (cm/sec)	D
Cris 50	1.8 x 10^{-7}	3.2 x 10^{-10}	2.19 x 10^{-7}	3.3 x 10^{-10}
Cris 15	0.95 x 10^{-7}	1.2 x 10^{-10}	1.65 x 10^{-7}	1.2 x 10^{-10}
Cris 0	0.98 x 10^{-7}	2.7 x 10^{-10}	2.08 x 10^{-7}	2.7 x 10^{-10}

Mass transfer coefficient deals with the drug release from the outer surface of the matrix material into the surrounding aqueous solution whereas diffusion coefficient determines rate f diffusion of drug molecule out of porous material and then into the aqueous solution.

In the experiment 2 when the initial loading time (24 hrs) was longer than that of in the Experiment 1, it caused more drug to accumulate on the surface of the disks. Thus mass transfer coefficients determined were higher greater than those obtained in experiment 1 with immersion time 4 hrs.

On the other hand, when drug molecules diffuse through the porous structure of matrix material, the process of desorption of drug molecules from the porous material is very slow compared to that of the dissolution phase. When the drug molecules are well inside the pores of the matrix material, the rate of drug molecules coming out of the pores depend on the distribution of the pores inside the material. The values of diffusion coefficients obtained for Cris 50, Cris 15 and Cris 0 were comparable to each other. Thus the amount of drug released in sustained release phase was also comparable. Therefore the total amount of drug released in sustained release phase was in conjunction with obtained diffusion coefficients values. Since there were no changes made in the geometry or the surface properties or the porosities of the samples for experiment 1 and experiment 2, the diffusion coefficient was expected to remain constant throughout the experiments despite of change in the loading time duration.

Different values of diffusion coefficients for one-dimensional and two-dimensional ax-

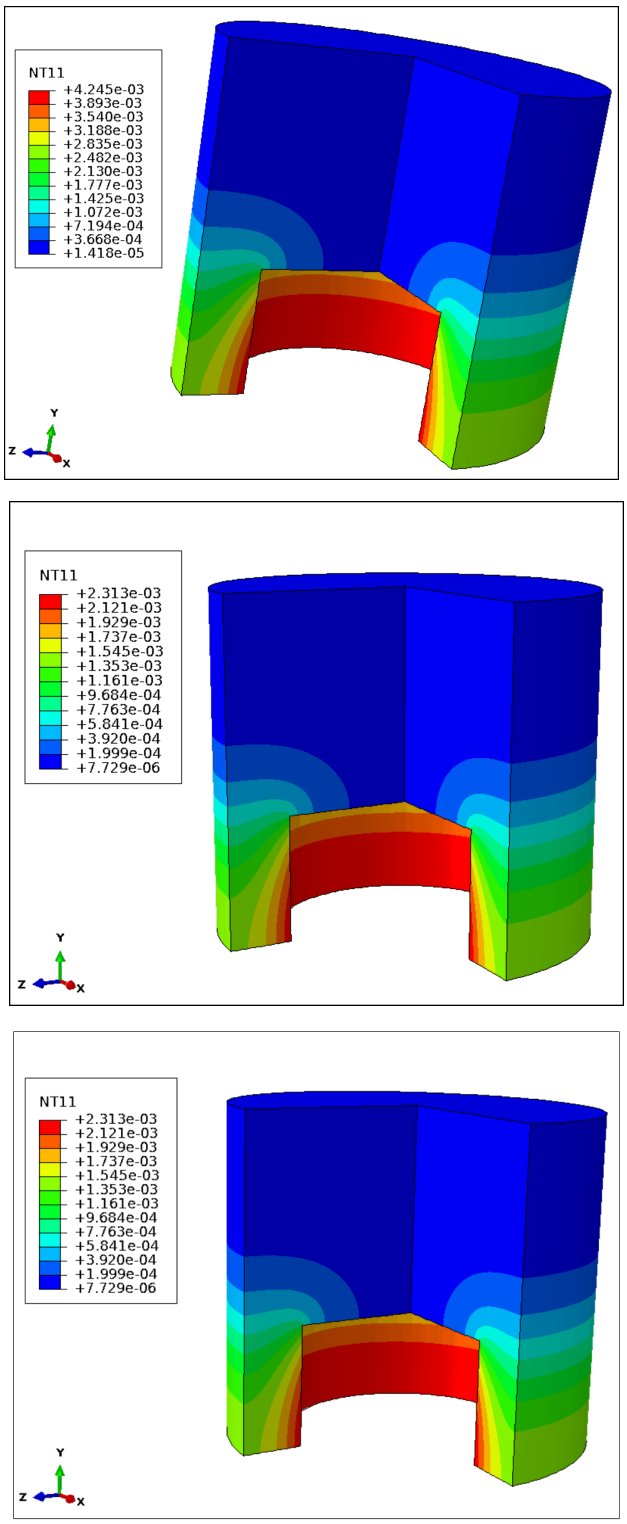

Figure 4.10: Contour plots for two-dimensional model of step 1-dissolution phase for Cris 50, Cris 15 and Cris 0 respectively.

