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ABSTRACT

THEORETICAL PREDICTION OF DRUG RELEASE IN GI TRACT FROM SPHERICAL DOSAGE FORMS

**by
Naga Lakshmi Ramana Susarla**

The significance of controlled release drug delivery systems (CRDDS) lies in their ability to deliver the drug at a steady rate thus reducing the dosage interval and providing a prolonged pharmacodynamic effect. But despite the steadily increasing practical importance of these devices, little is known regarding their underlying drug release mechanisms. Mathematical modeling of these drug delivery systems could help us understand the underlying mass transport mechanisms involved in the control of drug release. Mathematical modeling also plays an important role in providing us with valuable information such as the amount of drug released during a certain period of time and when the next dosage needs to be administered. Thus, potentially reducing the number of in-vitro and in-vivo experiments which in some cases are infeasible. There is a large spectrum of published mathematical models for predicting drug release from CRDDS in vitro following conventional approaches. These models describe drug release from various types of controlled delivery devices for perfect sink conditions. However in a real system (human body) a sink condition may not be applicable. For a CRDDS along with the physiochemical properties (solubility, diffusion, particle size, crystal form etc.) the physiological factors such as gastrointestinal tract (GI) pH, stomach emptying, (GI) motility, presence of food, elimination kinetics etc., also affect the rate of drug release. As the drug delivery system is expected to stay in the human body for a longer period of time when compared to an immediate release dosage form the process of drug release

occurs in conjunction with the absorption (for oral delivery systems) and elimination kinetics. Earlier work by Ouruemchi et.al.[71] include prediction of the plasma drug concentration for an oral diffusion controlled drug delivery system. Amidon et.al.[68] developed several models for predicting the amount of drug absorbed within through the intestine walls for immediate release dosage forms. However none of these models study the effect of absorption rate on the rate of drug release for an oral controlled drug delivery system.

In this work mathematical models are developed for prediction of drug release from both diffusion controlled and dissolution controlled drug delivery systems taking into account the affect of absorption rate. Spherical geometry of the particles is considered. The model is developed by assuming that the drug is release into a finite volume and is thereby absorbed through the intestine wall following first order kinetics. A closed form solution is obtained for the prediction of fraction of drug released for a diffusion controlled drug delivery system. The results are compared with both experimental data (taken from literature) as well as existing models in the literature. Whereas for a dissolution-diffusion controlled drug delivery system non linear dissolution kinetics are taken into consideration and the problem is solved by both numerical and analytical techniques. In addition two simple models are also presented for dissolution controlled drug delivery devices.

**THEORETICAL PREDICTION OF DRUG RELEASE IN GI TRACT FROM
SPHERICAL MATRIX SYSTEMS**

by
Naga Lakshmi Ramana Susarla

**A Dissertation
Submitted to the Faculty of
New Jersey Institute of Technology
in Partial Fulfillment of the Requirements for the Degree of
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**Otto H. York Department of
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To my parents

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LIST OF SYMBOLS

C	Concentration of dissolved drug within the polymer matrix (g/cm^3)
S	Concentration of solid drug within the polymer matrix (g/cm^3)
C_s	Solubility of the drug within the polymer matrix (g/cm^3)
C_l	Concentration of released drug within the compartment (g/cm^3)
k	Dissolution rate constant (s^{-1})
k_r	First order Absorption rate constant (s^{-1})
K	Partition coefficient
V_l	Volume of the liquid (cm^3)
V_s	Volume of the solid drug particles (cm^3)
D_{AB}	Diffusion coefficient of the drug (m^2/s)
r	Radial coordinate
θ_s	Dimensionless concentration of solid drug
θ	Dimensionless concentration of dissolved drug
$\bar{\theta}$	Dimensionless solubility
τ	Dimensionless time
ξ	Dimensionless radial coordinate
t	Time (min)
U	Fraction of drug released during initial phase of drug release
$u(\xi, s)$	Laplace transformed variable for concentration of dissolved drug
$v(s)$	Laplace transformed variable for concentration of drug within the liquid compartment.

LIST OF SYMBOLS
(continued)

\tilde{U} Laplace transformed variable for the concentration of solid drug

CHAPTER 1

INTRODUCTION

Controlled drug delivery devices or systems (CRDDS) have gained a lot of attention over the past few years. These devices help to deliver the drug at a controlled rate as opposed to the immediate release dosage forms, thus leading to a decrease in the number of dosages required and also reducing the possibility of side effects [1]. The devices can be in various sizes and shapes like spherical (nano or microparticles), cylindrical (millirods) or planar (thin films). The most common method of administration of these devices is either parenteral or via implants. The nanosized drug particles are expected to stay in the circulatory system for a long period of time without getting eliminated. Though oral route is not a common delivery option, a few studies have been done on utilizing the controlled drug delivery devices for oral drug delivery. The nanoparticle drug delivery system is either absorbed as a whole through the intestine walls or able to stay in the gastro intestinal system for a longer time thus releasing the drug in a controlled manner while protecting the drug from degradation [2].

There are various methods by which these devices are produced. The drug particle is encapsulated or dispersed within a polymer matrix. The drug-polymer system is classified as either a matrix type or a reservoir system. In the case of a matrix system the drug is commonly assumed to be uniformly distributed within the polymer matrix where the initial drug loading is either lower than the solubility of the drug inside the matrix (dissolved system) or higher than the solubility of the drug inside the polymer matrix (dispersed system)[5]. In Reservoir systems the drug is assumed to be confined within a given geometry such as an outer radius R and inner radius r [5]. The drug release

mechanisms have been identified as (i) diffusion-controlled (ii) dissolution-controlled (iii) erosion-controlled (iv) degradation-controlled or (v) swelling-controlled. In some cases two or more of these processes could be controlling the rate of drug release with each becoming the rate-controlling step at a particular time.

Despite having many advantages the knowledge about the underlying drug release mechanisms for these devices is not fully developed [3]. Mathematical modeling of the drug release process can help us to improve the understanding of the underlying mass transport and chemical processes as well as optimize the dosage form dimensions to achieve targeted desired release profiles [4]. Mathematical modeling can also help to reduce the number of in-vitro and in-vivo experiments which are not only expensive but in some cases infeasible. There is a large spectrum of mathematical models available in the literature ranging from the classical models like those developed by Higuchi [6] and Peppas [4,7] to some of the recent models [8,9].

Most of these mathematical models are developed for in-vitro conditions where sink conditions are maintained. However when it comes to a real system (human body) various factors like absorption rate of the drug, drug distribution, metabolism and elimination within the system (which intern depend on factors such as pH, temperature, blood flow rate, presence of food etc., in the gastro-intestinal (GI) tract [10]) come into play which the regular models do not take into consideration. This can result in a severe discrepancy between the in-vitro and in-vivo correlations for drug release [11]

The main objective of this work is to develop a mathematical model for prediction of drug release in the GI tract taking into account the absorption kinetics. When a CRDDS is administered orally it reaches the GI tract and releases the drug at a controlled

rate, the released drug is absorbed through the intestine wall and into the systemic circulation. After a certain period of time the drug release process and absorption of the drug occur in conjunction. Therefore absorption kinetics become important and they cannot be ignored. In this thesis an extensive review of mathematical models developed over the past decade is given (Chapter 2) followed by objectives (Chapter 3) and models developed (Chapter 4)

2. LITERATURE REVIEW

2.1 Mathematical Models for Diffusion and Diffusion-Degradation Controlled Drug Delivery Systems

Diffusion controlled drug delivery devices are very popular, the classical model describing solute release from a polymer matrix for various geometries was first developed by Crank [12]. As it will be seen from discussion to follow, most authors adopt this model to describe the process of drug release. Diffusion mechanism remains a part of drug release process even if it is not the rate controlling step. However a significant number of controlled release devices made now a days are either erosion or degradation controlled. Polymer degradation is defined as the chain scission process by which the polymer chains are cleaved into oligomers and monomers whereas erosion is defined as a process of material loss from polymer bulk [3]. Depending on the composition and geometry of the erodible device, numerous mass transport and chemical reaction phenomena affect the drug release kinetics. A few of them are (i) Water intrusion into the device (ii) drug dissolution (iii) polymer degradation (iii) creation of aqueous pores (iv) diffusion of the drug and/or polymer degradation products inside the polymer matrix (v) micro-environmental pH changes inside the polymer matrix pores by degradation products (vi) polymer swelling [3].

Charlier, A., et.al.,[13] proposed a diffusion-degradation model for the release of mifepristone an antiprogestative norsteroid drug from degradable PLGA planar matrix system. They postulated that the diffusion coefficient (D) depended on the polymer

Where k is the degradation constant and M_o , D_o are the initial polymer molecular weight and corresponding diffusion coefficient, respectively.

The amount of drug released in the assumption of steady state was taken as

$$dQ = C_o S . dh \quad (2.2)$$

Equations (2.1.1) and (2.1.2) were combined to give the final expression for the fraction of drug released as:

$$Q = S \sqrt{\frac{2C_o C_s D_o (e^{kt} - 1)}{k}} \quad (2.3)$$

Their results seemed to agree well with the experimental data and with the Higuchi equation [6] at early times.

Liggins and Burt [14] studied paclitaxel release from poly (L-lactic acid) microspheres. The main focus of their study was the effect of molecular weight of polymer on the release rate. The amount of paclitaxel released from polymers of different molecular weight was studied for a period of 14 days, as perfect sink conditions were not maintained during the in vitro experiments, the saturation of paclitaxel was observed within 3 days. It was found that 11-76 % of the drug released over the period of 14 days. Because of the incomplete release of paclitaxel the authors hypothesized that the release kinetics could be explained using a 'two compartmental model'. In this model compartment 1 was hypothesized to contain paclitaxel that could freely diffuse from the microspheres while compartment 2 contained immobilized by semi crystalline polymer matrix. To test this hypothesis the authors related the fraction of paclitaxel remaining

within the microsphere after the release studies with the polymer crystallinity and molecular weight. The studies indicated that as the mw and crystallinity increase the fraction of paclitaxel remaining increased. The authors used Baker's equations [15] given below to fit theoretical curves to the experimental data.

$$\frac{M_t}{M_o} = 6 \left(\frac{Dt}{r^2 \pi} \right)^{1/2} - \frac{3Dt}{r^2} \quad \text{for } 0 \leq M_t/M_o \leq 0.4 \quad (2.4)$$

$$\frac{M_t}{M_o} = 1 - \frac{6}{\pi^2} e^{-\left(\frac{Dt\pi^2}{r^2}\right)} - \frac{3Dt}{r^2} \quad \text{for } 0.6 \leq M_t/M_o \leq 1 \quad (2.5)$$

The authors also derived an empirical relationship between the polymer mw, crystallinity and diffusion coefficients. Though significant biodegradation of the polymer microspheres was observed after a period of 5 days the authors did not account for biodegradation in the model and only diffusion phenomena seemed to adequately account for the drug release.

Wong et al. [16] studied the in vitro sustained release of human immunoglobulin G (IgG) from PLA and PLGA biodegradable microspheres. The authors used two different models to explain the release kinetics of IgG. They used the diffusion model and the diffusion/dissolution model. For both of these models two cases of mass transfer were considered, one with finite mass transfer coefficient at the surface and one with infinite mass transfer coefficient (all the mathematical details are given below).

$$\frac{\partial C}{\partial t} = D \left(\frac{\partial^2 C}{\partial r^2} + \frac{2}{r} \frac{\partial C}{\partial r} \right) \quad (2.6)$$

The initial and boundary conditions taken are:

$$t = 0 \quad C = C_{in} \quad 0 < r < R \quad (2.7)$$

Case 1: For infinite mass transfer the boundary conditions were taken as

$$t > 0 \quad \frac{\partial C}{\partial r} = 0 \quad r = 0 \quad \text{and} \quad t > 0 \quad C = C_{\infty} \quad r = R \quad (2.8)$$

The fraction of mass of drug released to total mass was obtained as

$$\frac{M_t}{M_T} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(\frac{-n^2 \pi^2}{R^2} Dt\right) \quad (2.9)$$

Case 2: a finite mass transfer coefficient on the surface was assumed such that the concentration in the surroundings is constant. The boundary conditions were taken as

$$t > 0 \quad \frac{\partial C}{\partial r} = 0 \quad r = 0 \quad \text{and} \quad t > 0 \quad D \frac{\partial C}{\partial r} = h(C_s - C_{\infty}) \quad r = R \quad (2.10)$$

and the fraction of mass of drug released to total mass was obtained as

$$\frac{M_t}{M_T} = 1 - \sum_{n=1}^{\infty} \frac{6S^2}{\beta_n^2 (\beta_n^2 + S^2 - S)} \exp\left(\frac{-\beta_n^2}{R^2} Dt\right) \quad (2.11)$$

$$\text{Where } S = \frac{hR}{D} \quad (2.12)$$

And β_n s are the roots of the transcendental equation

$$\beta_n \cot \beta_n = 1 - S \quad (2.13)$$

Diffusion/Dissolution Model:

Case1:

$$\frac{\partial C}{\partial t} = D \left(\frac{\partial^2 C}{\partial r^2} + \frac{2}{r} \frac{\partial C}{\partial r} \right) + k(\epsilon C_{sat} - C) \quad (2.14)$$

Where C_{sat} represents the saturation concentration of the drug in the system and ϵ represents the porosity of the microspheres.

The initial condition was taken as

$$t=0 \quad C = C_{sat} \quad 0 < r < R \quad (2.15)$$

Same boundary conditions were used as Equation (2.8). After converting the Equations (2.14), (2.15) and (2.8) into dimensionless form and solving it [17] the final expression for amount of drug released was obtained as

$$\psi_t = \frac{M_t}{C_{sat} \frac{4}{3} \pi R^3} = 6 \sum_{n=1}^{\infty} \frac{(Di + n^2 \pi^2) Di \tau + n^2 \pi^2 \{1 - \exp[-(Di + n^2 \pi^2) \tau]\}}{(Di + n^2 \pi^2)^2} \quad (2.16)$$

Where Di is known as dissolution/diffusion number and is given as $Di = \frac{kR^2}{D}$

Case 2: For the case of finite mass transfer coefficient on the surface

$$\psi_t = \frac{M_t}{C_{sat} \frac{4}{3} \pi R^3} = 6S^2 \sum_{n=1}^{\infty} \frac{(Di + \beta_n^2 R^2) Di \tau - \beta_n^2 R^2 \{1 - \exp[-(Di + \beta_n^2 R^2) \tau - 1]\}}{(Di + \beta_n^2 R^2)^2 [\beta_n^2 R^2 + S(S-1)]} \quad (2.17)$$

Where the parameters S and β_n are given by Equations (2.12) and (2.13).

The experimental results were found to be in good agreement with the theoretical models presented.

Abdekhodaie [18] presented an exact solution for the diffusional release from theophylline microspheres coated with ethyl vinyl acetate copolymer into a finite external volume using the Laplace transform method. The solute was assumed to have very low solubility in the polymeric membrane and the diffusion coefficient was assumed to be independent of concentration. The diffusion of drug into the surroundings was described by Fick's second law of diffusion as:

$$\frac{\partial C}{\partial t} = \frac{D}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial C}{\partial r} \right) \quad (2.18)$$

The initial and boundary conditions were taken as:

$$C[r, 0] = C_s \quad a < r < b \quad (2.19)$$

$$C[a, t] = C_s \quad (2.20)$$

$$C[b, t] = KC_b(t) \quad (2.21)$$

Where C_s is the solubility limit of the drug K is the equilibrium distribution coefficient between polymeric membrane and external bulk concentration and C_b is the external bulk concentration at any time t . The expression for cumulative amount of solute released was obtained as:

$$\frac{M_t}{M_\infty} = 1 - \sum \frac{2\alpha\lambda_n^2}{(1 - \frac{a}{b})[\lambda_n^2 + (1 + \alpha\lambda_n^2)^2] + \alpha\lambda_n^2 - 1} \exp[-\lambda_n^2\tau] \quad 2.22$$

where α was defined as:

$$\alpha = \frac{V}{4\pi b^3 K} \quad (2.23)$$

The parameter α had significant affect on the drug release profile.

He et.al. [19] proposed a mathematical model accounting for polymer erosion and degradation. They considered a polymer matrix system where in the drug was molecularly dispersed. They assumed that the kinetics of the drug release from bioerodible polymer matrices followed a Fickian diffusion influenced by polymer degradation and that it accelerated at a certain time by polymer erosion. The polymer chain scission was described by first order auto catalyzed hydrolysis kinetics and the matrix was assumed to be fully eroded at the end of the drug release process. The authors

took into account the equations describing drug release by Fickian diffusion, developed by Baker and Lonsdale [20] and Ritger and Peppas [21] for spherical and disk matrix geometries, respectively.

$$m_d = 6\sqrt{\frac{Dt}{\pi r^2}} - 3\sqrt{\frac{Dt}{r^2}} \quad (2.24)$$

$$m_d = 4\sqrt{\frac{Dt}{\pi r^2}} - \frac{Dt}{r^2} - \frac{\pi}{3}\sqrt{\left(\frac{Dt}{\pi r^2}\right)^3} + 4\sqrt{\frac{Dt}{\pi l^2}} - \frac{2r}{l}\left[8\frac{Dt}{\pi r^2} - 2\pi\sqrt{\left(\frac{Dt}{\pi r^2}\right)^3} - \frac{2\pi}{3}\left(\frac{Dt}{\pi r^2}\right)^2\right] \quad (2.25)$$

They modified the diffusion coefficient in Equations (2.24) and (2.25) to $D_t = D_o \exp(k_s t)$ to account for the polymer degradation kinetics. Then the equations were combined with Equation (2.26) proposed by Fitzgerald and Corrigan [22] which describe the matrix erosion as a combined process of the branching and termination of polymer decomposition caused by formation of activated nuclei in the matrix.

$$m_e = \left[\frac{\exp(k_e t - k_e T_{Max})}{1 + \exp(k_e t - k_e T_{Max})} \right] \quad (2.26)$$

Where m_e is the fraction of drug released, k_e is the acceleratory coefficient describing the probability of branching from active sites during the time interval between oligomer generation and dissolution and T_{Max} is the time to maximum matrix erosion rate.

The total fraction of drug released obtained by combining Equations (2.23)-(2.26) is given by Equations (2.27) and (2.28). All the parameters needed to solve these Equations were taken from the literature.

$$\frac{M_t}{M_\infty} = 6\sqrt{\frac{D_t t}{\pi r^2}} - \frac{3D_t t}{r^2} + F_E \left[\frac{\exp(k_e t - k_e T_{Max})}{1 + \exp(k_e t - k_e T_{Max})} \right] \quad (2.27)$$

$$\frac{M_t}{M_\infty} = 4\sqrt{\frac{D_t t}{\pi r^2}} - \frac{D_t t}{r^2} - \frac{\pi}{3}\sqrt{\frac{D_t t}{\pi r^2}}^3 + 4\sqrt{\frac{D_t t}{\pi l^2}} - \frac{2r}{l} \left[8\frac{D_t t}{\pi r^2} - 2\pi\sqrt{\frac{D_t t}{\pi r^2}} - \frac{2\pi}{3}\left(\frac{D_t t}{\pi r^2}\right)^2 \right] + F_E \left[\frac{\exp(k_e t - k_e T_{Max})}{1 + \exp(k_e t - k_e T_{Max})} \right] \quad (2.28)$$

Where F_E is the factor accounting for the contribution of matrix erosion to drug released.

It indicates that a fraction of drug originally released through diffusion is now released through matrix erosion. The proposed model was able to describe triphasic drug release kinetics for bioerodible polymeric matrices which included an initial burst phase (caused by high initial drug release rate due to short diffusion pathways), an intermediate phase (an approximately zero order drug release phase resulting from drug diffusion and polymer degradation) and a second rapid drug release phase due to matrix erosion.

Raman et al. [23] developed a mathematical model to study the affect of polymer degradation and nonuniform drug distribution on the release of small molecules from degradable microspheres. The authors considered a diffusion coefficient which is dependent on polymer molecular weight.

$$\frac{\partial C}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 D(M_w) \frac{\partial C}{\partial r} \right) \quad (2.29)$$

The boundary conditions used were:

$$\left(\frac{\partial C}{\partial r} \right)_{r=0} = 0 \quad (2.30)$$

$$(C)_{r=R} = 0 \quad (2.31)$$

The initial condition used:

$$C(r)_{t=0} = f(r) \quad (2.32)$$

The model contained one fit parameter (D_0) which was used until the time dependent diffusivity [$D(M_w)$] was larger than D_0 . The authors solved Equations (2.29) - (2.32) using an adaptive Runge-Kutta methods using fifth and sixth order Runge- Kutta formulas to estimate error of integration. And since the molecular weight of the microspheres did not change for the first 4 days, the molecular weight loss was modeled as:

$$M_w = M_{w0} \quad t < t_{lag} \quad (2.33)$$

$$M_w = M_{w0} e^{k_d(t-t_{lag})} \quad t > t_{lag} \quad (2.34)$$

The release profiles generated by model were compared to the experimental data. The model was found to be a good fit to the data.

Faisant et al. [24] developed a simple mathematical model to elucidate the underlying drug release mechanisms of 5-FU (a drug used for fighting cancer) from PLGA erodible microspheres which exhibited a biphasic release profile (an initial burst phase followed by a zero order release phase). The system considered was a monolithic system (drug dispersed within the polymer matrix), where the drug was release by diffusion. The equation describing the system is given as

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x} \left(D \frac{\partial C}{\partial x} \right) + \frac{\partial}{\partial y} \left(D \frac{\partial C}{\partial y} \right) + \frac{\partial}{\partial z} \left(D \frac{\partial C}{\partial z} \right) \quad (35)$$

By making the following assumptions of constant drug diffusivity, perfect sink condition and uniform initial drug concentration smaller than the solubility of the drug within the system (monolithic solutions) the solution can be obtained [12] as:

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(-\frac{Dn^2\pi^2 t}{r^2}\right) \quad (2.36)$$

Where M_t and M_∞ denote the cumulative absolute amount of drug release at time t and at infinite time respectively. D is taken as apparent diffusivity taking into account the drug transfer through the polymer itself as well as possible drug transfer through water-filled nanopores. When equation (2.36) was fitted to the experimental drug release profile it was only able to describe the initial burst phase well but not the second zero-order release phase. A major assumption made in obtaining the above equation was that of monolithic solutions. So the authors adopted the Koizumi and Panomsuk [25] model (Equation (2.37)) to describe the drug release profile. They then combined Equation (2.37) with Equations (2.38) and (2.39) to account for the polymer degradation.

$$M_t = 4\pi R^2 \left[\sqrt{2(C_0 - C_s)C_s Dt} + \frac{4C_s Dt}{9R} \left(\frac{C_s}{2C_0 - C_s} - 3 \right) \right] \quad (2.37)$$

$$D(Mw) = D_0 + \frac{k}{Mw} \quad (2.38)$$

$$Mw(t) = 78.4 \exp(-k_{\text{deg.}} t) \quad (2.39)$$

Here $k_{\text{deg.}}$ is the pseudo-first order degradation rate constant. The mathematical model was fitted to the experimental drug release profile using C⁺⁺ program and it was found that the model was able to describe both the phases adequately. However there still were deviations between the experimental data and model. The authors concluded that these discrepancies could have occurred since not all the important physicochemical phenomena were taken into account. Though the drug release process is primarily controlled by diffusion phenomena there is a significant contribution by the polymer degradation process. During the degradation process water inhibition occurs thus

decreasing the average molecular weight of the macromolecules, leading to increased diffusion coefficients.