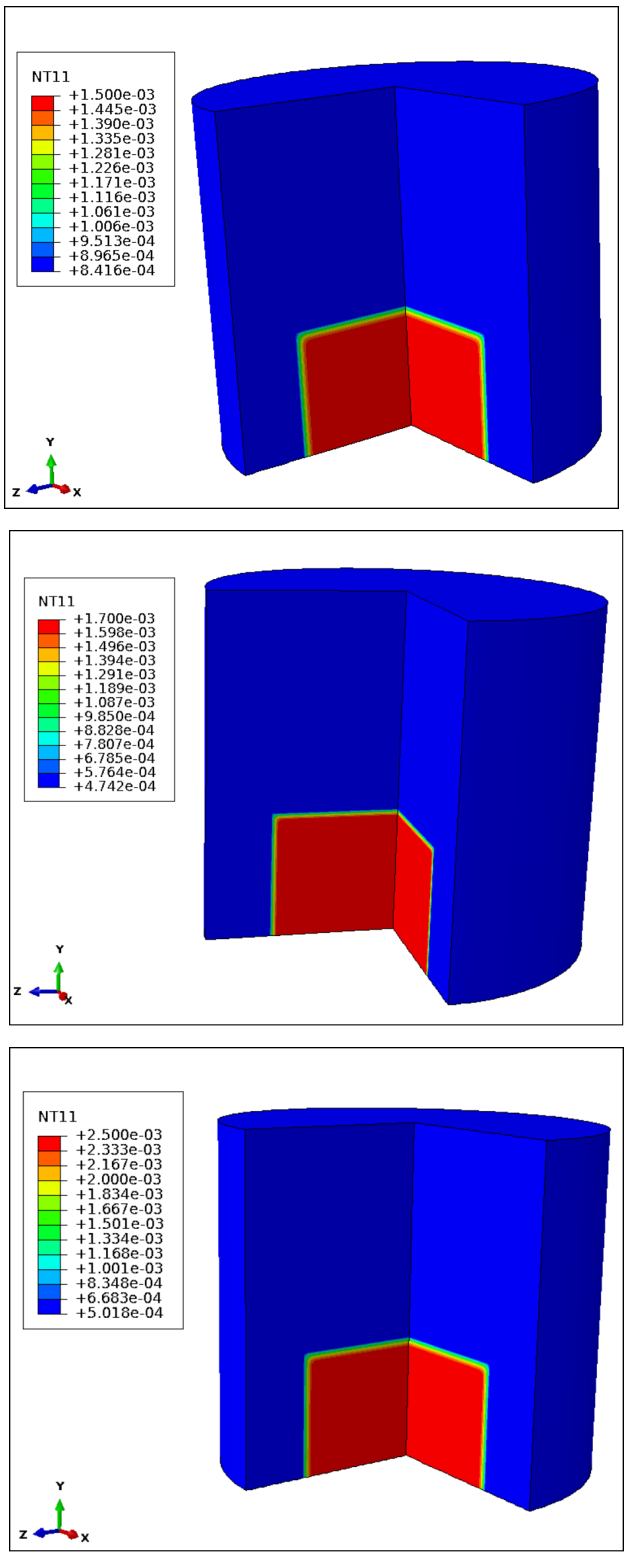

Figure 4.11: Contour plots for two-dimensional model of step 2-diffusion phase for Cris 50, Cris 15 and Cris 0 respectively.