Siepmann et al. [26] quantitatively studied the effect of size of biodegradable microspheres on the drug release rate. They studied the release of 5-Fluorouracil from PLGA microspheres applying a diffusion-degradation model [24]. The microspheres were prepared such that the initial drug loading is much higher than the solubility. The polymer matrix was in rubbery state. The polymer degradation was observed to follow pseudo-first order kinetics and the diffusion coefficient of the drug was seen to increase monotonically with time. The authors used Equation (2.37) developed by Koizumi and Panomsuk [25] for spherical non-erodible systems and combined it with Equation (2.39) to account for polymer degradation. The mathematical model was implemented using C⁺⁺ program. The authors found that as the size of the microparticles did not significantly effect the polymer degradation kinetics. However with increase in microsphere size the amount of initial drug loading increased and so did the amount of drug released. The reason for this was attributed to the increase in internal porosity of the microsphere with the increase in initial drug loading. Upon the increase of drug depletion the apparent drug diffusivities increased thus resulting in greater drug release rates. The authors also established a correlation for drug diffusivity and initial loading:

$$D_0 = 2.4 \exp(0.21(\text{drug loading \%}(w/w))) 10^{-14} \text{ cm}^2/\text{s} \quad (2.40)$$

The model (Equations (2.37) and (2.39)) was able to predict the drug release profile for particles of various sizes and the size of the particle was found to play a very important role in achieving the desired drug release profile.

It is interesting to note that Berkland et al. [27] in their study found that as the size of microsphere increased the rate of drug release decreased. In their study the authors prepared piroxicam and rhodamine (NSAID) loaded microspheres in the size range of 1-100 μm . The drug loading were about 1-20 %. The initial rate of drug release decreased with increase in the particle size. The release profile for large diameter microspheres followed a three-phase type of a release (an initial burst, an intermediate phase and a second rapid release phase) whereas the drug release from small diameter microparticles was uniform and it reached saturation after sometime. The reason for this was attributed to the decrease in area/volume ratio with the increase in particle size. The authors concluded that the large diameter microspheres were of a better application for prolonged release of drug. The conclusions drawn by Siepmann et.al.,[26] and Berkland et.al., [27] are drastically different. A possible reason for this could be that different polymers and different drug loading % were considered by both the authors respectively. The porosity of PLGA [26] could have increase with the increase in the particle size causing a rapid diffusion process as compared to PLG [27].

Siepmann et al. [28] quantitatively studied the effect of composition of the device (type and amount of plasticizer, type of polymer) on the diffusivities of the drug and its release kinetics. They chose water-insoluble polymers and considered monolithic solutions (dissolved systems) of planar and spherical geometries for the study. They applied Equations (2.37) – (2.39) to describe the process of drug release. They used theophylline as the model drug incorporated into 6 different plasticizers. They found that the diffusivities varied for different type of plasticizers and the amount of drug released was higher when large amounts of plasticizers were used. Also there was a pronounced

effect of type of polymer (polymers of different chain length) on the drug diffusivity as well. The authors explained these phenomena using the free volume theory (FVT) of diffusion that is the plasticizing effect of a substance is based on the reduction of the attractive forces between polymer chains. Decreasing attractive forces leads to increased mobilities of the macromolecules. According to FVT, the diffusion occurs by localized activated jumps from one pre-existing cavity to another [29]. When the diffusing species is larger than a pre-existing cavity, a certain number of monomer segments must first be rearranged to allow the diffusion of the molecule. In this step the mobility of the polymer chain is the decisive factor for the mass transfer rate. High mobilities lead to high rearrangement rates and thus to high drug diffusion rates. A quantitative relationship was developed for dependence of D on the type and amount of plasticizer as follows:

$$D(\%TBC) = 0.135 \cdot \exp(0.121 \cdot \%TBC) \cdot 10^{-10} \text{ cm}^2/\text{s} \quad (2.41)$$

Siepmann et al. [30] also studied the effect of drugs on the polymeric systems. Here the drugs themselves were considered to act as plasticizers. For device optimization it is important to know the effect of plasticizer on drug mobility within the polymeric system. The quantitative understanding of this phenomenon plays a vital role in controlled release formulations. The authors considered monolithic solution systems with planar geometries. They studied the effect of three drugs (metoprolol tartrate, chlorpheniramine maleate and ibuprofen) on Eudragit RS polymeric films. It was found that ibuprofen had more impact on the thermal (glass transition temperature) and mechanical properties (elongation) of the polymer than the other two drugs, however metoprolol tartarate released much faster than the other two drugs. One possible explanation for this is given to be the electrostatic interactions between drug and

polymer. Ibuprofen being negatively charged (at pH 7.4) interacts with the positively charged quaternary ammonium ions groups of Eudragit RS thus hindering the diffusion. Equations (2.37) to (2.39) were used to describe the drug release process from the monolithic solution systems into perfect sink conditions (in-vitro). This model was also useful in predicting the effect of initial loading and optimizing the dose dimensions to get the required release profiles.

Klose et al. [31] studied the effect of porosity and particle size on the drug release kinetics. They studied the release of Lidocaine from porous PLGA loaded microspheres (7.5 μm -75 μm). In their previous paper Siepmann, et.al., [32] studied the drug release from non-porous polymer matrices. For both porous and non porous lidocaine loaded microspheres Equation (2.36) was used to describe the drug release mechanism. The following assumptions were made (i) at time $t=0$ the drug was considered to be homogeneously distributed throughout the microsphere (ii) diffusion mechanism was solely responsible for drug release out of the microsphere (iii) there is no diffusional resistance for the drug release (iv) perfect sink conditions were maintained through out the (in-vitro) experiment. For a non-porous system the autocatalytic effect seemed to play a major role, but for porous microspheres autocatalytic effect was negligible and also as the pores increased in size so did the amount of drug released. Equation (2.36) could not describe the latter system adequately. This may be also partly due to the fact that as the size of pores increase the degradation of the polymer also increased which was not accounted for.

Cruz et al. [33] studied the diffusional release of drug from three types of nanocarriers (nanoemulsions (NE), nanocapsules (NC) and nanospheres (NS)). They

developed a mathematical model (Equations (2.42)-(2.43)) using MicroMath Scientist to analyze the probe disappearance profile. They also used this model to analyze the release profiles of indomethacin loaded and indomethacin ethyl ester loaded NE, NC and NS

$$C = C_0 e^{-kt} \quad (2.42)$$

$$C = ae^{-k_1 t} + be^{-k_2 t} \quad (2.43)$$

It was found that the release profiles for all three types of indomethacin loaded nanocarriers were well described by monoexponential model (Equation (2.41)). However biexponential model (Equation (2.42)) was found to be a better fit for release profile of indomethacin from ethyl ester loaded nanocarriers. Though the model fitted the experimental data well, it does not provide any insight into the underlying transport mechanisms responsible for drug release phenomena.

The drug release from lipid based implants was studied by Guse et al. [34]. Glycerol-trimyristate, -tripalmitate and -tristearate were used as model lipids and lysozyme and pyranine were used as model drugs. The drugs were compressed to form cylindrical geometries. The analytical solution for Fick's second law of diffusion (Equation (2.44)) was used to describe the drug release process from lipid implants [35]. It is interesting to note that the drug release profile differed significantly with the type of lipid used. When the drug loadings were low the model was able to describe the drug release process well, but at higher loadings the model could not explain the drug release profile. The authors also applied the model to describe the pyranine release from microspheres coated with PLGA layer. The model was able to describe the tri-phasic release profile well. The authors also found that the drug release profile changed significantly with varying compression strength.

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{q_n^2} \exp\left(-\frac{q_n^2}{R^2} Dt\right) \sum_{p=0}^{\infty} \frac{1}{(2p+1)^2} \exp\left(-\frac{(2p+1)^2 \pi^2}{H^2} Dt\right) \quad (2.44)$$

Lao et al. [36] developed a mathematical model to study the release behavior of paclitaxel (drug used for treating cancer) from biodegradable blended polymers. The drug release profile showed biphasic behavior. The drug release process was believed to follow three steps: (i) solvent penetration into the matrix (ii) a degradation-dependent “relaxation of the network” creating more free volume for the drug dissolution and (iii) finally the drug diffusion into the surrounding medium. Models were developed to describe the drug release process into perfect sink from pure PCL and PLGA films as well as blended films. Equation (2.45) which is the solution for Fick’s second law of diffusion for a planar system [12] was combined with equation (2.46) which describes the kinetics of initial burst as developed by Batycky [37].

$$\left\{ \frac{M_t}{M_\infty} \right\}_{diff} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp\left\{ \frac{-D(2n+1)^2 \pi^2 t}{4l^2} \right\} \quad (2.45)$$

$$\left\{ \frac{M_t}{M_\infty} \right\}_{burst} = 1 - \exp(-k_b t) \quad (2.46)$$

$$\left\{ \frac{M_t}{M_\infty} \right\}_{PCL} = \phi_{b,PCL} \{1 - \exp(-k_{b,PCL} t)\} + \phi_{b,PCL} \left\{ 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp\left\{ \frac{-D_{PCL} (2n+1)^2 \pi^2 (t - t_{b,PCL})}{4l^2} \right\} \right\} \quad (2.47)$$

For neat PLGA films a second term comes into picture (Equation (2.48)) because degradation-dependent relaxation of PLGA chains plays a critical role in drug dissolution and release process.

$$\left\{ \frac{M_t}{M_\infty} \right\}_{PLGA} = \phi_{b,PLGA} \{1 - \exp(-k_{b,PLGA}t)\} + \phi_{b,PLGA} \{ \text{Exp}[k_{r,PLGA}(t - t_{b,PLGA})] - 1 \} \\ + \phi_{b,PLGA} \left\{ 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp \left\{ -D_{PLGA} (2n+1)^2 \pi^2 (t - t_{b,PLGA}) / 4l^2 \right\} \right\} \quad (2.48)$$

As paclitaxel is expected to stay in the system for a period of 3 months, a blend of these two polymers is desired as PCL degrades too soon while PLGA takes a long time. When blended these polymers form two phases (one with PCL rich phase and one PLGA rich phase) because of their low miscibility. Thus the authors adopted a heuristic approach (Equation (2.49)) postulating that: “the drug partitions into each phase and remains there until released and the drug follows same mechanism of release for the respective phase”.

$$\left\{ \frac{M_t}{M_\infty} \right\}_{blend} = f_{PCL} \left\{ \frac{M_t}{M_\infty} \right\}_{PCL} + f_{PLGA} \left\{ \frac{M_t}{M_\infty} \right\}_{PLGA} \quad (2.49)$$

Where

$$f_{PCL} + f_{PLGA} = 1 \quad (2.50)$$

$$K = [PCL]/[PLGA] \quad (2.51)$$

$$f_{PCL} = \frac{W_{PCL}K}{W_{PCL}K + W_{PLGA}K} \quad (2.52)$$

The model results agreed well with the data except for PLGA/PCL ratio of 75/25. For this case the model results varied significantly from the experimental data. The explanation for this deviation was given as follows: as the blend model assumes that the total release is a sum of drug release contribution by two phases, the drug from each phase is released through interconnected paths of its own phase across the film. When the weight fraction of one of the component, is reduced considerably it is expected that the minor component

will assume the form of isolated islets in the major phase. The interconnectivity of the minor phase is thus lost. Therefore the drug released from the minor phase in this case PCL phase would be disrupted. Equations (2.45) through (2.52) were fit to the experimental data using MATLAB programming.

Muschert et al. [38] studied the release of diltiazem HCl from ethyl cellulose coated pellets. In order to determine the diffusion coefficient of drug within the coat the authors applied the Equations (2.45). The authors also found that by changing osmolality the drug release profile varied greatly. Fick's second law of diffusion for planar sheet is given by:

$$\frac{\partial C}{\partial t} = D \left(\frac{\partial^2 C}{\partial x^2} \right) \quad (2.53)$$

Initial and boundary conditions applied:

$$t = 0, C = C_{initial} \quad -L \leq x \leq +L \quad t > 0, \quad -D \left(\frac{\partial C}{\partial x} \right)_{x=\pm L} = h.(C_{surface} - C_{\infty}) \quad (2.54)$$

The solution for Equations (2.53)-(2.54) using the Laplace transform method [36] is given as:

$$\frac{M_t}{M_{\infty}} = 1 - \sum_{n=1}^{\infty} \frac{2G^2}{\beta_n^2 (\beta_n^2 + G^2 + G)} \exp \left(\frac{-\beta_n^2}{L^2} Dt \right) \quad (2.55)$$

$$\beta \tan \beta = G \quad (2.56)$$

$$G = \frac{Lh}{D} \quad (2.57)$$

The overall release of drug from the coated pellet into perfect sink was given by:

$$M_t = M_0 \left[1 - \exp \left(-\frac{ADKt}{Vl} \right) \right] \quad (2.58)$$

Where M_t , M_0 represent the amount of drug released at time t and 0 , A denotes the surface area of the pellet, D represents the diffusion coefficient, V, l represent the volume of the pellet and thickness of the film coating and K represents the partition coefficient.

2.2 Mathematical Models for Diffusion- Dissolution Controlled Drug Release

There is a wealth of mathematical models describing drug release from diffusion, degradation and swelling controlled drug delivery devices but very few articles deal with the dissolution controlled drug release kinetics. This phenomenon becomes especially important when the drugs are sparingly soluble.

Ayres and Lindstrom [39] developed a mathematical model taking into account both diffusion and dissolution phenomenon to explain the release kinetics of topically applied ointment (cortisone) through skin and into the blood stream. They assumed the diffusion coefficient to be constant. The equations describing the mass transport of the drug through the suspension (ointment) and a permeable barrier (skin) to a perfect sink are given as follows:

$$\frac{\partial C_1}{\partial t} = D_1 \left(\frac{\partial^2 C_1}{\partial x^2} \right) + K(C_s - C_1) \quad -L_1 < x < 0 \quad (2.59)$$

The equation for diffusion through medium II is given as:

$$\frac{\partial C_2}{\partial t} = D_2 \left(\frac{\partial^2 C_2}{\partial x^2} \right) \quad t > 0 \quad 0 < x < L_2 \quad (2.60)$$

The initial conditions are given as:

$$C_1(x, 0+) = C_s \quad -L_1 \leq x < 0 \quad (2.61)$$

$$C_2(x,0+) = 0 \quad 0 < x < L_2 \quad (2.62)$$

The boundary conditions assumed were

$$C_1(0,t) = PC_2(0,t) \quad t > 0 \quad (2.63)$$

$$D_1 \frac{\partial C_1(0,t)}{\partial x} = D_2 \frac{\partial C_2(0,t)}{\partial x} \quad t > 0 \quad (2.64)$$

$$\left(\frac{\partial C_1}{\partial x} \right)_{x=-L_1} = 0 \quad t \geq 0 \quad (2.65)$$

$$C_2(L_2,t) = 0 \quad t \geq 0 \quad (2.66)$$

Equations (2.59)-(2.66) were solved using Laplace transform method. The mass distribution functions for cumulative drug mass taken up by receptor (Equation (2.67)) and the cumulative mass loss from the ointment (Equation (2.68)) is given as:

$$M_{but}(t) = \int_0^t \left(-D_2 A \frac{\partial C_2}{\partial x} \right)_{x=L_2} d\tau \quad (2.67)$$

$$M_1(t) = \int_0^t \left(-D_1 A \frac{\partial C_1}{\partial x} \right)_{x=0} d\tau \quad (2.68)$$

Performing the indicated partial differentiation with subsequent evaluations of these at $x = L_2$ and $x = 0$ results in Equations (2.69) and (2.70) respectively.

$$M_{but}(t) = AC_s \sqrt{KD_1} t \frac{\sinh(L_1 \sqrt{\frac{K}{D_1}})}{\cosh(L_1 \sqrt{\frac{K}{D_1}}) + P \frac{L_2}{L_1} \sqrt{KD_1} \sinh(L_1 \sqrt{\frac{K}{D_1}})} + \frac{2AL_2 C_s}{P} \sum_{n=1}^{\infty} \frac{\cos \beta_n}{\beta_n^2 \Delta_n} [1 - \exp(-\beta_n^2 D_2 t / L_2^2)] \quad (2.69)$$

$$M_i(t) = AC_s \sqrt{KD_1 t} \frac{\sinh(L_1 \sqrt{\frac{K}{D_1}})}{\cosh(L_1 \sqrt{\frac{K}{D_1}}) + P \frac{L_2}{L_1} \sqrt{KD_1} \sinh(L_1 \sqrt{\frac{K}{D_1}})} + \frac{2AL_2 C_s}{P} \sum_{n=1}^{\infty} \frac{\cos^2 \beta_n}{\beta_n^2 \Delta_n} [1 - \exp(-\beta_n^2 D_2 t / L_2^2)] \quad (2.70)$$

Where A is the cross sectional area, D_1, D_2 are the diffusion coefficients for medium I and II respectively. K is the dissolution rate constant and P is the partition coefficient.

The relative cumulative receptor phase uptake $\mu_{but}(t) = M_{but}(t) / M_0$ and the cumulative drug mass loss from the ointment, μ_1 for finite D_1 and D_2 is given as:

$$\mu_{but}(t) \approx \frac{Kt}{1 + KP \frac{L_1 L_2}{D_2}} + 2 \left(\frac{L_2}{L_1} \right) \frac{\cos \beta_1}{P \beta_1^2 \Delta_1} \quad (2.71)$$

$$\mu_1(t) \approx \frac{Kt}{1 + KP \frac{L_1 L_2}{D_2}} + 2 \left(\frac{L_2}{L_1} \right) \frac{\cos \beta_1^2}{P \beta_1^2 \Delta_1} \quad (2.72)$$

Where $0 \leq K \leq 0.25(D_1 / L_1^2), t \geq (4L_2^2 / \beta_1^2 D_2)$ and $M_0 = AL_1 C_s$

And as $D_2 \rightarrow \infty$

$$\mu_{but}(t) \approx \frac{\sqrt{D_1 K}}{L_1} + \frac{1}{2L_1} \frac{\sqrt{D_1}}{K} \quad (2.73)$$

Where $K \geq 0.25(D_1 / L_1^2), t \geq 5 / [(9\pi^2 D_1 / 4L_2^2) + K]$

All the parameters required to solve Equations (2.69) - (2.73) were taken from the literature, except for the values of diffusion coefficient and dissolution constant which the authors could not find in the literature. The authors also studied two special cases to emphasize the effect of K on the drug release process.

Case (i) $D_2 \rightarrow \infty$ implies that the mass transport through the skin is carried out infinitely fast. This represents a case when the ointment is directly applied to open wounds. Now as $K \rightarrow \infty$ the solution phase concentration phase distribution in medium I (the ointment) tend to stay at a saturated concentration C_s which was well predicted by the model. The cumulative drug mass uptake by the blood versus time curves showed that when $K = 0$ only finite amount of original solution phase drug in the ointment can be taken up by the blood because this is the only drug mass available to be taken up. However, for $K > 0$, the blood uptake of the drug distribution of time can be seen.

The classical Higuchi equation (1961) can be recasted into the notion of proposed model as Equation (2.74) and compared with the cumulative amount of drug taken up by the receptor (Equation (2.73)). The difference between these two Equations was that μ_{but} was proportional to t for large values of time whereas μ_H is proportional to \sqrt{t} at all times.

$$\mu_H = \frac{\sqrt{D_1 t (2 \frac{M_{DT}}{M_0} - 1)}}{L_1} \quad (\text{where H stands for classical model}) \quad (2.74)$$

Following a similar procedure as case (i) the authors obtained the drug release profiles for case (ii) $D_1 \rightarrow \infty$ which corresponds to the transport rate limiting step in the skin. It was found that initially ($t < 1/4$ day) drug was lost rapidly from the ointment to the surface layer of the skin. For $K = 0$ about 87% of the drug was found to be lost from the ointment by the end of day 1. Since there is no dissolution from the suspension when $K = 0$, the only available drug is that in the solution phase initially. With the blood capillary system supposedly forming a perfect sink for the drug, both C_1 and $C_2 \rightarrow 0$ as

time $t \rightarrow \infty$. When $K > 0$, a finite steady state in the skin is easily observed as time $t \rightarrow \infty$. At small times, a rapid loss of drug from the ointment was observed. However, as time progresses the drug released from the ointment is being replaced by the finite dissolution rate process occurring in the suspension (medium I). From the drug release plots, it can also be inferred that as K value increases a deficit zone is generated. The drug in the ointment releases too rapidly for the drug to be replaced by dissolution from the suspension. Thus, by varying the values of K the authors obtained several plots for cumulative amount of drug taken by the blood and the cumulative mass loss of drug from the ointment. The drug release profiles differed greatly with the value of K , therefore establishing that the rate of dissolution has a significant role to play in the process of drug release. The authors concluded that the factors affecting the drug release process from semisolid suspensions are (i) powder density of particle size, (ii) partition coefficient between the vehicle and receptor phase, (iii) solubility of the drug in the vehicle, (iv) area of application, (v) viscosity of the vehicle, (vi) temperature and (vii) the total time the drug remains in contact with the receptor.

The same authors in a different paper [40] proposed a solution based on numerical methods to predict drug release from suspension of drug in semisolid vehicles. The mass transport model was given as:

$$\frac{\partial C_1}{\partial t} = D_1 \left(\frac{\partial^2 C_1}{\partial x^2} \right) + K(C_s - C_1) \left(\epsilon_0^{1/3} - \frac{K}{3\rho_s} \int_0^t [C_s - C_1(x, \tau)] d\tau \right)^2 \quad (2.75)$$

Initial condition taken was:

$$C(x, +0) = C_s \quad -L \leq x < 0 \quad (2.76)$$

The boundary conditions taken were:

$$\left(\frac{\partial C}{\partial x}\right)_{x=-L} = 0 ; C(0,t) = 0 \quad (2.77)$$

Equations (2.75) – (2.77) which form a non-linear system were solved using the method of backward finite differences, where the global error involved at any point in time and space always remains bounded and goes as $o(\Delta x^2 + \Delta t)$. Plots for cumulative release of ointment as a function of time were obtained for different K and ϵ_0 values. Though the model results were in good agreement with the Higuchi model [39] the release profiles were quite different. Cortisone powder was taken as the model drug.