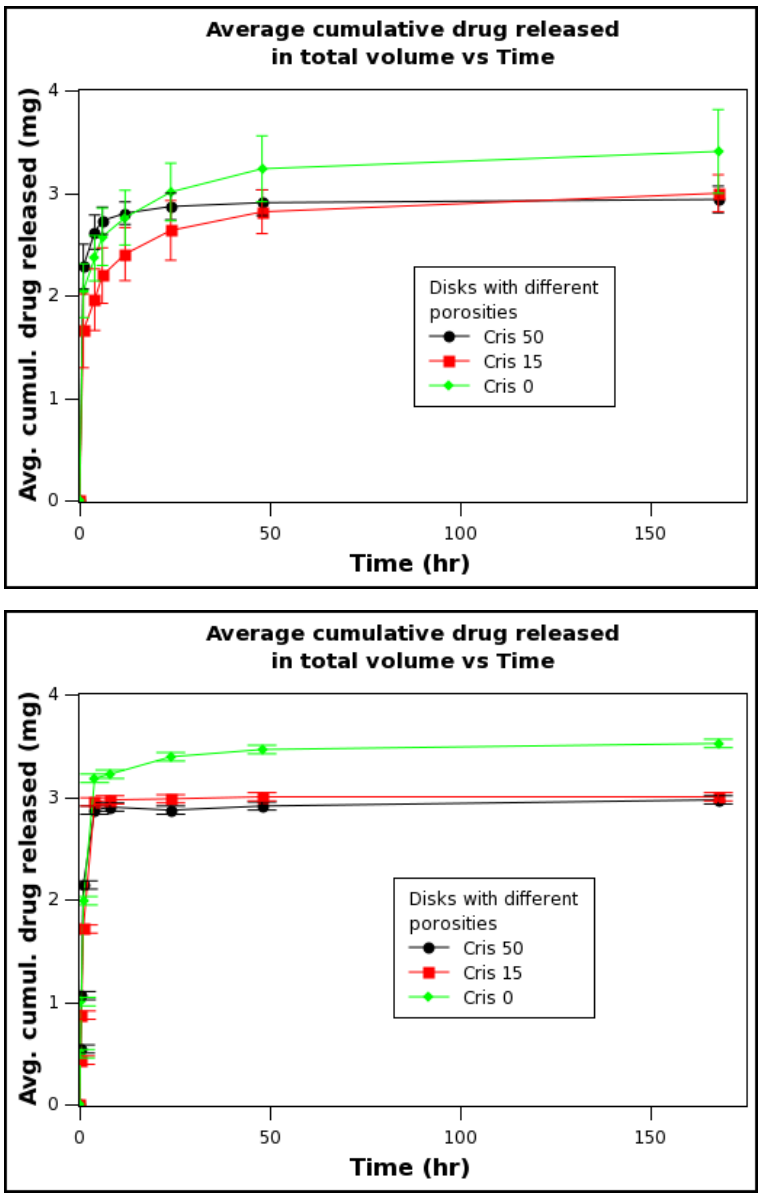

Figure 4.12: Average cumulative release for one-dimensional model in experiments 2 for experimental and computational model.

isymmetric models can be explained in accordance with assumption made while solving the problem that for one-dimensional problem the release is only in radial direction whereas for two-dimensional model the release was considered in both axial and radial direction.

4.3 Discussion

The mathematical model developed was successfully applied to analyze diffusion controlled drug release from cylindrical shaped ceramic disks. Y. Zhou and X. Y. Wu also used finite element methods to calculate total drug release for simple geometries with different assumptions. They developed computational model for both one dimensional and two dimensional models for perfect sink conditions and for well stirred medium [3]. Thus with the present study, computational model for different assumptions was built and successfully implemented to determine the coefficients which determine the rate of diffusion through ceramic matrix. The obtained values of diffusion coefficients were in good agreement with the values found in literatures [3]. With such finite element techniques, more complex geometries and structure of drug carrier devices can be handled. Thus drug delivery systems can be improved efficiently.

With the help of release profiles obtained for three different porosities, the release rate can be controlled by changing the physical properties of drug carrier device. Desired release profiles can be obtained by analyzing the physical characteristics of drug carrier devices and altering them according to the requirements. The different composition of drug carrier device results into different outcomes for release profiles [14].

The present study can be utilized as a base to study and develop more complex geometry for drug carrier devices. By changing the compositions of the material used in the present study, the changes in release profile, time of release and amount of released can be analyzed and modified as per the requirements.

4.4 Conclusions

From the porosimetry analysis it was inferred that Cris 50 showed significantly higher porosity than Cris 15 and cris 0. Moreover, Cris 50 has higher percentage of micropores than Cris 15 and Cris0. All the samples have the comparable surface areas.

The amount of drug adsorbed on disks depends on the immersion time period to load drug on disks. Thus by varying the time of loading, the amount of adsorbed drug can be varied. This would help in deciding the dosage of the drug to the patient depending on the severity of the disease. The burst phase/dissolution phase was stated to be one hour since the amount of drug released per unit time was the highest in the 1st hour. As the time passed, the release rate decreased significantly leading to the sustained release of drug for prolonged time.

The higher percentage of drug released from Cris50 in the burst stage is consistent with the significantly higher porosity (72%) contributed by the micro size pores. The high contribution of the nanopores to the total surface area of Cris0 and Cris 15 have resulted in a lower rate of drug release during the diffusion dependent sustained release stage.

Low values of diffusion coefficients indicates that diffusion of drug through porous ceramic matrix is very slow compared to the initial burst release/dissolution process. This also proves that the maximum amount of drug released is in the burst phase. The mass transfer coefficient value depends on how much drug is adsorbed on the surface and readily available when immersed in the aqueous solution. Diffusion coefficient value remains constant despite of the drug loading time as it depends on the travel of drug molecule through the porous structure of the material. The presence nanopores and channels interconnecting these pores decide the diffusion coefficient. the values obtained for diffusion coefficients for Cris 50, Cris 15 and Cris 0 are comparable which lead to comparable amount of drug release in sustained release phase. The values obtained for the mass transfer coefficients and diffusion coefficients are validated with the second set of experiment and thus computational model was validated.

4.5 Future Work

The future work of this study may involve analysis of burst release phase separately by producing the zero porosity structured matrix material which will allow only the initial burst release of the drug off its surface. Contrary, to determine the diffusion coefficient separately, wide range of porosity can be considered and maximum samples analyzed to study release rate in sustained release phase. The porous structure of the matrix material can be well captured by improvising the computational model with considering more variables. The release rate of the drug through carrier can be varied by changing the geometries, material or the porous structure of the carrier device and analyze the effects changing the variables.

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