Frenning and Stromme [41] developed a mathematical model taking into account drug dissolution, diffusion and immobilization to explain the delayed release of NaCl from agglomerated micronized cellulose. Following assumptions were made for the model development (i) the tablet contains a large number of drug crystals, of approximately same size and shape, dispersed into an insoluble matrix. (ii) When in contact with water, the tablet breaks up into a number of approximately spherical tablet fragments. (iii) Liquid absorption and tablet disintegration rate are much faster than the drug dissolution. Accordingly, the initial state is characterized by virtually complete liquid absorption, matrix swelling and disintegration but negligible drug dissolution. (iv) The surrounding liquid is well mixed, so that its concentration is independent of the space coordinates. The drug flux within each fragment was assumed to be caused by diffusion. Fick's law of diffusion was used with concentration-dependent chemical diffusion coefficient $D(c)$ was taken to be:

$$j = -D\nabla c \quad (2.78)$$

The diffusion coefficient was expressed as:

$$D = D_0[(1 - \varepsilon)\exp(-bc) + \varepsilon] \quad (2.80)$$

The total source density term was taken to be:

$$R = R_d - R_b \quad (2.81)$$

Where $R_d(t, x)$ is the contribution to the source density term due to dissolution process and $R_b(t, x)$ is the contribution due to adsorption process. The dissolution process was described using the well-known Noyes-Whitney equation [42] averaged over a small volume.

$$R_d = k_d \bar{A}(c_s - c) \quad (2.82)$$

Where k_d is the dissolution rate constant, c_s is the solubility of the drug, and $\bar{A}(t, x)$ is the average surface area of the undissolved drug per unit volume. The adsorption rate was taken as:

$$R_b = \frac{\partial s}{\partial t} \quad (2.83)$$

Where $s(t, x)$ represents the amount of drug adsorbed per unit volume. Following the assumption that if the adsorption by which the drug becomes immobilized proceeds very rapidly in comparison with the diffusion process, local equilibrium can exist between the mobile and immobilized components of diffusion substance [12] the authors adopted the Langmuir-Freundlich isotherm to describe the adsorption process:

$$\frac{s}{c_b} = \frac{(k_b c)^\delta}{[1 + (k_b c)^\delta]^2} \cdot \frac{\partial c}{\partial t} \quad (2.84)$$

Where k_b is the adsorption constant, and δ is the measure of the width of distribution of adsorption energies which assumes a value between 0 and 1.

Combining equations (2.78) through (2.84) a non-linear inhomogeneous diffusion equation was obtained as:

$$(1 + k_b c_b \delta) \frac{(k_b c)^{\delta-1}}{[1 + (k_b c)^\delta]^2} \cdot \frac{\partial c}{\partial t} = D_0 \nabla \{ [(1 - \varepsilon) \exp(-bc) + \varepsilon] \nabla c \} + k_d \bar{A} (c_s - c) \quad (2.85)$$

Following the assumptions given by Edwards [43] and Hixon and Crowell [44], the authors derived the following relation between average surface area of undissolved drug $\bar{A}(t, x)$ and mobile drug concentration $c(t, x)$:

$$\frac{\bar{A}}{A_0} = \left(\frac{\bar{m}}{m_0} \right)^{2/3} \quad (2.86)$$

The equation for average surface area of undissolved drug was taken as:

$$\frac{1}{A_0} \cdot \frac{\partial \bar{A}}{\partial t} = -\frac{2}{3} \frac{k_d \bar{A}_0}{m_0} \left(\frac{\bar{A}}{A_0} \right)^{1/2} (c_s - c) \quad (2.87)$$

Where $\bar{m}(t, x)$ denotes average mass of undissolved drug per unit volume and indexed quantities denote the initial values.

For a spherical system, Equation (2.85) can be written as:

$$(1 + k_b c_b \delta) \frac{(k_b c)^{\delta-1}}{[1 + (k_b c)^\delta]^2} \cdot \frac{\partial c}{\partial t} = \frac{D_0}{r^2} \frac{\partial}{\partial r} \{ r^2 [(1 - \varepsilon) \exp(-bc) + \varepsilon] \frac{\partial c}{\partial r} \} + k_d \bar{A} (c_s - c) \quad (2.88)$$

The boundary conditions were taken as:

$$\left(\frac{\partial c}{\partial r} \right)_{r=0} = 0, \quad t > 0 \quad (2.89)$$

$$\frac{dc(t, a)}{dt} = -3 \frac{\gamma \rho}{a} D \left(\frac{\partial c}{\partial r} \right)_{r=a} \quad (2.90)$$

$$\text{Where } c(t, a) = \gamma c_{sol}(t); c_{sol}(t) = \frac{m_{sol}(t)}{V_{sol}}; \rho = \frac{NV_{sph}}{V_{sol}} \quad (2.91)$$

γ represents the partition coefficient, $c_{sol}(t)$ represents the drug concentration in the surrounding solution at any time t and $m_{sol}(t)$ represents the mass of drug present in the surrounding liquid at time t . the rate of change of $m_{sol}(t)$ was computed from the total flux out from all N tablet fragments as:

$$\frac{dm_{sol}}{dt} = N \int_{r=a} j \cdot ds = -4\pi a^2 ND \left(\frac{\partial C}{\partial r} \right)_{r=a} \quad (2.92)$$

The problem was set up in dimensionless form as:

$$g(\psi) \frac{\partial \psi}{\partial \tau} = \frac{1}{\xi^2} \frac{\partial}{\partial \xi} \left(\xi^2 \frac{\partial \psi}{\partial \xi} \right) + k_d \alpha (\psi_s - \psi) \quad (2.93)$$

$$\frac{\partial \alpha}{\partial \tau} = -\frac{2}{3} k_d \alpha^{1/2} (\psi_s - \psi) \quad (2.94)$$

The boundary conditions became

$$\left(\frac{\partial \psi}{\partial \xi} \right)_{\xi=0} = 0 \quad (2.95)$$

$$\left(\frac{\partial \psi(\tau, 1)}{\partial \tau} \right)_{\xi=0} = -3\gamma \rho \left(\frac{\partial \psi}{\partial \xi} \right)_{\xi=1} \quad (2.96)$$

The initial conditions, obtained from the assumption that the entire drug is present in undissolved state initially were taken as:

$$\psi(0, \xi) = 0 \quad (2.97)$$

$$\alpha(0, \xi) = 1 \quad (2.98)$$

The drug concentration in the solution surrounding the tablet fragments was expressed as:

$$\psi_{sol}(\tau) \equiv \frac{c_{sol}}{m_0} = \frac{\psi(\tau, 1)}{\gamma} \quad (2.99)$$

Equations (2.93) and (2.94) were solved using finite difference method [45]. The numerically computed release profiles were in excellent agreement with the experimental data.

Frenning [46] developed a semi analytical solution for the release of slowly dissolving drugs from planar matrix systems and later on extended the idea to develop a model for spherical system [47]. Assumptions made for the model development are: (i) A planar matrix system is considered (ii) the boundary at $x=0$ is assumed to be impenetrable to the drug, while the matrix is in contact with liquid at $x=L$ (iii) the matrix is at all times in contact with a well stirred medium with volume large enough to maintain sink conditions. (iv) The liquid absorption is much faster than the drug dissolution and subsequent release (v) all the drug is present in solid form initially. The drug release process through diffusion and dissolution was described by coupled PDEs as follows (given in dimensionless form):

$$\frac{\partial C}{\partial \tau} = \left(\frac{\partial^2 C}{\partial \xi^2} \right) + kS^{\frac{2}{3}}(C_s - C) \quad (2.100)$$

$$\frac{\partial S}{\partial \tau} = -kS^{\frac{2}{3}}(C_s - C) \quad (2.101)$$

Where $C(t, x)$ represents the concentration of dissolved drug within the matrix and $S(t, x)$ is the concentration of solid drug within the matrix. The dimensionless variables were taken as:

$$C \equiv \frac{C}{S_0} \quad \text{and} \quad S \equiv \frac{S}{S_0} \quad (2.102)$$

$$\tau \equiv \frac{Dt}{L^2} \quad \text{and} \quad \xi \equiv \frac{x}{L} \quad (2.103)$$

Dimensionless solubility and dissolution constant were taken as:

$$C_s \equiv \frac{C_s}{S_0} \quad \text{and} \quad k \equiv \frac{kL^2 A_0}{D} \quad (2.104)$$

The initial conditions were taken as:

$$C(0, \xi) = 0 \quad (2.105)$$

$$S(0, \xi) = 1 \quad (2.106)$$

The boundary conditions were taken to be:

$$\left(\frac{\partial C}{\partial \xi} \right)_{\xi=0} = 0; C(\tau, 1) = 0; \quad (2.107)$$

$$\left(\frac{\partial S}{\partial \xi} \right)_{\xi=0} = 0 \quad (2.108)$$

The boundary condition for $\xi = 1$ was determined by putting $\xi = 1$ in Equation (2.101).

As a result of the boundary condition of Equation (2.107), Equation (2.101) then reduces to an ordinary differential equation for $S(\tau, 1)$. The solution to this Equation

$$S(\tau, 1) = \left(1 - \frac{kC_s\tau}{3} \right)^3 \quad (2.109)$$

then yields the desired boundary condition. The boundary condition of Equation (2.109)

is valid as long as $kC_s\tau < 3$ and it has to be replaced by $S(\tau, 1) = 0$ for larger values

of τ .

The fraction of drug released was expressed as:

$$Q = 1 - \int_0^1 (C + S) d\xi \quad (2.110)$$

Where the integral accounts for entire drug remaining in the matrix.

For the derivation of an approximate analytical solution, the authors made the following approximation:

$$U \equiv 1 - S \quad (2.111)$$

Where U is only valid during initial stages of drug release process. By keeping only the linear terms Equations (2.100) and (2.101) are converted into linear PDEs and solved using Laplace transform method. The final fraction of drug released was obtained as:

$$Q = kC_s \sum_{n=1}^{\infty} F_n^{-1} \left(\frac{e^{s_n^- \tau} - 1}{s_n^-} - \frac{e^{s_n^+ \tau}}{s_n^+} \right) \quad (2.112)$$

This equation is able to account for the decrease in surface area as opposed to the solution given by Aryes and Lindstrom [39] which assumes that the surface area remains constant. However, this Equation is only valid during early stages of the release process. Equations (2.100) and (2.101) were also solved numerically by using the FORTRAN routine D03PCF which was provided to them by The Numerical Algorithms Group (NAG, United Kingdom), this routine reduces the PDEs to ODEs and the resulting ODE system is solved by using backward differentiation formula method [48]. The drug release profiles obtained from the semi-analytical solution (Equation (2.112)) and numerical solution were compared with Crank's Equation (Equation (2.113)) and adjusted Higuchi Equation (2.114) proposed by Bunge [49] which were developed for the case of instantaneous dissolution.

$$Q_{\infty}(\tau) \equiv \lim_{k \rightarrow \infty} Q(\tau, k, C_s > 1) = 1 - \sum_{n=1}^{\infty} \frac{8}{(2n-1)^2 \pi^2} e^{-(2n-1)^2 \pi^2 \tau / 4} \quad (2.113)$$

$$Q = \sqrt{2 \left[1 - C_s \left(\frac{\pi - 2}{\pi} \right) \right]} C_s \tau \quad (2.114)$$

It was seen that as the k and C_s values were varied the rate of drug released also varied. The drug release profile obtained by the semi-analytical equation and the numerical solution were in good agreement with each other. The authors concluded that by retaining the non linear terms the overestimation of the fraction of drug released could be avoided which normally occurs due to linearized treatment of the problem.

Polakovic et al. [50] adopted two mathematical models to describe the release of lidocaine from PLA nanospheres. They applied the diffusion model and dissolution model separately to describe lidocaine release from nanospheres. They found that the diffusion model Equation (2.115) – (2.116) [12] accounted well for the drug release from particles containing low drug loadings and dissolution model (Eq. (2.117)) accounted well for drug release from particles with higher drug loading. For the derivation of dissolution model they assumed that (i) the dissolution of lidocaine crystals was the rate-controlling step implying a homogeneous distribution of drug within the matrix.(ii) The mass of dissolved drug inside the particle was negligible compared to the crystalline drug form. (iii) As the crystal specific area was unknown, the driving force of dissolution was defined as the difference of the concentration of the solid drug and its equilibrium concentration corresponding to the bulk liquid drug content.

$$\frac{c_1}{c_\infty} = 1 - \sum_{n=1}^{\infty} \frac{6\alpha(1+\alpha)}{9+9\alpha+(\alpha q_n)^2} \exp\left(-\frac{Dq_n^2 t}{R^2}\right) \quad (2.115)$$

$$\tan q_n = \frac{3q_n}{3+\alpha q_n^2} \quad (2.116)$$

$$c_1 = \frac{c_0}{K_p(\alpha+1)} \left[1 - \exp\left(-\frac{\alpha+1}{\alpha} kt\right)\right] \quad (2.117)$$

It was observed that for low drug loading the process of drug release was controlled by diffusion process whereas at high drug loadings the drug release process was controlled by dissolution process.

When, compared with the model developed by Frenning [46, 47] Polakovic's model does not predict the initial time delay for drug release, but is valid for drug release over all time periods.

Jo et al. [51] applied Polakovic's model (Equation (2.117)) to describe the dissolution controlled release of indomethacin from PLG-PEO nanospheres. However, for modeling diffusion controlled drug release the authors proposed a new model (Equation (2.118)) which contradicts the classical solution given by Crank [12] for the release of solute from a spherical matrix due to diffusion.

$$\frac{c_1}{c_\infty} = 1 - \sum_{n=1}^{\infty} \frac{6\alpha(1+\alpha)}{9+3\alpha+(\alpha q_n)^2} \exp\left(-\frac{Dq_n^2 t}{R^2}\right) \quad (2.118)$$

Notice that the coefficient in the denominator of Equation (2.118) differs from Equation (2.115). Their observations were in agreement with Polakovic's observations, that for small particles diffusion was the main mechanism controlling the drug release process whereas for larger nanospheres dissolution was more dominant in controlling the drug release process. However, the dissolution model significantly under predicted the drug release profile when compared to the diffusion model.

2.3 Mathematical Models for Prediction of Drug Release In Vivo

There are various factors that affect the process of drug release. The size of the drug particles and the type of polymer used has an effect of the rate of drug release apart from the transport processes involved. The effect of acidic pH on the degradation and release

of dexamethosone from PLGA microspheres was investigated by Zolnik B.S and Burgess [52, 53]. They reported that there was no evident effect of pH on the burst phase of the release however the pH did significantly affect the second phase of release (bi-phasic release). Faisant et.al. [54] found that the drug release profile from microspheres were markedly different for different osmolalities, temperatures and pH. Excipients also seem to have an effect on drug release rate [55, 56]. All the models discussed so far have been for in-vitro drug release kinetics wherein perfect sink conditions are maintained. And all the factors recognized to be affecting the drug release process are physiochemical in nature. However when it comes to a real system (human body) the physiological factors also come into play. The presence of food, type of food, blood flow rate to the gastrointestinal (GI) tract, GI tract motility etc., are a few of them [10]. Presence of one drug in the system before the admission of another drug can also effect the absorption rate of drug in the GI tract [57]. Mechanistic modeling cannot be applied directly for prediction of amount of drug in the system (plasma). This is where physiological or compartmental modeling might reveal better information. While mechanistic modeling is concerned with understanding the underlying drug release phenomena compartmental modeling is concerned with understanding the physiological phenomena [58]. Pharmacokinetic modeling can broadly be classified as: One compartmental modeling, two compartmental modeling, multi compartmental modeling [10, 59] and physiologically based pharmacokinetic modeling [60]. There are also various compartmental model developed for orally administered drugs taking into account the hepatic first pass metabolism, GI tract motility, absorption in small intestine etc., [61, 62, 63, 64]. In one compartmental model the whole body is thought of as one compartment and the absorption and

elimination kinetics of the drug are studied, where as in two compartmental modeling a second compartment accounting for drug uptake by the tissue is also considered. In physiologically based pharmacokinetic modeling the pertinent biochemical and physiological constants for metabolism and solubility in each compartment are included. Routes of dosing are included in their proper relationship to the overall physiology. Each compartment in the model is described by differential mass balance equations whose terms mathematically represent the biological process [60]. These equations are then solved using numerical methods and software packages [10].

There is a large spectrum of pharmacokinetic models available in the literature [10, 57, 58, 59], but most of these models consider the entire drug to be present in the compartment at time $t = 0$ which is not the case with controlled release drug delivery devices. Therefore there are discrepancies in the in-vitro in-vivo correlations [65, 66, and 67]. There are very few models which take into account both the in-vitro parameters (like diffusion coefficient) and the in-vivo parameters like absorption and elimination coefficients. Nia et.al., [68] developed a simple mathematical model taking into accounting both in-vitro and in-vivo parameters to calculate the amount of drug released into the plasma for a diffusion controlled oral dosage form. They made the following assumptions: (i) the oral dosage form was cylindrical in shape and the drug concentration was uniform initially (ii) the process of drug release out of the dosage form is solely controlled by diffusion (iii) the drug releases out of the dosage into the GI tract thereby is absorbed into the blood compartment and eliminated. The absorption and elimination constants were taken from the data. The radial and longitudinal diffusion was defined by equation (2.119)

$$\frac{\partial C}{\partial t} = D \left[\frac{\partial^2 C}{\partial Z^2} + \frac{\partial^2 C}{\partial r^2} + \frac{1}{r} \cdot \frac{\partial C}{\partial r} \right] \quad (2.119)$$

The boundary conditions taken were:

$$t > 0 \quad r = R \quad -D \frac{\partial C}{\partial r} = h(C_R - C_{ext}) \quad (2.120)$$

$$z = \pm L \quad -D \frac{\partial C}{\partial z} = h(C_L - C_{ext}) \quad (2.121)$$

The solution for Equations (83)-(84) is given as [70]:

$$\frac{M_\infty - M_t}{M_\infty} = \sum \frac{2R_1^2}{\beta_{ln}^2 (\beta_{ln}^2 + R_1^2 + R_1)} \exp\left(-\frac{\beta_{ln}^2}{L^2} Dt\right) \times \sum \frac{4R_r^2}{\beta_{rm}^2 (\beta_{rm}^2 + R_r^2)} \exp\left(-\frac{\beta_{rm}^2}{R^2} Dt\right) \quad (2.122)$$

Where β_{ln} and β_{rm} are the roots of the equation given by

$$\beta \cdot \tan \beta = R_1 \quad (2.123)$$

$$\beta_r \cdot J_1(\beta_r) = R_r \cdot J_0(\beta_r) \quad (2.124)$$

$$\text{And } R_1 = \frac{Lh}{D} \quad R_r = \frac{Rh}{D} \quad (2.125)$$

The Equations for rate of drug release into the blood compartment and rate of elimination of drug were taken as

$$\frac{dY}{dt} = k_a \cdot X - k_e \cdot Y \quad (2.126)$$

$$\frac{dW}{dt} = k_e Y \quad (2.127)$$

Equations (2.122)-(2.127) were solved using finite difference method.

Ouriemchi et al. [71] presented a numerical solution to calculate the amount of drug released in-vivo. They studied the effects of absorption rate, elimination rate and volume of liquid in the stomach on the rate of drug release. They considered a diffusion controlled spherical matrix system. The absorption and elimination rate coefficients were assumed to be constant. The volume of the gastric liquid was taken to be constant and the concentration of drug in the stomach and blood compartment were taken to be uniform.

$$\frac{\partial C}{\partial t} = \frac{D}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial C}{\partial r} \right) \quad (2.128)$$

$$C = K_p C_s = K_p \frac{Y}{V_s} \quad r = R \quad (2.129)$$

Following the Crank-Nicolson method [70], the authors obtained the amount of drug in the dosage form at any time t as

$$\frac{M_t'}{4\pi(\Delta r)^3} = \frac{C_0}{24} + \frac{C_{N-0.25}}{3} [N^3 - (N-0.5)^3 + \sum_{n=1}^{N-1} (N^2 + \frac{1}{12}) \cdot C_n] \quad (2.130)$$

The equations for flow of drug leaving the dosage form, flow of drug passing into the stomach and the flow of drug eliminated out of the blood are given by Equations (2.131)-(2.132)

$$F_{form} = -S D \frac{\partial C}{\partial t} \quad (2.131)$$

$$F_s = k_a Y \quad (2.132)$$

$$\frac{dW}{dt} = k_e Z \quad (2.133)$$

The rate of increase in the amount of drug in the plasma compartment and gastric liquid is given by:

$$\frac{dZ}{dt} = k_a Y - \left(\frac{k_a V_s}{K_b V_b} + k_e \right) Z \quad (2.134)$$

$$\frac{dY}{dt} = -S D \frac{\partial C}{\partial t} - k_a Y + \frac{k_a V_s}{K_b V_b} Z \quad (2.135)$$

Where k_a is the absorption rate constant, k_e is the elimination rate constant, K_b is the partition coefficient between of drug between stomach and blood and V_s, V_b are the volume of gastric liquid and blood respectively. Equations (2.133)-(2.135) were resolved step by step by increasing the amount of drug Y, Z and W during each time interval $[t, t + \Delta t]$ using the crank-Nicolson method and Equations (2.134)- (2.135) was solved with parabolic approximation of grid points N, N-1, N-2 of the dosage form. The effect of absorption rate was found to be negligible but when the volumetric liquid volume was lowered the elimination kinetics changed significantly.

Ouriemchi et al. [72] studied the drug release from a spherical core and shell type of dosage form in the plasma compartment. The drug transfer at the core-shell interface is taken to be the same. The Equation for radial diffusion from a spherical particle is same as Equation (2.128). The rate of drug release out of the dosage form was taken as

$$F_t = -AD \frac{\partial C}{\partial t} \quad (2.136)$$

Amount of drug in the GI tract, Plasma and the drug eliminated were taken as:

$$\frac{dX}{dt} = F_t - k_a X \quad (2.137)$$

$$\frac{dY}{dt} = k_a X - k_e Y \quad (2.138)$$

$$\frac{dZ}{dt} = k_e Y \quad (2.139)$$

Equations (2.136)-(2.139) were also solved using the Crank-Nicolson method.

Following a similar approach [73] Bakhouya et al. [74] calculated the antibiotic levels in the plasma for oral erosion –controlled drug dosage form. They considered two dosage forms one immediate release dosage form and another erosion controlled dosage form. The calculated release profiles for both the dosages were compared and it was found that the rate constant of elimination played a significant role. Drug release profiles were compared for both single dosage and multiple dosages. The erosion–controlled release profiles showed a steady release rate compared to the immediate release profiles.

The rate of drug release from the erosion-controlled dosage was taken to be:

$$\left(1 - \frac{M_t}{M_{in}}\right)^{1/3} = 1 - K_{er} t \quad (2.140)$$

Where M_t represents the amount of drug released after time t , M_{in} is the amount of drug initially present in the dosage form and K_{er} is the rate constant of erosion.

The amount of drug located in the GI compartment, plasma compartment and amount of drug eliminated are given by Equations (2.141)-(2.143)

$$\frac{dY}{dt} = R_{er} - k_a Y_t \quad (2.141)$$

$$\frac{dZ}{dt} = k_a Y_t - k_e Z_t \quad (2.142)$$

$$\frac{dW}{dt} = k_e Z_t \quad (2.143)$$

Where R_{er} represents the rate at which the drug is released out of the dosage.

Ainaoui et al. [2] also followed a similar approach to calculate the dimensions of dosage forms required for achieving the desired release profile. Monolithic diffusion-controlled drug delivery devices of spherical, cylindrical and parallelepiped geometries were considered. Equations (2.144)-(2.146) were used to describe the drug released from spherical, cylindrical and parallelepiped system respectively.

$$\frac{M_{\infty} - M_t}{M_{\infty}} = \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(-\frac{n^2 \pi^2}{R^2} Dt\right) \quad (2.144)$$

$$\frac{M_{\infty} - M_t}{M_{\infty}} = \frac{32}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{q_n^2} \exp\left(-\frac{q_n^2}{R^2} Dt\right) \sum_{p=0}^{\infty} \frac{1}{(2p+1)^2} \exp\left(-\frac{(2p+1)^2 \pi^2}{H^2} Dt\right) \quad (2.145)$$

$$\begin{aligned} \frac{M_{\infty} - M_t}{M_{\infty}} &= \frac{516}{\pi^6} \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \exp\left(-\frac{(2n+1)^2 \pi^2}{L_1^2} Dt\right) \\ &\times \sum_{p=0}^{\infty} \frac{1}{(2p+1)^2} \exp\left(-\frac{(2p+1)^2 \pi^2}{L_2^2} Dt\right) \\ &\times \sum_{m=0}^{\infty} \frac{1}{(2m+1)^2} \exp\left(-\frac{(2m+1)^2 \pi^2}{L_3^2} Dt\right) \end{aligned} \quad (2.146)$$

Where M_{∞} and M_t represent the amounts of drug released at time t and infinity.

L_1, L_2, L_3 represent the three lengths of the parallelepiped and n, m, p are the integers.

R, H represent the radius and height of the spherical and cylindrical system respectively.

Equations (2.141)-(2.143) are combined with Equations (2.144)-(2.146) and solved numerically.

Holz and Fahr [58] developed a pharmacokinetic model for transdermal drug delivery system. The release of estradiol from the patch was modeled by considering the Fick's law of diffusion to describe the drug release from a homogeneous layer. The following assumptions were made: (i) as estradiol has good water solubility, the stratum corneum (skin) is the primary barrier of concern and no additional diffusion step through the viable dermis is considered. (ii) Initially the skin and the capillaries are free of drug. (iii) The efflux through the left side of the patch is zero. (iv) The efflux from the patch compartment at $x=0$ equals the input flux into the skin compartment and the efflux from right side of the skin to the blood capillaries follows a first order rate constant k_d . (v) The estradiol release from the patch at $x=0$ is assumed to follow the Higuchi law which was in accordance with the in vitro experiments performed.

The mass efflux rate out of the patch/skin system was given as:

$$\frac{dm}{dt} = -D \frac{\partial^2 C}{\partial x^2} \quad (2.147)$$

Where D is constant diffusivity, C is the concentration, t is the time and x is the integration path through the skin and L is the thickness of the skin.

The authors assumed a semi-infinite membrane for the patch, and applied the following boundary conditions:

$$\frac{D}{H} \cdot \frac{\partial C(0,t)}{\partial x} = -\frac{A \cdot \sqrt{2 \cdot D_p \cdot C_s \cdot C_p}}{2 \cdot \sqrt{t}} \quad (2.148)$$

$$\frac{D}{H} \cdot \frac{\partial C(L,t)}{\partial x} = -k_e \cdot C(L,t) \quad (2.149)$$

Where H is the thickness of the patch, D_p is the diffusion constant in the patch, C_s is the solubility in the skin and C_p is the solubility in the patch.

Equations (2.147)-(2.149) were transformed into dimensionless form using the following dimensionless variables:

$$\tau = D/L^2 t; X = \frac{x}{L}; u = C/C_0; \omega = k_c L^2 / D = \frac{k_c}{k_d}; \gamma = (A \cdot \sqrt{2 \cdot D_p \cdot C_s \cdot C_p}) / (2 \cdot \sqrt{\pi}) \quad (2.150)$$

Laplace transform method [37] was then used to solve the problem. The final expression for amount of drug released into the blood stream was obtained as:

$$M(\tau) = M_\infty \cdot \gamma \cdot L^{-1} \left\{ \frac{1}{s \cdot \sqrt{s} \cdot \sinh(\sqrt{s}) \cdot [1 + \frac{\omega}{\sqrt{s}} \cdot \coth(\sqrt{s})]} \right\} \quad (2.151)$$

Where M_∞ is the amount of drug released from the patch/skin system at infinite time.

The inverse Laplace transform for equation (2.151) was performed numerically [74].

Weinberg et al. [75] presented a model to simulate doxorubicin transport in non-ablated and radiofrequency (RF) ablated liver tumor. The method of ablation using RF is known to have improved efficacy in treatment where 80% of the tumors cannot be removed by surgery. The authors applied the computational modeling technique using finite element method implemented in COMSOL 3.3. One-dimensional and three-dimensional models were used to simulate the intratumoral doxorubicin release from PLGA millirods. The doxorubicin transport into the tumor from these implants was analyzed using the following Equation:

$$\frac{\partial C}{\partial t} = D \nabla^2 C - \gamma C \quad (2.152)$$

Here γ represents the elimination coefficient.

The boundary conditions taken were

$$r = R_{IB}; C = f(t) \quad (2.153)$$

$$r = R_{OB}; C = 0 \quad (2.154)$$

Here R_{IB} , R_{OB} represent the inner implant boundary and the maximum extent of normal liver tissue included in the model.

The initial condition was taken as

$$t = 0; C = 0 \quad (2.155)$$

The diffusion and elimination coefficients in both ablated and non-ablated tumor tissues were determined by least-squares fitting technique. *Isqcurvefit* function in MATLAB 7.1 was applied for implementation of curve fitting. In, the case of ablated tumors it was observed that the model did not yield a close fit when constant D and γ values were used. Therefore for more accurate prediction of drug transport the authors considered the diffusion coefficient to be a function of radius and elimination coefficient to be a function of time.

The RF ablation reduced the drug elimination rate from the implant and also increased the diffusion process thus providing an effective treatment. Overall the computational model provided an adequate fit for the drug release profile for ablated tumors and it was found to be a useful tool for future studies like predicting the changes in drug release profile with change in implant design and also for clinical applications.

CHAPTER 3

OBJECTIVES

Controlled release drug delivery systems (CRDDS) have several advantages over conventional dosage forms, they are able to reduce the discrepancies in the therapeutic regime by delivering the drug in a controlled manner. Mathematical modeling for such systems not only helps us in identifying the underlying transport mechanisms responsible for the drug release but also helps in reducing the number of experiments needed. In vitro and in vivo experiments are not only very expensive but in some cases they are infeasible, in such situations mathematical models can aid in reducing the number of experiments needed [75].

As seen from the discussions above, there are many models describing drug release from CRDD forms for in vitro conditions. And these models help us in recognizing the underlying drug transport mechanisms for these conditions. But when it comes to an actual biological system there are a number of parameters both physiological and physiochemical which may influence the rate of drug release. Conventional pharmacokinetic modeling is also performed taking the entire drug to be present in the system once (immediate release systems), which cannot be applicable to controlled release or extended release dosage forms [76]. As controlled release dosages are expected to stay within the system over a period of few weeks to few months, these devices may undergo number of changes which are not accounted for both in the in vitro experiments and in mathematical models developed.

The model applied by Ouriemchi [71] and other [69, 70] clearly shows that the absorption and elimination rate coefficients play a major role in the drug release process. However none of these models take into account the effect of absorption rate kinetics on rate of drug release.

The objectives of the present work are (1) to develop a mathematical model for a diffusion-dissolution controlled drug delivery system [47] and analyze the effect of absorption rate on the rate of drug release. (2) To study the effect of diffusion, drug dissolution and rate of absorption on rate of drug release. (3) Compare the models to established models [47, 51] which do not take absorption rate into account.

A closed form solution was obtained for prediction of drug released from a diffusion controlled drug delivery system taking into account the absorption kinetics [77]. This can be considered as a reduced case of the diffusion-dissolution problem. Results show that absorption rate has a significant effect on the drug release profile within the GI tract.

A numerical approach is followed to obtain the solution for a dissolution-diffusion controlled drug delivery model (including all nonlinearities). An approximate analytical solution and an asymptotic solution are also derived. Results from these models are given in the proceeding sections.

CHAPTER 4

MATHEMATICAL MODELING OF DRUG RELEASE FROM SPHERICAL MATRIX SYSTEMS: ANALYSIS OF THE AFFECT OF FINITE DISSOLUTION RATE AND ABSORPTION RATE ON THE RATE OF DRUG RELEASE

4.1 Introduction

The phenomenon of drug dissolution plays a very important role in the drug release kinetics. The drug dissolution rate has pronounced effect on the drug absorption. Noyes – Whitney equation is most commonly applied for describing the drug dissolution process. Most of the pharmacokinetic models are also developed taking into account the drug dissolution kinetics. However for the case of a CRDDS drug diffusion also plays a major role in drug release process. And in some cases the encapsulated drug dissolution can also become a rate controlling step as seen in section 2.2. Thus both drug dissolution and diffusion contribute towards the drug release process. Frenning [47] developed a model to predict the amount of drug released from a polymer matrix containing solid drug particles. Unlike the existing models the developed model accounted for the change in particle size. Thus capturing the phenomena of delayed release of the drug which is seen during the initial stage of drug release process. However, the model was developed for sink conditions and did not take into account the absorption kinetics of the drug through the GI tract. In the preceding section a new model is proposed which takes into account the diffusion-dissolution equations proposed by Frenning as well as the absorption kinetics through the GI tract.

4.2 Problem Description

Consider an encapsulated drug in a polymer matrix system. The drug is uniformly dispersed within the spherical matrix and it is in crystalline form. When the drug reaches the GI tract the fluid from the surroundings diffuses into the sphere and dissolves some of the drug. Therefore, at one point there is both dissolved and undissolved drug present within the polymer matrix. The dissolved drug then enters into the GI tract where it is eventually absorbed. Following absorption in the GI tract the drug thereby enters into the plasma compartment. The rate of absorption depends on various factors such as the amount of food present in the stomach, type of food taken, pH etc., [11]. This situation can be interpreted as an encapsulated drug matrix system of radius R and volume V_s placed in a liquid compartment of finite volume V_l . The concentration of the solid drug within the matrix is taken as S . The concentration of dissolved drug in the matrix is taken as C . The drug enters the liquid phase by the process of mass diffusion at time $t = 0$. The concentration of the drug in the liquid phase is taken as C_l . A well-stirred tank assumption is made such that C_l is independent of position. Thereby the drug is consumed by a first order absorption (Figure 4.1).

Assumptions

1. A matrix type of a system is considered wherein the drug particles are encapsulated within a polymer matrix. The entire drug is assumed to be present in solid form initially.
2. As the liquid enters the matrix, some of the drug is dissolved, and released into the compartment (simulating the GI tract) through the process of diffusion. At some point there is both dissolved and undissolved drug present within the matrix.

3. The drug releases from the polymer matrix into the GI tract. Only absorption of the drug in the GI tract is considered and the transport of the drug into the plasma compartment is not considered. Thus the effect of absorption rate on the rate of drug release in the GI tract is the only consideration.
4. Initially no drug is present in the liquid compartment.
5. When the rate of diffusion and drug dissolution are fast rate of absorption is expected to become the rate controlling step.

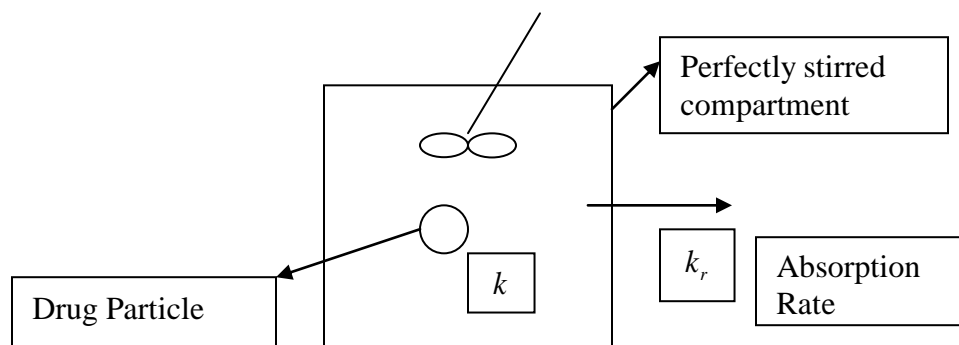


Figure 4.1 Schematic Representation of Drug Release from Dissolution Controlled Drug Delivery System in the GI Tract.

4.3 Model Development

The basic equations governing the system Equations (5.1) and (5.2) were originally introduced by Frenning [47]. The same nomenclature has been retained. The first term on the RHS of Equation (4.1) accounts for the diffusion of the dissolved drug and the second term accounts for the dissolution of solid drug particles.

$$\frac{\partial C}{\partial t} = D_{AB} \left(\frac{\partial^2 C}{\partial r^2} + \frac{2}{r} \frac{\partial C}{\partial r} \right) + k \left(\frac{S}{S_0} \right)^{\frac{2}{3}} (C_s - C) \quad (4.1)$$

$$\frac{\partial S}{\partial t} = -k \left(\frac{S}{S_0} \right)^{\frac{2}{3}} (C_s - C) \quad (4.2)$$

Surface boundary condition subject to absorption in the GI tract is treated here as:

$$-\left(\frac{3}{R} \right) V_s D_{AB} \left(\frac{\partial C}{\partial r} \right)_{r=R} = V_l \frac{dC_l}{dt} + V_l k_r C_l \quad (4.3)$$

Boundary conditions:

$$C(r,0) = 0 \quad (4.4)$$

$$C_l(0) = 0 \quad (4.5)$$

$$C = KC_l \quad \text{at} \quad r = R \quad (4.6)$$

$$C(0,t) \text{ is finite Or } \left(\frac{\partial C}{\partial r} \right)_{r=0} = 0 \quad (4.7)$$

Equations (4.1)-(4.7) are converted into dimensionless form using the following dimensionless variables:

$$\text{Dimensionless concentration of undissolved (solid) drug } \theta_s = \frac{S}{S_0} \quad (4.8)$$

$$\text{Dimensionless concentration of dissolved drug } \theta = \frac{C}{S_0} \quad (4.9)$$

Dimensionless concentration of dissolved drug present in the liquid compartment

$$\theta_l = \frac{C_l K_p}{S_0} \quad (4.10)$$

$$\text{Dimensionless solubility: } \bar{\theta} = \frac{C_s}{S_0} \quad (4.11)$$

$$\text{Dimensionless time: } \tau = \frac{D_{AB} t}{R^2} \quad (4.12)$$

$$\text{Dimensionless radial coordinate: } \xi = \frac{r}{R} \quad (4.13)$$

$$B = \frac{V_l}{V_s K_p} \quad (4.14)$$

$$N = \frac{kR^2}{D_{AB}} \quad (4.15)$$

$$M = \frac{k_r R^2}{D_{AB}} \quad (4.16)$$

Equations (4.1)-(4.3) in dimensionless form are given by:

$$\frac{\partial \theta}{\partial \tau} = \left(\frac{\partial^2 \theta}{\partial \xi^2} + \frac{2}{\xi} \frac{\partial \theta}{\partial \xi} \right) + N \theta_s^{\frac{2}{3}} (\bar{\theta} - \theta) \quad (4.17)$$

Provided that the particles are of the same size initially and retain their shape during the dissolution process the surface area of the undissolved drug is proportional to the volume.

Hence θ_s power 2/3 [47]. This assumption has been previously used to describe the dissolution of dispersed material [43, 44].

$$\frac{\partial \theta_s}{\partial \tau} = -N \theta_s^{\frac{2}{3}} (\bar{\theta} - \theta) \quad (4.18)$$

$$-\left(\frac{3}{B} \right) \left(\frac{\partial \theta}{\partial \xi} \right)_{\xi=1} = \frac{d\theta_l}{d\tau} + M \theta_l \quad (4.19)$$

The boundary conditions in dimensionless form are given as:

$$\theta(\xi, 0) = 0 \quad (4.20)$$

$$\theta(1, \tau) = \theta_l(\tau) \quad (4.21)$$

$$\theta_s(\xi, 0) = 1 \quad (4.22)$$

$$\theta_l(0) = 0 \quad (4.23)$$

$$\left(\frac{\partial \theta}{\partial \xi}\right)_{\xi=0} = 0 \quad (4.24)$$

4.4 Approximate Semi Analytical Solution

Equations (4.18)-(4.19) form a non linear problem which has to be solved using numerical methods. However by making some approximations a semi analytical solution can be obtained. It is beneficial to get an approximate solution as the drug concentration profiles obtained from both the numerical and approximate solutions can be compared. This will help us in gauging the accuracy of the numerical solution. Equations (4.18) and (4.19) which have the non linear term have to be linearized using making some approximations. The approach followed is very similar to that of Frenning's [47]. **However, it should be noted that in his work Frenning neither considered the accumulation of the drug nor the effect of absorption rate. His model was developed for perfect sink conditions and the Equations for obtaining Eigen values were much simpler than the problem described in section. An approximate solution can be obtained by considering only the initial stages of drug release.**

The following approximation can be made during early stages of drug release [47].

$$U = 1 - \theta_s \quad (4.25)$$

From the initial condition of Equations (4.1) and (4.2) it can be concluded that both θ and U are equal to zero initially. And hence are $\ll 1$. Therefore during early stages of release $U \ll 1$. Now θ_s can be written in terms of U as:

$$\theta_s^{\frac{2}{3}} = (1 - U)^{\frac{2}{3}} \cong 1 - \frac{2}{3}U \quad (4.26)$$

Therefore equations (4.17) and (4.18) become:

$$\frac{\partial \theta}{\partial \tau} = \left(\frac{\partial^2 \theta}{\partial \xi^2} + \frac{2}{\xi} \frac{\partial \theta}{\partial \xi} \right) + \left(1 - \frac{2}{3} U \right) (\bar{\theta} - \theta) N \quad (4.27)$$

$$\begin{aligned} -\frac{\partial U}{\partial \tau} &= -N(\bar{\theta} - \theta) \left(1 - \frac{2}{3} U \right) (\bar{\theta} - \theta) \\ &= -N(\bar{\theta} - \theta) + N\bar{\theta} \frac{2}{3} U + N\theta \frac{2}{3} U \end{aligned} \quad (4.28)$$

Keeping only the linear terms we get:

$$\frac{\partial U}{\partial \tau} = N(\bar{\theta} - \theta) - (\alpha U) \quad (4.29)$$

$$\text{Where } \alpha = \frac{2}{3} N\bar{\theta} \quad (4.30)$$

An equation (4.27) becomes:

$$\frac{\partial \theta}{\partial \tau} = \left(\frac{\partial^2 \theta}{\partial \xi^2} + \frac{2}{\xi} \frac{\partial \theta}{\partial \xi} \right) + (\bar{\theta} - \theta) N - \alpha U \quad (4.31)$$

Applying the Laplace transform method Equations (4.17) and (4.18) become:

$$s u(\xi, s) - u(\xi, 0) = \left(\frac{d^2 u(\xi, s)}{d\xi^2} + \frac{2}{\xi} \frac{du(\xi, s)}{d\xi} \right) - \alpha U \quad (4.32)$$

$$s \tilde{U} - \tilde{U}(\xi, 0) = N \left(\frac{\bar{\theta}}{s} - u(\xi, s) \right) - \alpha U \quad (4.33)$$

Using the boundary condition $\theta_s(\xi, 0) = 1$ and eliminating \tilde{U} we get

$$\frac{d^2 u}{d\xi^2} + \frac{2}{\xi} \frac{du}{d\xi} - u \left(\frac{s(s + \alpha + N)}{s + \alpha} \right) = -N \left(\frac{\bar{\theta}}{s + \alpha} \right) \quad (4.34)$$

$$\text{Where } \lambda^2 = \frac{s(s + \alpha + M)}{(s + \alpha)} \quad (4.35)$$

Substituting $q = \xi u(\xi, s)$ into Equation (4.80) results in

$$\left(\frac{d^2 q}{d\xi^2}\right) - q(\lambda^2) = -N\left(\frac{\bar{\theta}}{s + \alpha}\right)\xi \quad (4.36)$$

$$\text{Say } \beta = -N\left(\frac{\bar{\theta}}{s + \alpha}\right) \quad (4.37)$$

Then Equation (4.82) can be written as

$$\left(\frac{d^2 q}{d\xi^2}\right) - q(\lambda^2) = \beta\xi \quad (4.38)$$

The characteristic equation of the above Equation is given as

$$\frac{d^2}{d\xi^2} \left(\frac{d^2 q}{d\xi} - \lambda^2 q \right) = 0 \quad (4.39)$$

The solution for this equation is given as

$$q(\xi) = a_1 + a_2 \xi + a_3 \cosh \lambda \xi + a_4 \sinh \lambda \xi \quad (4.40)$$

$$q'(\xi) = a_2; q''(\xi) = 0 \quad (4.41)$$

$$-\lambda^2 (a_1 + a_2 \xi) = \beta \xi \quad (4.42)$$

$$a_2 = -\frac{\beta}{\lambda^2} \quad (4.43)$$

$$a_1 = 0 \quad (4.44)$$

$$q(\xi) = -\frac{\beta}{\lambda^2} \xi + a_3 \cosh \lambda \xi + a_4 \sinh \lambda \xi \quad (4.45)$$

Therefore

$$u(\xi, s) = \frac{q}{\xi} = -\frac{\beta}{\lambda^2} + a_3 \frac{\cosh \lambda \xi}{\xi} + a_4 \frac{\sinh \lambda \xi}{\xi} \quad (4.46)$$

By substituting the boundary condition $u(0, s) = 0$ we get $a_3 = 0$.

By applying the boundary condition $u(1, s) = v(s)$ we get

$$v(s) = a_4 \sinh \lambda - \frac{\beta}{\lambda^2} \quad (4.47)$$

$$\text{Therefore } a_4 = \frac{v(s) + \frac{\beta}{\lambda^2}}{\sinh \lambda} \quad (4.48)$$

Applying Laplace transform method to Equation (4.19) we get

$$-\left(\frac{3}{B}\right)\left(\frac{du}{d\xi}\right)_{\xi=1} = v(s)(M + s) \quad (4.49)$$

Differentiating Equation (4.49) we get

$$\frac{du}{d\xi} = a_4 \left[\frac{\lambda \xi \cosh \lambda \xi - \sinh \lambda \xi}{\xi^2} \right] \quad (4.50)$$

$$\left(\frac{du}{d\xi}\right)_{\xi=1} = a_4 [\lambda \cosh \lambda - \sinh \lambda] \quad (4.51)$$

Substituting for a_4 from Equation (4.51) we get:

$$\left(\frac{du}{d\xi}\right)_{\xi=1} = \frac{\left(v(s) + \frac{\beta}{\lambda^2}\right)(\lambda \cosh \lambda - \sinh \lambda)}{\sinh \lambda} \quad (4.52)$$

$$-\left(\frac{B}{3}\right)v(s)(M + s) = \left[\frac{v(s)(\lambda \cosh \lambda - \sinh \lambda)}{\sinh \lambda} + \frac{\beta[\lambda \cosh \lambda - \sinh \lambda]}{\lambda^2 \sinh \lambda} \right] \quad (4.53)$$

$$-\frac{\beta[\lambda \cosh \lambda - \sinh \lambda]}{\lambda^2 \sinh \lambda} = \left[\frac{v(s)(\lambda \cosh \lambda - \sinh \lambda)}{\sinh \lambda} + \left(\frac{B}{3}\right)v(s)(M + s) \right] \quad (4.54)$$

$$v(s) = -\frac{\beta(\lambda \operatorname{Cosh} \lambda - \operatorname{Sinh} \lambda)}{\lambda^2 \operatorname{Sinh} \lambda \left[\frac{(\lambda \operatorname{Cosh} \lambda - \operatorname{Sinh} \lambda)}{\operatorname{Sinh} \lambda} + \left(\frac{B}{3}\right)(M+s) \right]} \quad (4.55)$$

$$v(s) = -\frac{\beta(\lambda \operatorname{Cosh} \lambda - \operatorname{Sinh} \lambda)}{\lambda^2 \left[(\lambda \operatorname{Cosh} \lambda - \operatorname{Sinh} \lambda) + \left(\frac{B}{3}\right)(M+s) \operatorname{Sinh} \lambda \right]} \quad (4.56)$$

$$v(s) = -\frac{\beta(\lambda \cosh \lambda - \sinh \lambda)}{\lambda^2 \left[(\lambda \cosh \lambda) + \left(\frac{B}{3}\right)(M+s-1) \sinh \lambda \right]} \quad (4.57)$$

$$v(s) = \frac{-\beta \left[\left(1 + \frac{\lambda^2}{2!} - \frac{\lambda^4}{4!} + \dots \right) - \left(\lambda + \frac{\lambda^3}{3!} + \frac{\lambda^5}{5!} + \dots \right) \right]}{\left\{ \lambda^2 \left[\lambda \left(1 + \frac{\lambda^2}{2!} + \frac{\lambda^4}{4!} + \dots \right) + \left(\frac{B}{3}\right) (M+s-1) \left(\lambda + \frac{\lambda^2}{3!} + \frac{\lambda^4}{5!} + \dots \right) \right] \right\}} \quad (4.58)$$

On rearranging we get

$$v(s) = \frac{-\beta \left[\left(\frac{1}{2!} - \frac{1}{3!} \right) \lambda^2 + \left(\frac{1}{4!} - \frac{1}{5!} \right) \lambda^4 + \dots \right]}{\left\{ \lambda^2 \left[\left(1 + \frac{\lambda^2}{2!} + \frac{\lambda^4}{4!} + \dots \right) + \left(\frac{B}{3}\right) (M+s-1) \left(1 + \frac{\lambda^2}{3!} + \frac{\lambda^4}{5!} + \dots \right) \right] \right\}} \quad (4.59)$$

Substituting back for β we get

$$v(s) = \frac{N \left(\frac{\bar{\theta}}{s+\alpha} \right) \left[\left(\frac{1}{2!} - \frac{1}{3!} \right) \lambda^2 + \left(\frac{1}{4!} - \frac{1}{5!} \right) \lambda^4 + \dots \right]}{\left\{ \lambda^2 \left[\left(1 + \frac{\lambda^2}{2!} + \frac{\lambda^4}{4!} + \dots \right) + \left(\frac{B}{3}\right) (M+s-1) \left(1 + \frac{\lambda^2}{3!} + \frac{\lambda^4}{5!} + \dots \right) \right] \right\}} \quad (4.60)$$

$$v(s) = \frac{N\bar{\theta} \left[\left(\frac{1}{2!} - \frac{1}{3!} \right) \lambda^2 + \left(\frac{1}{4!} - \frac{1}{5!} \right) \lambda^4 + \dots \right]}{\left\{ (s(s + \alpha + N)) \left[\left(1 + \frac{\lambda^2}{2!} + \frac{\lambda^4}{4!} + \dots \right) + \left(\frac{B}{3} \right) \left((M + s - 1) \left(1 + \frac{\lambda^2}{3!} + \frac{\lambda^4}{5!} + \dots \right) \right) \right] \right\}} \quad (4.61)$$

Using the residue theorem [37] for carrying out the Laplace inversion Let:

$$v(s) = \frac{P(s)}{Q(s)} \quad (4.62)$$

$$\text{So that } \theta_l(\tau) = L^{-1} \{v(s)\} = \sum_{n=0}^{\infty} \rho_n(\tau) \quad (4.63)$$

$$\text{Where } P(s_n) = N\bar{\theta} \left[\left(\frac{1}{2!} - \frac{1}{3!} \right) \lambda^2 + \left(\frac{1}{4!} - \frac{1}{5!} \right) \lambda^4 + \dots \right] \quad (4.64)$$

$$Q(s) = \left\{ (s(s + \alpha + N)) \left[\left(1 + \frac{\lambda^2}{2!} + \frac{\lambda^4}{4!} + \dots \right) + \left(\frac{B}{3} \right) \left((M + s - 1) \left(1 + \frac{\lambda^2}{3!} + \frac{\lambda^4}{5!} + \dots \right) \right) \right] \right\} \quad (4.65)$$

Since $s = 0$ is a simple pole of $v(s)$ the residue is given by:

$$\rho_0(\tau) = \lim_{s \rightarrow 0} \left(\frac{N\bar{\theta} \left[\left(\frac{1}{2!} - \frac{1}{3!} \right) \frac{s(s + \alpha + N)}{s + \alpha} + \left(\frac{1}{4!} - \frac{1}{5!} \right) \left(\frac{s(s + \alpha + N)}{s + \alpha} \right)^2 + \dots \right]}{\left\{ (s)(s + \alpha + N) \left[\left(1 + \frac{s + \alpha}{2!} + \dots \right) + \left(\frac{B}{3} \right) \left((M + s - 1) \left(1 + \frac{s + \alpha}{3!} + \dots \right) \right) \right] \right\}} \right) \quad (4.66)$$

And the residue at $s = -(\alpha + N)$ is given by:

$$\rho_1(\tau) = \lim_{s \rightarrow -(\alpha + N)} \left(\frac{N\bar{\theta} \left[\left(\frac{1}{2!} - \frac{1}{3!} \right) \frac{s(s + \alpha + N)}{s + \alpha} + \left(\frac{1}{4!} - \frac{1}{5!} \right) \left(\frac{s(s + \alpha + N)}{s + \alpha} \right)^2 + \dots \right]}{\left\{ (s)(s + \alpha + N) \left[\left(1 + \frac{s + \alpha}{2!} + \dots \right) + \left(\frac{B}{3} \right) \left((M + s - 1) \left(1 + \frac{s + \alpha}{3!} + \dots \right) \right) \right] \right\}} \right) \quad (4.67)$$

Which yield $\rho_0, \rho_1 = 0$

For $s_n \neq 0, n \geq 1$

$$\rho_n = \frac{P(s)}{Q(s)} \text{Exp}\{-\lambda^2 \tau\} \quad (4.68)$$

$$\text{Let } \lambda = i\sqrt{\mu} \Rightarrow -\lambda^2 = \mu \quad (4.69)$$

By setting the denominator of Equation (4.57) to zero we get the Eigen value as:

$$\text{Tanh}[\lambda] = \frac{3\lambda}{3 - B(M + s)} \quad (4.70)$$

As it can be seen the above Equation is in implicit form. The s term is recast in terms of lambda. To compute the final fraction of drug released $Q'(s)$ is calculated as follows:

$$Q'(s) = s \left((\lambda) \text{Cos}[\lambda] + \frac{B(M + s) - 3}{3} \text{Sin}[\lambda] \right) + (N + s + \alpha) \left((\lambda) \text{Cos}[\lambda] + \frac{B(M + s) - 3}{3} \text{Sin}[\lambda] \right) + \frac{(s + N + \alpha)}{6} \left(\left(\frac{3(s^2 + 2s\alpha + \alpha(N + \alpha)) \text{Cos}[\lambda]}{(s + \alpha)^2 \lambda} \right) + \frac{B(M + s) - 3(s^2 + 2s\alpha + \alpha(N + s)) \text{Cos}[\lambda]}{(s + \alpha)^2 \lambda} + 2B \text{Sin}[\lambda] - \frac{3(s^2 + 2s\alpha + \alpha(N + \alpha)) \text{Sin}[\lambda]}{(s + \alpha)^2} \right) \quad (4.71)$$

Substituting back for P(s) and Q(s) in Equation (4.68) we get the fraction of drug released as:

$$\theta_i(\tau) = \sum_{n=1}^{\infty} \frac{N\bar{\theta}(\lambda \text{Cos}[\lambda] - \text{Sin}[\lambda]) \text{Exp}[s_n \tau]}{s \left((\lambda) \text{Cos}[\lambda] + \frac{B(M + s) - 3}{3} \text{Sin}[\lambda] \right) + (N + s + \alpha) \left((\lambda) \text{Cos}[\lambda] + \frac{B(M + s) - 3}{3} \text{Sin}[\lambda] \right) + \frac{(s + N + \alpha)}{6} \left(\left(\frac{3(s^2 + 2s\alpha + \alpha(N + \alpha)) \text{Cos}[\lambda]}{(s + \alpha)^2 \lambda} \right) + \frac{B(M + s) - 3(s^2 + 2s\alpha + \alpha(N + s)) \text{Cos}[\lambda]}{(s + \alpha)^2 \lambda} + 2B \text{Sin}[\lambda] - \frac{3(s^2 + 2s\alpha + \alpha(N + \alpha)) \text{Sin}[\lambda]}{(s + \alpha)^2} \right)} \quad (4.72)$$

4.5 Results and Discussions

Fraction of drug released into the liquid compartment is computed using Equation (4.72). By changing the parameter values (in Equation (4.72)) effect of absorption rate, dissolution rate and solubility on rate of drug released can be analyzed. The corresponding Eigen values can be computed using Equation (4.70). Equation (4.35) gives the relation between s and λ , for every λ_n value we get two values for s_n one positive and one negative. Both the values were incorporated into Equation (4.72) for computing the fraction of drug released. The drug release profiles are computed and discussed in chapter 8. The semi analytical results are also compared with the numerical results.

CHAPTER 5

MATHEMATICAL MODELING OF DRUG RELEASE FROM SPHERICAL MATRIX SYSTEMS: ANALYSIS OF THE AFFECT OF DIFFUSION RATE AND ABSORPTION RATE ON RATE OF DRUG RELEASE

5.1 Introduction

The dissolution term in Equation (4.1) is only valid as long as there is solid drug present. When the concentration of the dispersed drug within the matrix is very small an assumption of instantaneous dissolution can be made. So the second term in the Equation (4.1) is dropped and only the diffusion term is considered. Now the problem at hand becomes drug release from a diffusion controlled drug delivery system.

5.2 Problem statement

Consider an encapsulated drug in a polymer matrix system. When administered orally the drug reaches the GI tract where it is released and eventually absorbed. Following absorption in the GI tract the drug enters the plasma compartment. The rate of absorption depends on various factors such as the amount of food present in the stomach, type of food taken, pH etc., [11]. This situation can be interpreted as an encapsulated drug matrix system of radius R and volume V_s placed in a liquid compartment of finite volume V_l . The concentration of the drug is C . The drug enters the liquid phase by the process of mass diffusion at time $t = 0$. The concentration of the drug in the liquid phase is taken as C_l . A well- stirred tank assumption is made such that C_l is independent of position. Thereby the drug is consumed by a first order absorption (Figure 4.2).

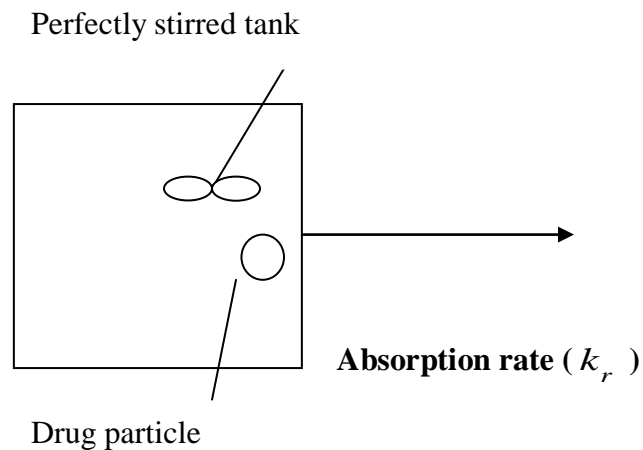


Figure 5.1 Schematic representation of drug release from diffusion controlled drug delivery System in the GI Tract.

Assumptions

1. A matrix type of a system is considered wherein the drug particles are encapsulated within a polymer matrix. The liquid from the compartment enters the polymer matrix, dissolving the drug within the matrix instantaneously thus enabling it to release.
2. The process of drug release from the spherical matrix into the finite reservoir (simulating the GI tract) is assumed to be controlled by diffusion.
3. The drug releases from the polymer matrix into the GI tract. Only absorption of the drug in the GI tract is considered and the transport of the drug into the plasma compartment is not considered. Thus the effect of absorption rate on the rate of drug release in the GI tract is the only consideration.
4. The radius of the drug particles is assumed to remain constant during the release process and in this model is appropriate for small particles (micro and nano).
5. The drug is assumed to release with a constant diffusivity.
6. Initially there is no drug present in the compartment.

5.3 Model Development

For a spherical drug particle, the drug concentration is given by:

$$\frac{\partial C}{\partial t} = \left(\frac{\partial^2 C}{\partial r^2} + \frac{2}{r} \frac{\partial C}{\partial r} \right) \quad (5.1)$$

where D_{AB} is the diffusivity of the drug in the matrix.

A material balance of the drug in the liquid results in:

$$-\frac{3}{R} V_s D_{AB} \left(\frac{\partial C}{\partial r} \right)_{r=R} = V_l \frac{dC_l}{dt} + V_l k_r C_l \quad (5.2)$$

where k_r is a first order absorption rate coefficient.

If one were to assume that equilibrium exists at the solid-liquid interface, then at $r = R$ and any time t :

$$C_s = K C_l \quad (5.3)$$

where K is the equilibrium constant.

The initial and boundary conditions governing Equation (4.25) are:

$$C(r,0) = C_1 \quad (5.4)$$

$$C_l(0) = 0 \quad (5.5)$$

$$C(0,t) \text{ is finite.} \quad (5.6)$$

Dimensionless variables used:

We proceed by first transforming the model (Equations (5.1)-(5.6)) into dimensionless form using the following scale factors:

for the dimensionless concentration in the solid we have:

$$\theta(\xi, \tau) = \left(\frac{C_1 - C}{C_1} \right) \quad (5.7)$$

for the dimensionless concentration in liquid

$$\theta_l = \frac{C_1 - C_l K}{C_1} \quad (5.8)$$

Dimensionless radius

$$\xi = \frac{r}{R} \quad (5.9)$$

Dimensionless time

$$\tau = \frac{D_{AB} t}{R^2} \quad (5.10)$$

The quantities B and M are defined as:

$$B = \frac{V_l}{V_s K} \quad (5.11)$$

$$M = \frac{k_r R^2}{D_{AB}} \quad (5.12)$$

By making use of these dimensionless quantities Equation (5.1) becomes:

$$\frac{\partial \theta}{\partial \tau} = \frac{\partial^2 \theta}{\partial \xi^2} + \frac{2}{\xi} \frac{\partial \theta}{\partial \xi} \quad (5.13)$$

Subject to the dimensionless boundary conditions

$$\theta(\xi, 0) = 0 \quad (5.14)$$

$$\theta(0, \tau) \text{ is finite} \quad (5.15)$$

$$\theta(1, \tau) = \theta_l(\tau) \quad (5.16)$$

$$\theta_l(0) = 0 \quad (5.17)$$

While Equation (5.2) becomes

$$-\frac{3}{B} \left(\frac{\partial \theta}{\partial \xi} \right)_{\xi=1} = \frac{d\theta_l}{d\tau} + M\theta_l - M \quad (5.18)$$

5.4 Method of Solution

A Laplace transform method [37] is used to solve Equations (4.36)-(4.41).

$$\text{Let } L\{\theta(\xi, \tau)\} = \int \theta(\xi, \tau) e^{-s\tau} d\tau = u(\xi, s) \text{ and } L\{\theta_l(\tau)\} = v(s) \quad (5.19)$$

Equation (5.13) then transforms into

$$s u = \frac{d^2 u}{d\xi^2} + \frac{2}{\xi} \frac{du}{d\xi} \quad (5.20)$$

Subject to the following conditions

$$u(0, s) \text{ is finite} \quad (5.21)$$

$$u(1, s) = v(s) \quad (5.22)$$

The General solution for Equation (4.43) is given as:

$$u(\xi, s) = m_1 \xi^{-\frac{1}{2}} J_{1/2}(i\sqrt{s}\xi) + m_2 \xi^{-\frac{1}{2}} J_{-1/2}(i\sqrt{s}\xi) \quad (5.23)$$

$$\text{Where } J_{1/2}(i\sqrt{s}\xi) = \sqrt{\frac{2}{\pi x}} \sin(i\sqrt{s}\xi) \text{ and } J_{-1/2}(i\sqrt{s}\xi) = \sqrt{\frac{2}{\pi x}} \cos(i\sqrt{s}\xi) \quad (5.24)$$

Applying the condition that the solution is bounded such that m_2 must be chosen as zero

in order for $u(\xi, s)$ to remain finite as $\xi \rightarrow 0$. This results in the solution:

$$u(\xi, s) = m_1 \sqrt{\frac{2}{\pi}} \frac{\sin(i\sqrt{s}\xi)}{\xi} \quad (5.25)$$

$$\text{At } \xi = 1; u(1, s) = m_1 \sqrt{\frac{2}{\pi}} \sin(i\sqrt{s}) = v(s) \quad (5.26)$$

Therefore $m_1 = \frac{v(s)}{\sqrt{\frac{2}{\pi}} \sin(i\sqrt{s})}$ (5.27)

Application of Laplace transform to Equation (4.41) results in:

$$-\frac{3}{B} \left(\frac{du}{d\xi} \right)_{\xi=1} = -(sv(s) - \theta_l(0)) - Mv(s) + \frac{M}{s} \quad (5.28)$$

Substituting Equations (4.28) into Equation (4.26) results in:

$$\frac{3m_1}{B} \sqrt{\frac{2}{\pi}} \left\{ -\sin(i\sqrt{s}) + i\sqrt{s} \cos(i\sqrt{s}) \right\} = -sv(s) + \theta_l(0) - Mv(s) + \frac{M}{s} \quad (5.29)$$

and substituting for m_1 from Equation (5.29) and carrying out the appropriate algebraic manipulations we get:

$$v(s) = \frac{[s\theta_l(0) + M] \frac{B}{3} \sin(i\sqrt{s})}{\left\{ i\sqrt{s} \cos(i\sqrt{s}) - \sin(i\sqrt{s}) + (s + M) \frac{B}{3} \sin(i\sqrt{s}) \right\} s} \quad (5.30)$$

Or
$$v(s) = \frac{[s\theta_l(0) + M] \frac{B}{3}}{\left\{ i\sqrt{s} \cot(i\sqrt{s}) - 1 + (s + M) \frac{B}{3} \right\} s} \quad (5.31)$$

Also Equation (5.25) becomes:

$$u(\xi, s) = \frac{[s\theta_l(0) + M] \frac{B}{3} \frac{\sin(i\sqrt{s}\xi)}{\xi}}{s \left\{ i\sqrt{s} \cos(i\sqrt{s}) - \sin(i\sqrt{s}) + (s + M) \frac{B}{3} \sin(i\sqrt{s}) \right\}} \quad (4.32)$$

Using the residue theorem [37] for carrying out the Laplace inversion let:

$$v(s) = \frac{P(s)}{Q(s)} \quad (5.33)$$

$$\text{So that } \theta_l(\tau) = L^{-1} \{v(s)\} = \sum_{n=0}^{\infty} \rho_n(\tau) \quad (5.34)$$

$$\text{Where } P(s_n) = [s\theta_l(0) + M] \frac{B}{3} \quad (5.35)$$

$$Q(s_n) = \left\{ i\sqrt{s} \cot(i\sqrt{s}) - 1 + (s + M) \frac{B}{3} \right\} s \quad (5.36)$$

Since $s = 0$ is a simple pole of $v(s)$ the residue is given by:

$$\rho_0(\tau) = \lim_{s \rightarrow 0} \frac{[s\theta_l(0) + M] \frac{B}{3}}{\left\{ i\sqrt{s} \cot(i\sqrt{s}) - 1 + (s + M) \frac{B}{3} \right\}} = 1 \quad (5.37)$$

$$\text{Since } \cot x = \frac{1}{x} - \frac{x}{3} - \frac{x^3}{45} - \dots \quad (5.38)$$

$$\text{Then } x \cot x \rightarrow 1 \text{ as } x \rightarrow 0 \quad (5.39)$$

$$\text{Therefore } \rho_0(\tau) = 1 \quad (5.40)$$

For $s_n \neq 0, n \geq 1$

$$\left\{ i\sqrt{s} \cot(i\sqrt{s_n}) - 1 + (s_n + M) \frac{B}{3} \right\} = 0 \quad (5.41)$$

Equation (5.41) can be further rearranged to give the form:

$$\tan(i\sqrt{s}) = \frac{-3i\sqrt{s}}{(s_n + M)B - 3} = \frac{3i\sqrt{s_n}}{(-M - s_n)B + 3} \quad (5.42)$$

The Eigen values, λ_n can be defined as

$$\tan(\lambda_n) = \frac{3\lambda_n}{(\lambda_n^2 - M)B + 3} \quad (5.43)$$

Where $\lambda_n = i\sqrt{s_n} \Rightarrow s_n = -\lambda_n^2$ is the transformation

The quantity $Q'(s_n)$ is derived from Equation (5.41) as

$$Q'(s) = \left(\frac{1}{2} + \frac{B}{3}\right)s \sin(i\sqrt{s}) + (s+M) \frac{B}{3} \frac{i\sqrt{s} \cos(i\sqrt{s})}{2} \quad (5.44)$$

In terms of the real variable, λ_n

$$Q'(s_n) = -\lambda_n^2 \left(\frac{1}{2} + \frac{B}{3}\right) \sin \lambda_n + (-\lambda_n^2 + M) \frac{B}{6} \lambda_n \cos \lambda_n \quad (5.45)$$

Therefore, the dimensionless liquid concentration profile is given by:

$$\theta_l(\tau) = L^{-1}\{v(s)\} = 1 + \sum_{n=1}^{\infty} \frac{[-\lambda_n^2 \theta_l(0) + M] \frac{B}{3} \sin(\lambda_n) e^{-\lambda_n^2 \tau}}{\left\{ -\lambda_n^2 \left(\frac{1}{2} + \frac{B}{3}\right) \sin(\lambda_n) + (-\lambda_n^2 + M) \frac{B}{6} \lambda_n \cos(\lambda_n) \right\}} \quad (5.46)$$

$$= 1 + \sum_{n=1}^{\infty} \frac{6[M - \lambda_n^2 \theta_l(0)] B e^{-\lambda_n^2 \tau}}{\left\{ B(M - \lambda_n^2)[(\lambda_n^2 - M)B + 3] - 3\lambda_n^2(3 + 2B) \right\}} \quad (5.47)$$

5.5 Results and Discussion

Using Equation (5.47) the fraction of drug released in the liquid compartment can be calculated. All the parameter values such as diffusion coefficient, volume of drug, radius of the spherical drug particles, are taken for lidocaine release from PLGA biodegradable spherical particles Polakovic et.al. [50]. The Eigenvalues given by equation (5.43) were determined using the FindRoot function in Mathematica[®] (Wolfram, 1996). The parameter M accounts for the effect of the absorption constant.

Gorner et.al, [78] studied the lidocaine release from small nanosized drug particles with low percentages of drug loadings. The authors reported that no biodegradation of the polymer occurred over the observed period of time. The drug release was monitored over a period of 4 days. To benchmark our model, the model predicted drug release profiles were compared with the experimental data (provided by Prof. Polakovic).

Figures 5.2 and 5.3 compare the drug release profiles between the in vitro experimental data, diffusion only model and the proposed model; for 6.5 % (w/w) and 8.5 % (w/w) lidocaine loaded nanospheres. From Figure 5.2, one can observe that the diffusion model over predicts the experimental release profile by about 25%; while the largest difference between the proposed model and the experimental data occurs much later in the release and is under predicting the profile there by about 14%.

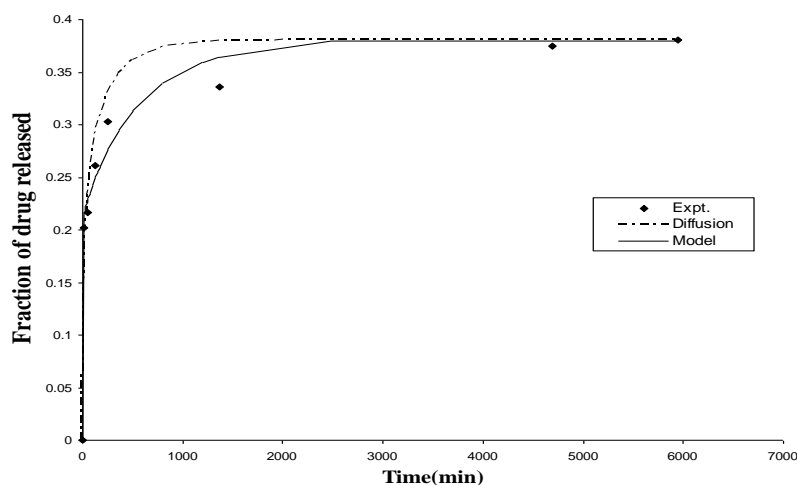


Figure 5.2 Drug release for a loading of 6.5 % (w/w).

In the case of Figure 5.2, the difference increases to 35% under prediction for the diffusion only case whereas the proposed model yields about a 9% difference.

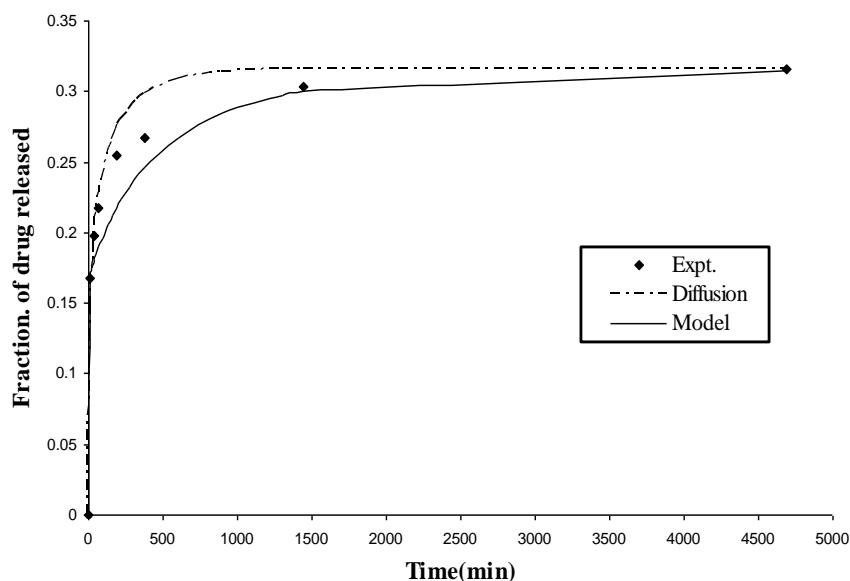


Figure 5.3 Drug release for a loading of 8.4 % (w/w).

Though, it is stated in the literature that the absorption and distribution of lidocaine is relatively fast [79] there are various factors that can affect the absorption kinetics. Although oral delivery is not the most popular method for lidocaine admission there are a few studies in the literature for oral absorption of lidocaine [80]. Adjepon-Yamoah, K. K., et al. [81], studies the effect of presence of atropine in the system on the absorption rate of orally administered lidocaine while Isohanni N.H., et al. [82] studied the effect of fluvoxamine and erythromycin on the pharmacokinetics of orally administered lidocaine. Therefore it is sufficient to consider the effect of different absorption rates on the lidocaine release rate. Since the drug dissolution is assumed to be very quick

(instantaneous) therefore when absorption rate is very slow it becomes the rate controlling step.

Three values of absorption rate constants were considered one high ($2k$) value, a medium value (k) which is about 1h^{-1} [79]) and a low value ($k/2$) to see its affect on drug release (Figures 5.4 and 5.5). In Figure 5.4 the solid line represents the calculated fraction of drug release taking into account an arbitrary value of the absorption rate constant, the dashed line represents the diffusion only model and the diamond dots represent the a doubling of the arbitrary k_r value. It can be seen from Figure 5.4 that for fast absorption rate there is virtually no difference between a diffusion only model and a model taking into account the absorption rate constant.

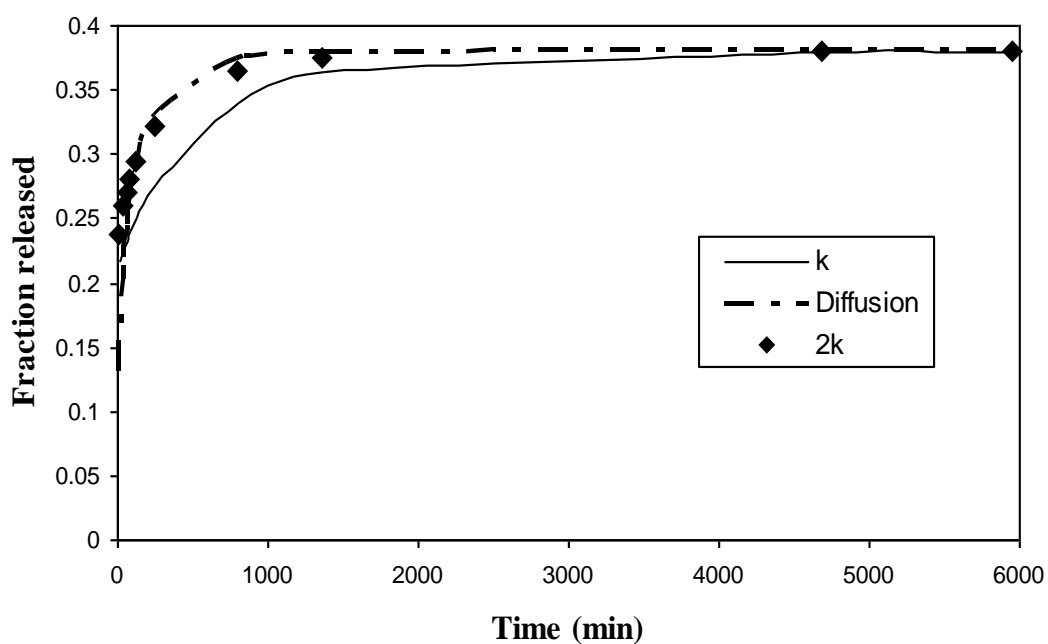


Figure 5.4 Drug Release for Fast Absorption Rate.

In Figure 5.5 the solid line represents the calculated value of drug release taking into account an arbitrary (same as in Figure 5.4) value of absorption rate constant, and the diamond dots represent a halving of the arbitrary k_r value. It appears that when the absorption rate is slowed to half of the comparative standard, the drug release profile is markedly different from that exhibited by the diffusion only model.

This suggests that during the mass transfer of the drug into the GI tract, the overall rate of mass transfer is sensitive to the rate of absorption of the drug in the GI tract. Specifically, if the absorption rate is relatively fast then its effect on the overall rate of mass transfer is negligible. However if the absorption rate is relatively slow the overall rate of mass transfer to the GI tract will be significantly reduced.

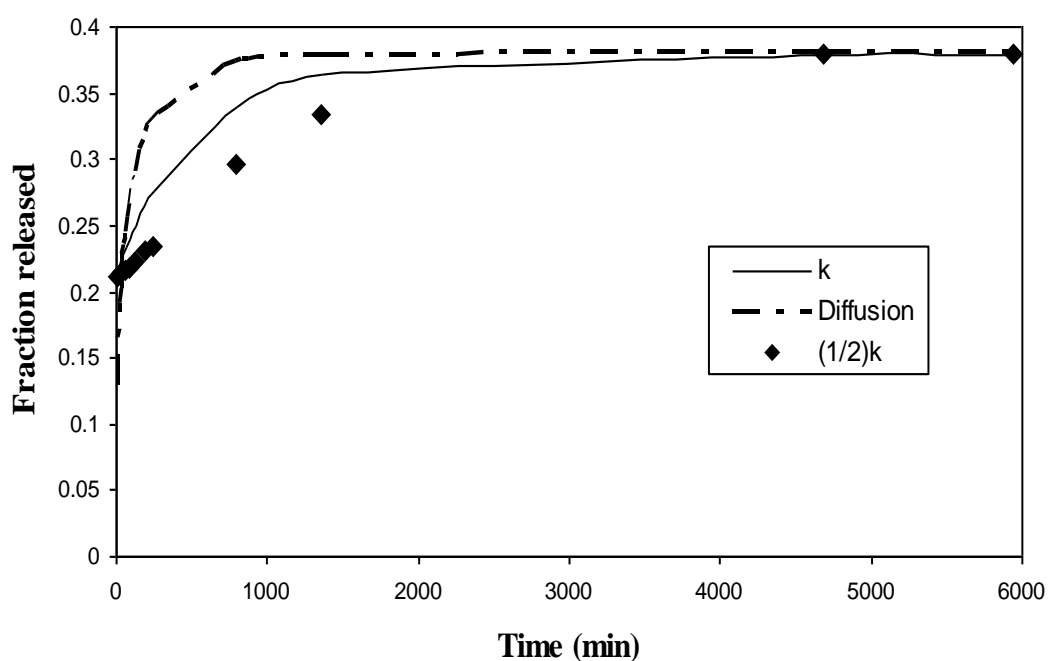


Figure 5.5 Drug Release for Slow Absorption Rate.

5.6 Conclusions

The fraction of drug released in the liquid compartment was obtained from the model. There is significant difference between the release profiles calculated using a diffusion only model and a diffusion model accounting for the effect of absorption. Therefore the rate of absorption plays an important role in the drug release process. Although many of the mathematical models take into account the perfect sink condition, in a real system this assumption may not be true as there are many physiological parameters which may affect the drug delivery process. To establish a good in vitro and in vivo drug release correlation, mathematical models will need to incorporate more parameters. This study does establish a significant step in the kinetics of drug delivery by including absorption in the delivery pathway of an oral drug dosage.

CHAPTER 6

ASYMPTOTIC SOLUTION: ANALYSIS OF THE AFFECT OF ABSORPTION RATE AND DISSOLUTION RATE ON RATE OF DRUG RELEASED

6.1 Problem Description

The problem description is similar to the one in section 4.1. However, now Equations (4.1)-(4.3) are taken to be time dependent and independent of position (which neglects diffusion). Therefore now we have a set of ordinary differential equations represented by Equations (6.1) through (6.7). This solution is termed as asymptotic solution as we make some limiting approximations. This type of analysis is useful for tablet formulations of BCS class II compounds [1], where diffusion of drug is very fast in comparison with the dissolution of the drug. Therefore the diffusion term is removed from Equation (4.1). The drug release process is now completely dissolution controlled. The surface boundary condition (Equation (4.3)) is now recast in a different form (Equation (6.3)) which is a simple mass balance of drug across the particle and bulk liquid. The solution method is very similar to that carried out in the previous chapters. Equation (6.1) through (6.7) is also solved numerically using the MATLAB programming. The result for the asymptotic solution solved analytically is only valid for certain time range short times in other words. Whereas the numerical solution describes the drug release process over all time periods. However this analysis is only valid as long as dissolution is controlling the drug release process and diffusion is very fast.

6.2 Solution Method

$$\frac{dC}{dt} = k \left(\frac{S - S_0}{S_0} \right)^{2/3} (C_s - C) \quad (6.1)$$

$$\frac{dS}{dt} = -k \left(\frac{S - S_0}{S_0} \right)^{2/3} (C_s - C) \quad (6.2)$$

$$-V_s \left(\frac{dC}{dt} \right) = V_l \frac{dC_l}{dt} + V_l k_a C_l \quad (6.3)$$

The Boundary and Initial conditions are given by

$$C(r,0) = 0 \quad (6.4)$$

$$C_l(0) = 0 \quad (6.5)$$

$$S(0) = S_0 \quad (6.6)$$

$$C = KC_l \quad \text{at} \quad r = R \quad (6.7)$$

The dimensionless parameters used are:

$$\text{Dimensionless concentration of dissolved drug } \theta_s = \frac{S_0 - C}{S_0} \quad (6.8)$$

Dimensionless concentration of dissolved drug present in the liquid compartment

$$\theta_l = \frac{S_0 - C_l K_p}{S_0} \quad (6.9)$$

$$\text{Dimensionless solubility: } \bar{\theta} = \frac{S_0 - C_s}{S_0} \quad (6.10)$$

$$\text{Dimensionless time: } \tau = \frac{D_{AB} t}{R^2} \quad (6.11)$$

$$\text{Dimensionless radial coordinate: } \xi = \frac{r}{R} \quad (6.12)$$

$$B = \frac{V_l}{V_s K_p} \quad (6.13)$$

$$N = \frac{kR^2}{D_{AB}} \quad (6.14)$$

$$M = \frac{k_r R^2}{D_{AB}} \quad (6.15)$$

Problem recast in non dimensional form:

$$\frac{d\theta}{d\tau} = N(\theta_s)^{2/3}(\bar{\theta} - \theta) \quad (6.16)$$

$$\frac{d\theta_s}{d\tau} = -N(\theta_s)^{2/3}(\bar{\theta} - \theta) \quad (6.17)$$

$$\left(\frac{1}{B}\right)\frac{d\theta}{d\tau} = \left(\frac{d\theta_l}{dt}\right) - M\theta_l + M \quad (6.18)$$

The boundary and initial conditions become

$$\theta(\xi, 0) = 0 \quad (6.19)$$

$$\theta_s(\xi, 0) = 1 \quad (6.20)$$

$$\theta_l(0) = 0 \quad (6.21)$$

Following section 4.3 the following assumption is made for obtaining an approximate solution. The following approximation can be made during early stages of drug release [47].

$$U = 1 - \theta_s \quad (6.22)$$

From the initial condition given by Equations (6.4) and (6.6) it can be concluded that both θ and U are equal to zero initially. And hence are $\ll 1$.

Therefore during early stages of release $U \ll 1$. Now θ_s can be written in terms of U as:

$$\theta_s^{\frac{2}{3}} = (1-U)^{\frac{2}{3}} \cong 1 - \frac{2}{3}U \quad (6.23)$$

Replacing θ_s in Equation (6.23) we get:

$$\frac{dU}{d\tau} = N(\bar{\theta} - \theta) - \frac{2UN\bar{\theta}}{3} + \frac{2UN\theta}{3} \quad (6.24)$$

Keeping only the linear terms we get

$$\frac{dU}{d\tau} = N(\bar{\theta} - \theta) - \frac{2UN\bar{\theta}}{3} \quad (6.25)$$

$$\text{Say } \alpha = \frac{2N\bar{\theta}}{3} \quad (6.26)$$

Applying Laplace transform method to Equation (4) we get:

$$s\tilde{U}(s) - U(0) = N\left\{\frac{\bar{\theta}}{s} - u(s)\right\} - \alpha\tilde{U} \quad (6.27)$$

$$\tilde{U}(s)(s + \alpha) = N\left(\frac{\bar{\theta}}{s}\right) - Nu(s) \quad (6.28)$$

$$\tilde{U}(s) = \frac{N\left(\frac{\bar{\theta}}{s}\right) - Nu(s)}{(s + \alpha)} \quad (6.29)$$

Equation (6.17) becomes:

$$\frac{d\theta}{d\tau} = N(1-U)^{2/3}(\bar{\theta} - \theta) \quad (6.30)$$

$$\frac{d\theta}{d\tau} = N(\bar{\theta} - \theta) - \alpha U \quad (6.31)$$

Now applying Laplace transform method to (6.31) we get:

$$su(s) - \theta(0) = \frac{N\bar{\theta}}{s} - Nu - \alpha\tilde{U} \quad (6.32)$$

$$u(s + N) - 1 = \frac{N\bar{\theta}}{s} - \alpha\tilde{U} \quad (6.33)$$

$$u(s + N) = 1 + \frac{N\bar{\theta}}{s} - \alpha\tilde{U} \quad (6.34)$$

Substituting for $\tilde{U}(s)$ from Equation (6.29) and on rearranging terms we get

$$u(s) = \frac{N(\bar{\theta} - 1)}{s(s + \alpha + N)} \quad (6.35)$$

Now from Equation (6.) we have:

$$\left(\frac{1}{B}\right) \frac{d\theta}{d\tau} = \left(\frac{d\theta_t}{dt}\right) - M\theta_t + M \quad (6.36)$$

On applying Laplace transform method to (6.36) we get:

$$\left(\frac{1}{B}\right) su(s) - \theta(0) = sv(s) - \theta_t(0) - Mv(s) + \frac{M}{s} \quad (6.37)$$

Applying the boundary conditions (6.19) and (6.21) we get

$$\frac{s}{B} \left(\frac{N(\bar{\theta} - 1)}{s(s + \alpha + N)} \right) = v(s)(-M + s) - \frac{(M + s)}{s} \quad (6.38)$$

$$v(s) = \frac{s}{B} \left(\frac{N(\bar{\theta} - 1)}{s(s + \alpha + N)(s - M)} \right) + \frac{(M + s)}{s} \quad (6.39)$$

$$v(s) = \frac{1}{B} \left(\frac{N(\bar{\theta} - 1)}{(s - M)(s + \alpha + N)} \right) + \frac{1}{s} \quad (6.40)$$

Using the residue theorem [37] for carrying out the Laplace inversion let:

$$v(s) = \frac{P(s)}{Q(s)} \quad (6.41)$$

$$\text{So that } \theta_l(\tau) = L^{-1}\{v(s)\} = \sum_{n=0}^{\infty} \rho_n(\tau) \quad (6.42)$$

$$\text{Where } P(s_n) = sN(\bar{\theta} - 1) + B(s - M)(s + \alpha + M) \quad (6.43)$$

$$Q(s) = Bs(s - M)(s + \alpha + M) \quad (6.44)$$

Since $s = 0$ is a simple pole of $v(s)$ the residue is given by:

$$\rho_0 = 1 \quad (6.45)$$

The residue at $s = -(\alpha + N)$ is given by:

$$\rho_1 = \frac{N(1 - \bar{\theta})}{B(M - \alpha - N)} \text{Exp}\{-(\alpha + N)\tau\} \quad (6.46)$$

The residue at $s = -(M)$ is given by:

$$\rho_2 = -\frac{N(1 - \bar{\theta})}{B(M - \alpha - N)} \text{Exp}\{-(M)\tau\} \quad (6.47)$$

Therefore

$$\theta_l(\tau) = \rho_0 + \rho_1 \text{Exp}\{-(\alpha + N)\tau\} + \rho_2 \text{Exp}\{-M\tau\} \quad (6.48)$$

Substituting Equations (6.45), (6.46) and (6.47) into Equation (6.48) the final expression

for fraction of drug released is obtained as

$$\frac{C_l K_p}{S_0} = \left[\frac{N(1 - \bar{\theta})}{B(M - \alpha - N)} \text{Exp}\{-(\alpha + N)\tau\} - \frac{N(1 - \bar{\theta})}{B(M - \alpha - N)} \text{Exp}\{-M\tau\} \right] \quad (6.49)$$

6.3 Results and Discussion

Plots are made for fraction of drug release (Equation (6.49) versus square root of time τ and are displayed as Figure 6.1 and Figure 6.2 below. By changing the value of M in Equation (6.49) the fraction of drug released is obtained for different rates of absorption. The value for B and N are kept constant and the values of M are varied. Similarly the effect of dissolution rate N can be analyzed by keeping B and M constant. All the parameter values are taken from Polakovic's article [50] the solubility of drug is taken to be 0.5 [47].

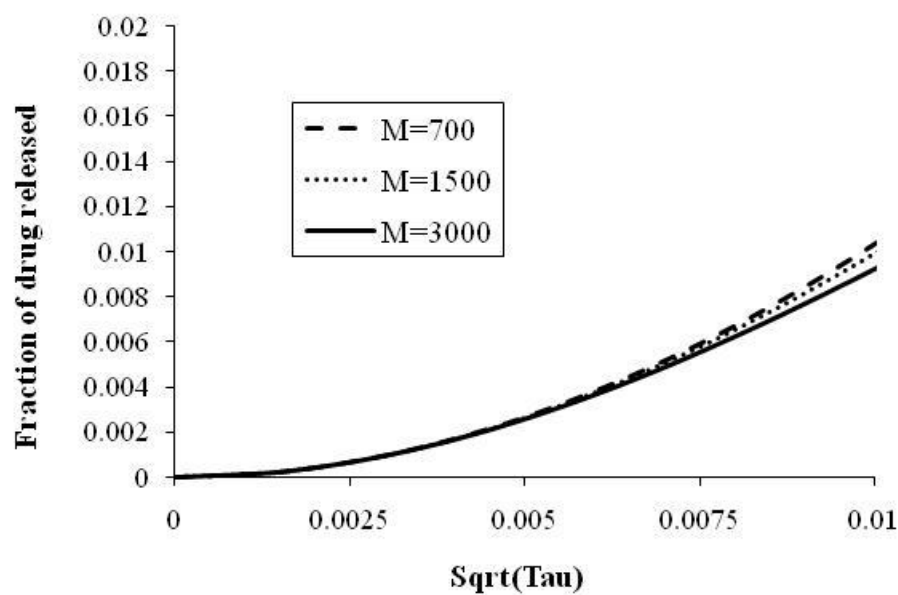


Figure 6.1 Affect of absorption rate on rate of drug release for initial period of release.

Figure 6.1 shows the effect of absorption rate on rate of drug released during initial period, which is up to 800 minutes of release time. As it can be seen there is not much difference in the release rates or fraction of drug released for three different absorption rate values.

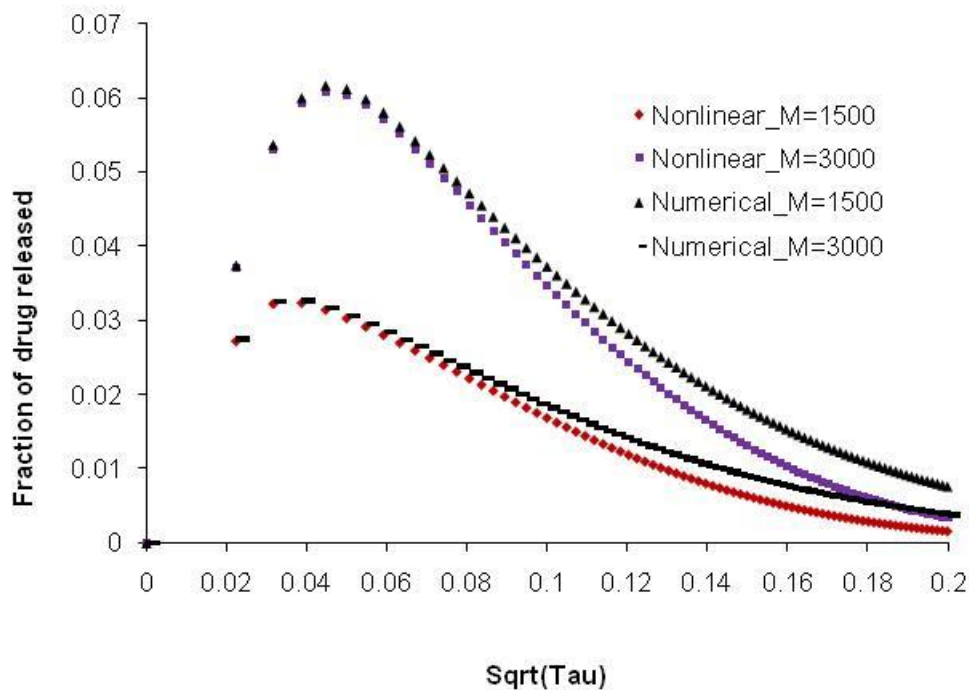


Figure 6.2 Comparison of asymptotic and numerical solutions.

Figure 6.2 shows the effect of absorption rate for a time period beyond 3000 minutes. The effect of absorption rate is now evident. The fraction of drug released out of a dissolution controlled dosage form is substantially low at a higher absorption rate. The fraction of drug released reaches a maximum peak at about 0.06 when the rate of absorption is low. The plot also sheds light on when the drug release process stops thus providing valuable information on when the next dosage form needs to be administered. The plot also shows that there is a good agreement between the asymptotic and numerical predictions. The agreement reduces beyond time period of 0.12. As the solubility limit is placed at 50% the fraction of drug released is very low.

CHAPTER 7

ANALYTICAL SOLUTION: ANALYSIS OF THE AFFECT OF DISSOLUTION RATE AND ABSORPTION RATE ON RATE OF DRUG RELEASE

7.1 Problem Description

Polakovic et al. [50] developed a simple model to describe the drug release process from a dissolution controlled drug delivery system. The change in concentration of the solid drug with respect to time is equal to the dissolution coefficient times the difference in solid and bulk liquid concentration. Diffusion of the dissolved drug out of the dosage form is considered to be very fast when compared to the dissolution of the drug. Therefore the Equation (7.1) only takes into account the dissolution of drug. The drug delivery system is similar to the one described in section 4.1 and 5.1. A uniformly distributed matrix system is considered. The concentration of solid drug is taken to be a function of time only. When administered orally the drug reaches the GI tract where it is released and eventually absorbed. This situation can be described mathematically by Equations (7.1) through (7.5) where R is the radius of the spherical particle, V_s the volume of the solid particles V_l the volume of liquid compartment and S is the concentration of solid drug. The drug enters the liquid phase by process of diffusion at time $t = 0$. The concentration of the drug in the liquid phase is taken as C_l . A well- stirred tank assumption is made such that C_l is

independent of position. Thereby the drug is consumed by a first order absorption (Figure 4.1).

7.2 Solution Method

$$\frac{dS}{dt} = -k(S - K_p C_l) \quad (7.1)$$

$$-V_s \left(\frac{dS}{dt} \right) = V_l \frac{dC_l}{dt} + V_l k_a C_l \quad (7.2)$$

The boundary and initial conditions are given by

$$S(r,0) = S_0 \quad (7.3)$$

$$C_l(0) = 0 \quad (7.4)$$

$$S(R,0) = K_p C_l \quad (7.5)$$

The dimensionless parameters are given by:

$$\text{Dimensionless concentration of dissolved drug } \theta = \frac{S_0 - S(\tau)}{S_0} \quad (7.6)$$

Dimensionless concentration of dissolved drug present in the liquid compartment

$$\theta_l = \frac{S_0 - C_l K_p}{S_0} \quad (7.7)$$

$$\text{Dimensionless time: } \tau = \frac{D_{AB} t}{R^2} \quad (7.8)$$

$$\text{Dimensionless radial coordinate: } \xi = \frac{r}{R} \quad (7.9)$$

$$B = \frac{V_l}{V_s K_p} \quad (7.10)$$

$$N = \frac{k R^2}{D_{AB}} \quad (7.11)$$

$$M = \frac{k_r R^2}{D_{AB}} \quad (7.12)$$

The problem is recast in non dimensional form as

$$\frac{d\theta_s}{d\tau} = N(\theta_l - \theta_s) \quad (7.13)$$

$$-\left(\frac{1}{B}\right) \frac{d\theta_s}{d\tau} = \left(\frac{d\theta_l}{dt}\right) + M - M\theta_l \quad (7.14)$$

The initial conditions are given as

$$\theta_s(0) = 1 \quad (7.15)$$

$$\theta_l(0) = 0 \quad (7.16)$$

Applying Laplace transform method on equation (7.14) we get

$$s u(s) - u(0) = N(v(s) - u(s)) \quad (7.17)$$

$$u(s) = \frac{N(v(s))}{N + s} \quad (7.18)$$

Equation (7.14) becomes

$$\frac{1}{B}(s u(s) - \theta_s(0)) = -(s v(s) - \theta_l(0)) + \frac{M}{s} - M(v(s)) \quad (7.19)$$

On substituting the boundary condition () and rearranging

$$v(s) \left(\frac{sN}{(N+s)B} + (s+M) \right) = \left(\frac{M+s}{s} \right) \quad (7.20)$$

Therefore:

$$v(s) = \frac{B(M+s)(s+N)}{s(sN+B(s+N)(s+M))} \quad (7.21)$$

Using the residue theorem [37] for carrying out the Laplace inversion Let:

$$v(s) = \frac{P(s)}{Q(s)} \quad (7.22)$$

$$\text{Where } P(s_n) = s(sN+B(s+M)(s+N)) \quad (7.23)$$

$$Q(s) = Bs(s-M)(s+\alpha+M) \quad (7.24)$$

$$\text{So that } \theta_i(\tau) = L^{-1}\{v(s)\} = \sum_{n=0}^{\infty} \rho_n(\tau) \quad (7.25)$$

Since $s = 0$ is a simple pole of $v(s)$ the residue is given by:

$$\rho_0 = (s-0) \left(\frac{B(M+s)(s+N)}{s(sN+B(s+N)(s+M))} \right) \quad (7.26)$$

$$\rho_0 = \left(\frac{B(M)(N)}{(B(N)(M))} \right) = 1 \quad (7.27)$$

$$\rho_n = \left(\frac{B(M+s)(s+N)}{s(sN+B(s+N)(s+M))} \right) = \frac{P(s)}{Q(s)} \quad (7.28)$$

$$Q(s) = 0 \quad (7.29)$$

$$Q(s) = s(sN+B(s+N)(s+M)) = 0 \quad (7.30)$$

The Eigen values are given by

$$\lambda = i\sqrt{s} \Rightarrow -\lambda^2 = s^2 \quad (7.31)$$

Setting $Q(s) = 0$

$$-\lambda^2 N + B(-\lambda^2 + N)(-\lambda^2 + M) = 0 \quad (7.32)$$

$$\rho_n = \left(\frac{B(M - \lambda^2)(N - \lambda^2)}{(-2N\lambda^2 + B(3\lambda^4 - 2\lambda^2(M + N) + MN))} \right) \exp\{-\lambda^2 \tau\} = \frac{P(s)}{Q'(s)} \quad (7.33)$$

$$\text{Therefore } \theta_l(\tau) = 1 + \left(\frac{B(M - \lambda^2)(N - \lambda^2)}{(-2N\lambda^2 + B(3\lambda^4 - 2\lambda^2(M + N) + MN))} \right) \exp\{-\lambda^2 \tau\} \quad (7.34)$$

The fraction of drug released is given as:

$$\left(\frac{C_l K_p}{S_0} \right) = \left(\frac{B(M - \lambda^2)(N - \lambda^2)}{(-2N\lambda^2 + B(3\lambda^4 - 2\lambda^2(M + N) + MN))} \right) \exp\{-\lambda^2 \tau\} \quad (7.35)$$

7.3 Results and Discussions

The Eigen values λ are obtained using Mathematica. All the parameter values are taken from Polakovic's article [50]. The particles are up to 400 nanometers and have a drug loading of 20% (w/w) therefore the dissolution of drug within the polymer matrix becomes the rate controlling step. Plots are made for fraction of drug release (Equation (7.35) versus square root of time (τ)). By changing the value of M in Equation (7.35) the fraction of drug released is obtained for different rates of absorption. The value for B and N are kept constant and the values of M are varied.

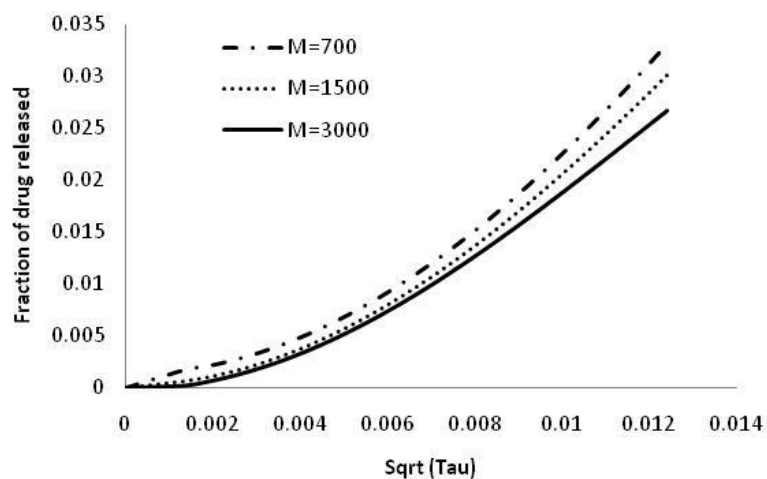


Figure 7.1 Affect of absorption rate on rate of drug release for initial period of release.

The effect of absorption rate on rate of drug released during initial period of release is shown in figure 7.1. The time period of release is up to 800 minutes. As it can be seen there is not much difference in the release rates or fraction of drug released for three different absorption rate values.

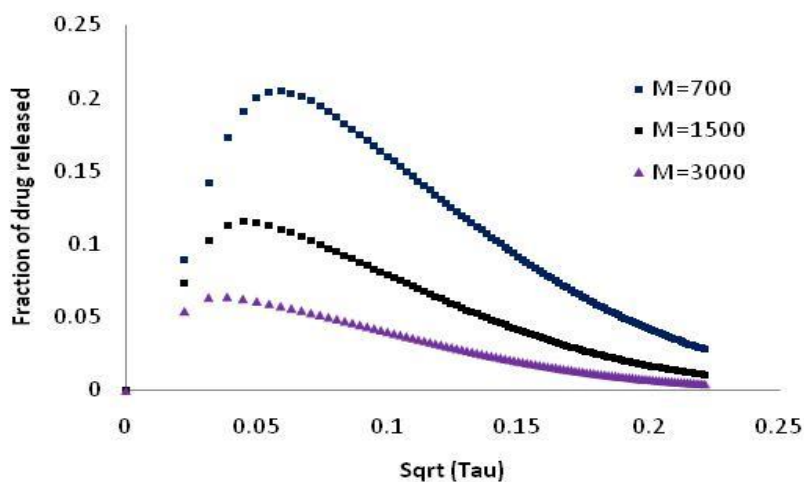


Figure 7.2 Affect of absorption rate on rate of drug release.

Figure 7.2 shows the effect of absorption rate for a time period beyond 3000 minutes. The effect of absorption rate is now evident. The fraction of drug released out of a dissolution controlled dosage form is substantially low at a higher absorption rate. The fraction of drug released reaches a maximum peak at about 0.2 when the rate of absorption is low. The plot also gives information on when the drug release process stops thus providing valuable information on when the next dosage form needs to be administered.

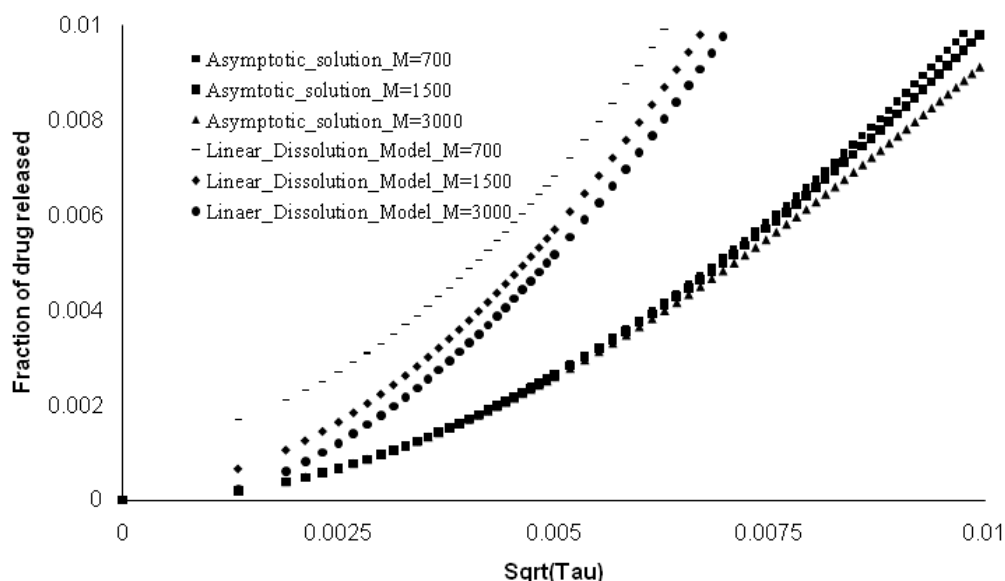


Figure 7.3 Comparison of drug release profiles for nonlinear and linear dissolution models for initial release period.

Figure 7.3 gives a comparison of drug release profiles obtained from asymptotic solution (chapter 6) and linear dissolution model. For both the models the effect of absorption rate on rate of drug released is less significant for the initial phase of release. However the nonlinear dissolution model captures the delay in release well than the linear dissolution model. Also the predicted rate of release is slightly higher for the linear dissolution model than the nonlinear model.

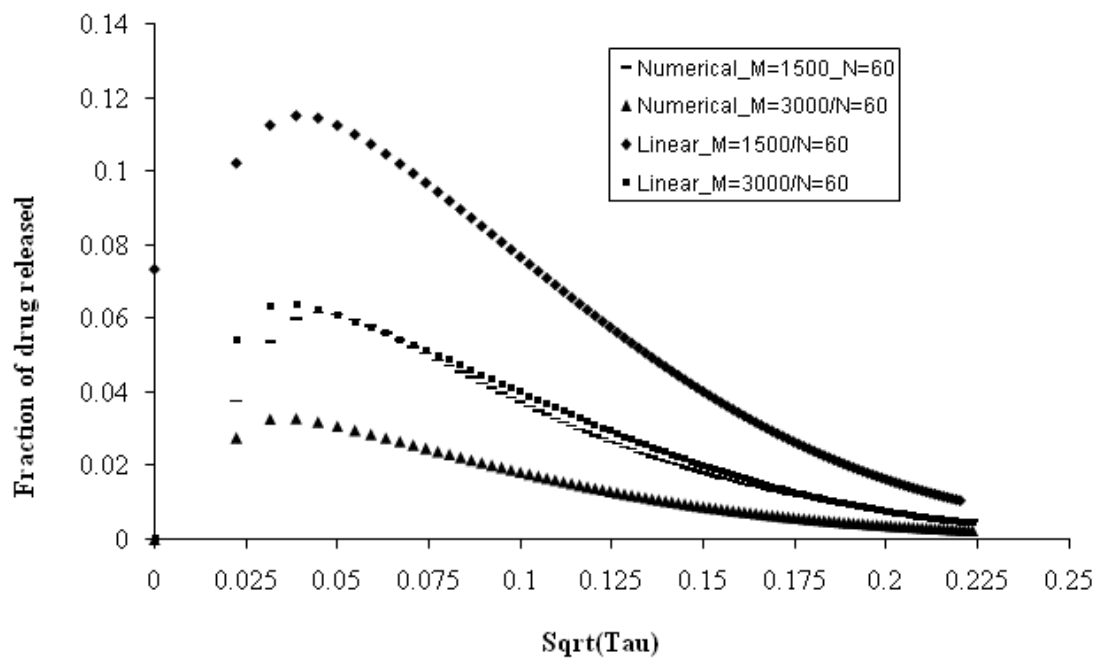


Figure 7.4 Comparison of drug release profiles (asymptotic solution and linear dissolution model) for entire time period.

Figure 7.4 shows the release profiles predicted by both the models over the entire time period. For both the models the rate of drug release is higher when absorption rate is lower. However the fraction of drug released is significantly higher when nonlinear dissolution is not considered. As solubility limit of 50% is taken in the asymptotic solution this imposes a limit on the fraction of drug released into liquid. The models should be applied based on the type of dosage forms used. For a tablet or compact which has mostly API powder the chance of solubility being low is high especially if it's a BCS class II drug. For controlled release dosage form with drug particles encapsulated in a polymer matrix the solubility is significantly higher or improved yet dissolution can be slow enough to control the drug release process.

CHAPTER 8
NUMERICAL SOLUTION

8.1 Introduction

Since the problem discussed in section 4.1 is a non linear problem, it has to be solved using numerical methods. MATLAB program is implemented to get the numerical solution. The equations are discretized using the finite difference numerical method of lines scheme and the resulting system of ODEs is solved using one of MATLAB's built in solver. Given below are the equations to be solved (same as those listed in section 4.1)

$$\frac{\partial C}{\partial t} = D_{AB} \left(\frac{\partial^2 C}{\partial r^2} + \frac{2}{r} \frac{\partial C}{\partial r} \right) + k \left(\frac{S}{S_0} \right)^{\frac{2}{3}} (C_s - C) \quad (4.1)$$

$$\frac{\partial S}{\partial t} = -k \left(\frac{S}{S_0} \right)^{\frac{2}{3}} (C_s - C) \quad (4.2)$$

$$-\left(\frac{3}{R} \right) V_s D_{AB} \left(\frac{\partial C}{\partial r} \right)_{r=R} = V_l \frac{dC_l}{dt} + V_l k_r C_l \quad (4.3)$$

The corresponding boundary conditions are given as

$$C(r,0) = 0 \quad (4.4)$$

$$C_l(0) = 0 \quad (4.5)$$

$$S(r,0) = S_0 \quad (4.6)$$

$$C = KC_l \quad \text{at} \quad r = R \quad (4.7)$$

$$C(0,t) \text{ is finite Or } \left(\frac{\partial C}{\partial r} \right)_{r=0} = 0 \quad (4.8)$$

The equations in dimensionless form are given as

$$\frac{\partial \theta}{\partial \tau} = \left(\frac{\partial^2 \theta}{\partial \xi^2} + \frac{2}{\xi} \frac{\partial \theta}{\partial \xi} \right) + N \theta_s^{\frac{2}{3}} (\bar{\theta} - \theta) \quad (4.17)$$

$$\frac{\partial \theta_s}{\partial \tau} = -N \theta_s^{\frac{2}{3}} (\bar{\theta} - \theta) \quad (4.18)$$

$$-\left(\frac{3}{B} \right) \left(\frac{\partial \theta}{\partial \xi} \right)_{\xi=1} = \frac{d\theta_l}{d\tau} + M \theta_l \quad (4.19)$$

With the corresponding boundary conditions in dimensionless form

$$\theta(\xi, 0) = 0 \quad (4.20)$$

$$\theta(1, \tau) = \theta_l(\tau) \quad (4.21)$$

$$\theta_s(\xi, 0) = 1 \quad (4.22)$$

$$\theta_l(0) = 0 \quad (4.23)$$

$$\left(\frac{\partial \theta}{\partial \xi} \right)_{\xi=0} = 0 \quad (4.24)$$

8.2 Discretized Equations

Central and 2nd order accurate 3-point Backward Difference differentiation formula is used for this purpose [83]. For the purpose of numerical computation new variables are introduced.

Say

$$\phi_1 = \frac{kR^2}{D_{AB}} \quad (8.1)$$

$$\phi_2 = \frac{k_r R^2}{D_{AB}} \quad (8.2)$$

And

$$u \equiv \theta, \quad t \equiv \tau, \quad x \equiv \xi \quad w \equiv \theta_s \quad V \equiv \theta_t \quad \theta_b \equiv \bar{\theta} \quad (8.3)$$

Now Equation (4.17) becomes

$$\frac{du_i}{dt} = \frac{u_{i+1} - 2u_i + u_{i-1}}{\Delta x^2} + \frac{2}{x} \left(\frac{u_{i+1} - u_{i-1}}{2\Delta x} \right) + \varphi_1 w_i^{2/3} (\theta_b - u_i) \quad (8.4)$$

For $i=1,2,\dots,n$

Equation (4.18) becomes

$$\frac{dw_i}{dt} \cong -\varphi_1 w_i^{2/3} (\theta_b - u_i) \quad (8.5)$$

Equation (4.19) becomes

$$-\left(\frac{3}{B} \right) \left(\frac{u_{i+1} - u_{i-1}}{2\Delta x} \right) = \frac{dV_i}{dt} + \varphi_2 V_i \quad (8.6)$$

The boundary conditions become

$$u(x_i, 0) = u_i = 0 \quad (\text{initial values for } \theta) \quad (8.7)$$

$$\theta(1, \tau) = u(x_n, t) = u_n(t) = V_n(t) \quad (\text{boundary condition for } \theta) \quad (8.8)$$

$$w(x_i, 0) = w_i = 1 \quad (\text{initial values for } \theta_s) \quad (8.9)$$

$$\text{We have } \theta(0, \tau) \text{ is finite} \quad (8.10)$$

$$\Rightarrow u(x_n, t) \equiv u_1(t) \text{ is finite} \quad (8.11)$$

This may be translated to:

$$\frac{\partial \theta}{\partial \xi} = 0 \Rightarrow \frac{u_{i+1} - u_{i-1}}{2\Delta x} = 0 \quad (8.12)$$

And for the left boundary condition ($i = 1$) would mean that

$$\frac{u_2 - u_1}{2\Delta x} = 0 \quad \text{Or} \quad u_2 = u_0 \Leftrightarrow u(2) = u_0 \quad (8.13)$$

$$-\left(\frac{3}{B}\right)\left(\frac{u_{i+1} - u_{i-1}}{2\Delta x}\right) = \frac{dV_i}{dt} + \varphi_2 V_i \quad \text{for} \quad \xi = 1 \equiv x_n \quad (8.14)$$

This means that

$$-\left(\frac{3}{B}\right)\left(\frac{u_{i+1}(t) - u_{i-1}(t)}{2\Delta x}\right) = \frac{dV_i(t)}{dt} + \varphi_2 V_i(t) \quad (8.15)$$

Or

$$-\varphi_2 V_n - \left(\frac{3}{B}\right)\left(\frac{u_{i+1}(t) - u_{i-1}(t)}{2\Delta x}\right) = \frac{dV_n}{dt} \quad (8.16)$$

8.3 Method of Lines (MOL method) [83]

When using this method the spatial derivatives (boundary value) are approximated algebraically. The resulting system of ODEs in the initial value variables (typically time) is then integrated by an initial value ODE (ordinary differential equation) integrator (eg. Euler method, Modified Euler method, RKF 45). MOL has several advantages a few of them are listed below:

- The temporal and spatial integrations are separated in the sense that they can be treated separately in the coding; this adds a very attractive degree of flexibility. Library routines can be used for the temporal and spatial integrations.
- All major classes of PDEs (partial differential equations) can be accommodated (elliptical, hyperbolic and parabolic)

- Systems of ODEs and PDEs (in one, two and three spatial dimensions plus time), linear and nonlinear can be naturally accommodated within the MOL; for example ODEs can serve as boundary conditions for PDEs. However application of MOL with even two spatial dimensions is extremely computationally expensive, and with 3D even more so.

8.4 MATLAB Program

The discretized equations are solved using MATLAB programming. *ODE15S* integrator was used to solve the problem. The MATLAB code and discretization of Equations is given in Appendix A and Appendix B.

8.5 Results and Discussions

Figure 8.1 shows the drug release profiles for different absorption rates generated using the MATLAB code. The trend is very similar to that observed in the chapters 6 and 7. As the absorption rate is high the rate of drug released is low. The drug release curve shows a slight delay in release during initial time due to the non linear dissolution term, thus capturing the phenomena explained by Frenning [47]. Figure 8.2 compares the drug release profiles for different absorption rates (low to high) and also the case with no absorption. The drug release is maximum for the case with no absorption considered. As the rate of removal of drug from the liquid compartment is 0 the amount or fraction of drug in the liquid is maximum. As the rate of removal of drug increases the amount accumulated in the liquid compartment decreases and also it reaches a very small peak.

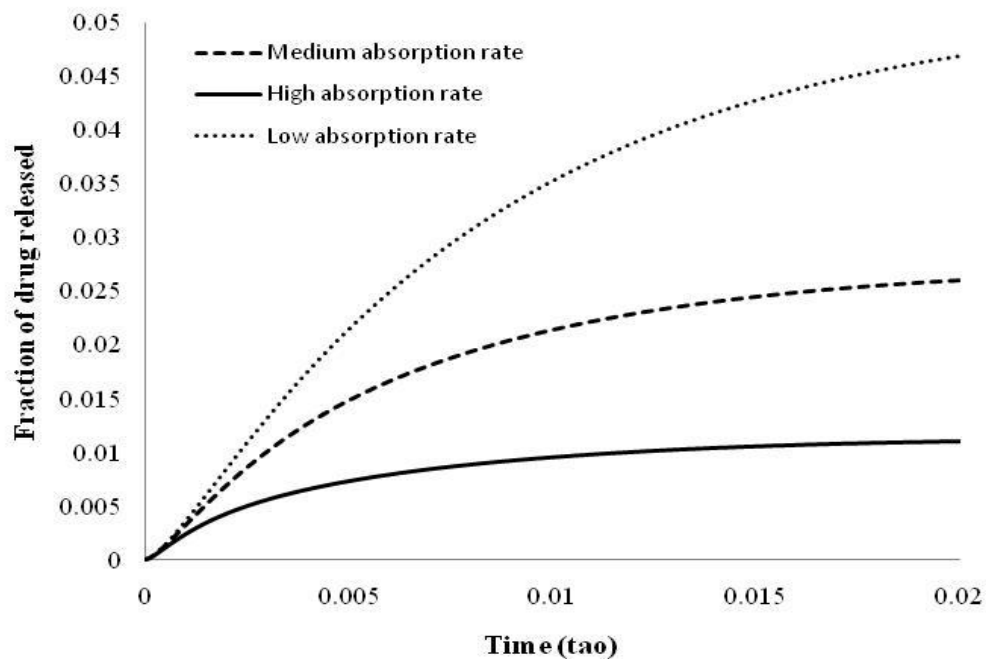


Figure 8.1 Comparison of drug release profiles for different absorption rates

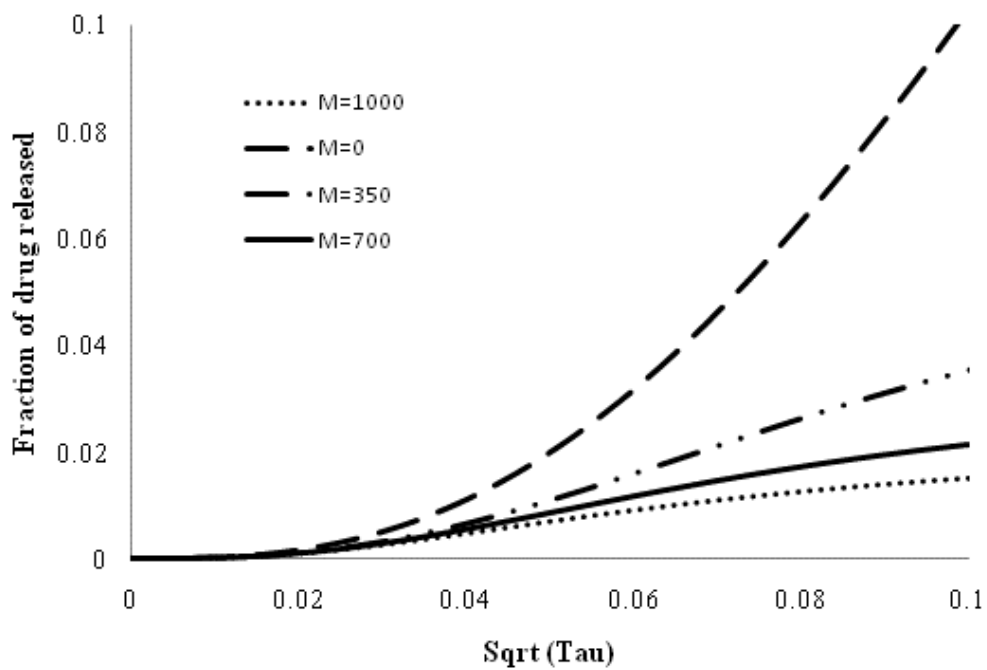


Figure 8.2 Comparison of drug release profiles with and without absorption.

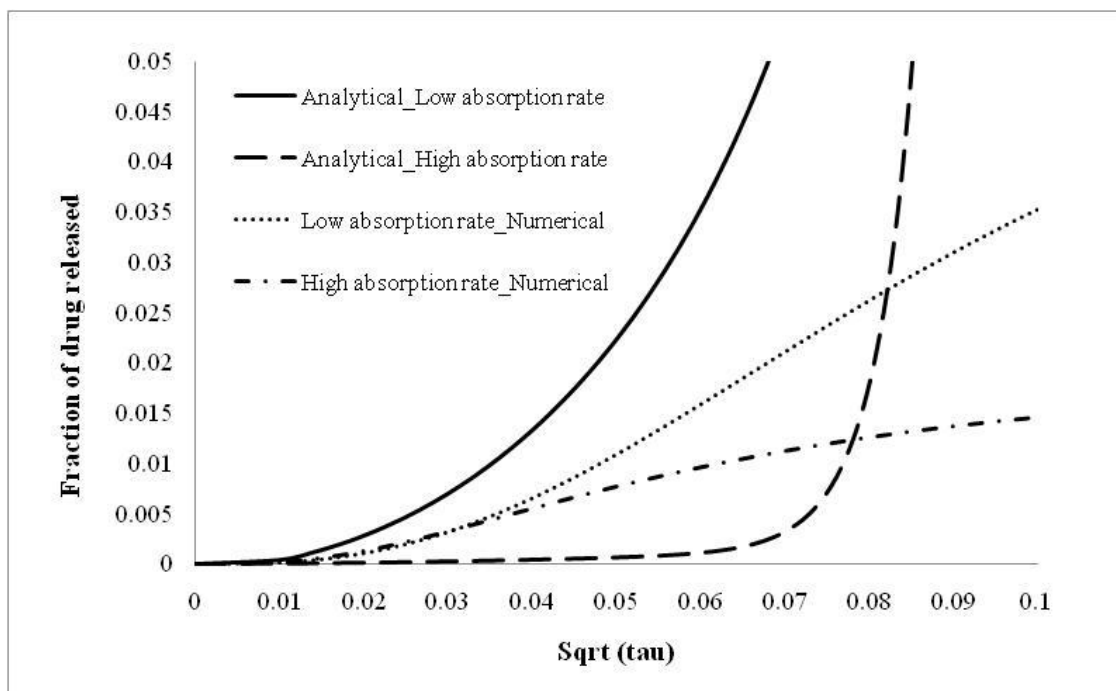


Figure 8.3 Comparison of semi analytical and numerical results

The analytical (chapter 4) and the numerical results for high and low absorption rates are compared in figure 8.3. During initial time at about a time scale of 0.015 in the above figure the effect of absorption rate is negligible. The numerical results agree well with the analytical values only up to a time scale of 0.03. However after this time period the semi analytical solution blows up, and cannot be considered for explaining the drug release behavior. These findings are coherent with those of Frenning's [47].

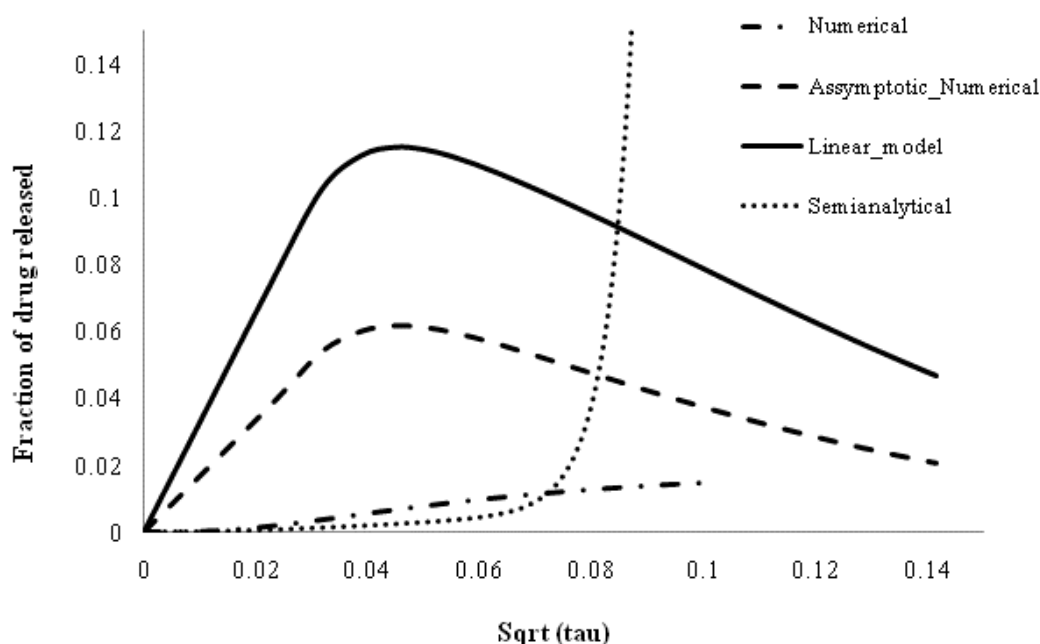


Figure 8.4 Comparison of semi analytical, asymptotic, numerical and linear dissolution model

Finally the drug release profiles computed using all the four models discussed in chapters 4, 6, 7 and 8 are plotted in figure 8.4. The time period (square root of τ) of 0.04 in the figure makes up to more than 5000 minutes of drug release time [50]. In their article Polakovic et.al. reported release from a controlled release drug delivery system for up to 3 days. During this period they found that the drug reached a peak value of approximately 2.5 (fraction of drug released) and stayed at that value for a time period of 3 days. From figure it can be seen that the asymptotic solution and the linear dissolution model predict a much higher and faster release than the semi analytical solution and the numerical solution (considering both diffusion and dissolution). The value of absorption rate was fixed at $M=1500$ for all the models. Therefore it is advisable to apply the diffusion-dissolution model (chapter 4 and 8) when the drug release period is very large ranging from weeks to months.

CHAPTER 9

CONCLUSIONS

The objective of the work was to present mathematical models for prediction of drug release in the GI tract. The models took into account the absorption rate of drug through the intestine wall along with the physiochemical properties of drug like solubility, diffusion and dissolution rate. Five models were presented in this work. These models mainly targeted three types of drug delivery systems, first model which took into account both diffusion and dissolution (Chapter 4), second model was for purely diffusion controlled dosage forms (Chapter 5) and the third model was for purely dissolution controlled drug delivery systems (Chapter 6 and 7).

It was observed that absorption rate of a drug has significant impact on the rate of drug released. For diffusion controlled delivery forms as the rate of absorption increased the prediction of drug released came closer to the values predicted by pure diffusion model. However for dissolution controlled drug delivery devices the rate of absorption had a different effect. The fraction of drug was higher for low values of absorption rate. Therefore it is evident that when absorption rate is not included in the modeling process it can lead to significant errors in prediction of drug released. It can either over predict or under predict the rate of drug release.

However, it is very important to know where to apply the model. For small times or during initial time period of release the impact of absorption rate is very less on the rate of drug released. So for immediate dosage forms or for drug delivery systems where the period of drug release is very small the prediction of drug released with and without

inclusion of absorption rate does not differ significantly. For oral dosage form containing BCS class II compounds (tablets, compacts of API powders etc...) dissolution of the drug becomes the main rate controlling step. In such cases the models presented in Chapter 6 and 7 which take diffusion to be much faster than dissolution and therefore a non contributing factor in drug release process should be considered. However, for a controlled release dosage form where the drug release process is expected to proceed for days, weeks or even months both diffusion and dissolution play a major role and the models presented in chapter 4 and 8 can be correctly applied to predict drug release. And for cases where the drug loading is low or where the drug dissolution is fast (BCS class I compounds) diffusion becomes the rate controlling step and model presented in Chapter 5 can be applied.

Most of the models in literature take into account only the dissolution kinetics of the dosage form, and pharmacokinetic modeling is applied only for dissolution controlled delivery systems [68]. However most of the dosage forms being developed in recent times aim at improving the solubility and dissolution kinetics of dosage forms and the drug diffusion through the polymer matrix plays a major role in drug delivery process. Thus the model developed in this work throws light at how such a dosage system would behave at different absorption rates.

CHAPTER 10

FUTURE STUDIES

1. Modeling of Drug Release from Rectangular and Cylindrical matrix systems

One of the objectives of the future studies will be to expand or extend the models developed in this work to non spherical matrix systems. Drug delivery systems in cylindrical matrices (e.g. needle shaped etc.) are common in literature and depending on application are preferred over spherical matrix systems. Similarly polymer films containing drug (e.g. transdermal patch or buccal, muccoadhesive strips) also have a wide range of application. Mathematical modeling of drug release from such systems has been studied widely in literature. However, the affect of absorption rate, diffusion rate and dissolution rate on these matrix types has not yet been explored. It will also be interesting to see how the geometry in conjunction with physiological and physiochemical parameters affects the drug release process.

2. Drug Release from Thin Film Drug Delivery Systems (ERC related work)

Future studies will also focus on attempting to apply the developed models to experimental data for drug release from polymer films or polymer thin film strips. As mentioned previously polymer thin films have a wide range of applications and depending on the type of polymer used, the drug release mechanism can be manipulated, the diffusion rate can be controlled etc. In the ERC- NSF funded project at NJIT efforts are currently being made for development of polymer thin films containing dispersed BCS class II drug nano particle. By varying the thickness of the film the drug loading and polymer content vary and thus the release mechanism can also vary. As the drug

compounds have low solubility, dissolution might also become a rate controlling mechanism depending on the drug loading of the system.

3. Analysis of Results

Further analysis has to be done for the results obtained in Chapters 4 through 8. The effect of each parameter value (B, M and N) on the drug release behavior is to be investigated in depth. It is also of interest to compare the drug release behavior for sink and non sink conditions (with and without inclusion of absorption rate).

Finally, it is a common notion to represent drug release profiles as a ratio of $\frac{M_t}{M_\infty}$.

All the results obtained in this work have been represented as a ratio of drug released to initial drug present within the system. These results have to be recast in terms of the mass ratio.

APPENDIX A

Numerical Methods

For $i=1$

$$\frac{du_1}{dt} = 3 \left(\frac{2u_2 - 2u_1}{\Delta x^2} \right) + \varphi_1 w_1^{2/3} (\theta_b - u_1)$$

$$\frac{dw_1}{dt} - \varphi_1 w_1^{2/3} (\theta_b - u_1)$$

For $i=2$ to $i=N-1$

$$\frac{du_i}{dt} = \frac{u_{i+1} - 2u_i + u_{i-1}}{\Delta x^2} + \left(\frac{2}{x_i} \right) \left(\frac{u_{i+1} - u_{i-1}}{2\Delta x} \right) + \varphi_1 w_i^{2/3} (\theta_b - u_i)$$

$$\frac{dw_i}{dt} - \varphi_1 w_i^{2/3} (\theta_b - u_i)$$

For $i = N$

$$\frac{dv_n}{dt} = -\frac{3}{B} \left(\frac{3u_n - 4u_{N-1} + u_{N-2}}{2\Delta x} \right) - \varphi_2 v_N$$

$$\frac{dw_N}{dt} - \varphi_1 w_N^{2/3} (\theta_b - u_N)$$

APPENDIX B

MATLAB Code

```
clear
clc
clear all
%-----Constants-----
phi2 = 5.205152486; %M
phi1 = 9.93E-01; %N
B = 0.30922449;
thb = .2; %Theta B
%-----
N = 321; %Number of nodes

dx=1/(N-1); %Step size

u0 = zeros(2*N+1,1); %Initial Condition at t=0 for u

%Initial Condition at t=0 for w
for i=(N+2):(2*N+1)
    u0(i)=1;
end

global x %Array of x values
for i=1:N
    x(i) = (i-1)*dx;
end

options = odeset('RelTol',1e-6,'AbsTol',1e-6); %Error tolerance

tstep = (0:.0001:.02); %Time step

%Calls ODE Solver
[t,u] = ode15s(@ode_uvw,tstep,u0,options,dx,N,B,phi2,phi1,thb);

%Extracts V from u matrix
V1 = u(1:end,N);

%Extracts U from u matrix
U1 = u(1:end,1:N);

plot(t(1:end),V1(1:end,1))
title(['Concentration of Dissolved Drug outside Sphere w/ step size of',
    num2str(dx)]);
ylabel('V(tao)')
xlabel('tao')
legend(['B = ',num2str(B),', phi1 = ',num2str(phi1),',
    phi2=',num2str(phi2)])
```

```

function dt=ode_uvw(t,u,dx,N,B,phi2,phil,thb)

global x %Array of x values

dt = zeros(2*N+1,1); %Initiates Size of dt

%In matrix, u is represented from i=1 to i=N
%w is represented from i = N+2 to i = 2N +1

%Solves for u when i=1
dt(1) = 3*((2*u(2)-2*u(1))/(dx^2))+((phil)*(u(N+2))^(2/3))*(thb-u(1));

%Solves for w when i=1
dt(N+2) = ((-phil)*(u(N+2))^(2/3))*(thb-u(1));

%Solves for inner nodes of u and w
for i=2:N-1
    %u(i) Equation:
    dt(i) = ((u(i-1)-2*u(i)+u(i+1))/(dx^2))+((2/x(i))*(u(i+1)-u(i-1))/(2*dx)))+(phil*(u(N+1+i))^(2/3))*(thb-u(i));

    %w(i) Equation:
    dt(N+1+i) = (-phil*(u(N+1+i))^(2/3))*(thb-u(i));
end

%Solves for u/v when i=N
dt(N) = (-phi2)*(u(N))-(3/B)*((3*u(N)-4*u(N-1)+u(N-2))/(2*dx));

%Solves for W when i=N
dt(2*N+1) = (-phil*(u(2*N+1))^(2/3))*(thb-u(N));

```

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