Numerical modeling of controlled release of drugs from silicone elastomers

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60 ECTS thesis submitted in partial fulfillment of a
Magister Scientiarum degree in Mechanical engineering

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Úrdráttur

Lyfjafræðileg lyfjalosunarkerfi eru í auknum mæli að færast frá einföldum pillum og sprautum í átt að háþróuðum lyfjalosunarkerfum þar sem lyf eru losuð til að viðhalda ákveðnum styrk til lengri tíma litið. Lyfjalosunarkerfi af þessum toga geta aukið lífsgæði sjúklinga auk þess að ábyrgjast rétta lyfjaskammta.

Þróun kerfa með stýrða lyfjalosun er flókið ferli og er enn sem komið er á tilraunastigi, byggt á mörgum tilraunum með tilheyrandi kostnaði bæði varðandi tíma og efni. Með þessu verkefni er reynt að auka við hefðbundnar tilraunaleiðir og þær nálgaðar með tölulegum líkönum. Í stuttu máli sagt er líkanið byggt á tveimur ólínulegum samtengdum hlutafleiðlujöfnum sem leystar eru tölulega. Markmiðið er líkan sem getur með mikilli nákvæmni sagt fyrir um hraða lyfjalosunar frá sílikon himnum, auk þess að að geta sagt til um magn óuppleysts lyfs í himnunni í hverjum tímapunkti.

Þetta er samstarfsverkefni á milli Vélaverkfræði- og Lyfjafræðideildar við Háskóla Íslands. Enn sem komið er lofa niðurstöður fyrir einföld marglaga tilvik góðu. En rannsaka þarf betur marglaga sílokonhimnur fyrir mismunandi rúmfræðilega lögun sem er lokamarkmið þessa verkefnis.

Abstract

Pharmaceutical drug delivery systems are moving away from simple pills and injections towards more sophisticated controlled release systems that release the drug in a controlled fashion to maintain an appropriate concentration for a long period of time. Drug delivery systems of this type can improve the quality of life for patients, as well as helping to guarantee correct dosages.

Development of controlled release systems is a rather involved process and still quite an experimental science, based on a large number of trials, with the associated cost in time and materials. With this project it is proposed to augment the more traditional experimental approach with numerical modeling techniques. Briefly, the model is based on two non-linear coupled partial differential equations (PDEs) and solved numerically. The target is a model which can accurately predict the rate of drug release from silicone elastomers, as well as solid drug concentration in the material at each point in time.

This project is collaboration between the Mechanical Engineering and the Pharmaceutical Departments of the University of Iceland. To date, promising results for simple multi-layered

cases have been achieved. However, work remains to accurately model multi-layered silicone-based drug delivery systems with various geometries, which is the ultimate goal of this project.

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Nomenclature

A	Surface area of membrane intact with contact face, [cm^2]
A_0	Initial surface area of the solid drug per volume unit matrix, [cm^2/cm^3]
A_{NW}	Initial surface area of the solid drug per volume unit matrix, [cm^2/cm^3]
C	Concentration of dissolved drug within the matrix, [mg/cm^3]
C_0	Initial concentration of dissolved drug in the matrix, [mg/cm^3]
C_s	Dimensional solubility of drug in the polymer matrix, [mg/cm^3]
D	Diffusion coefficient for the drug in the matrix, [cm^2/hour]
dS/dt	Rate of dissolution, [$mg/(hour \cdot cm^3)$]
k	Dimensional dissolution rate constant [cm/hour]
k'	Effective dimensional dissolution rate constant [1/hour]
κ	Non-dimensional dissolution rate constant
L	Membrane thickness, [cm]
M_0	Initial amount of drug, [mg]
Q	Total amount of drug released per unit area of the matrix, [mg/cm^2]
q_t	Total amount of drug in a unit volume of matrix, [mg/cm^3]
S	Concentration of solid drug within the matrix, [mg/cm^3]
S_0	Initial concentration of solid drug in the matrix, [mg/cm^3]
t	Time, [hours]
τ	Non-dimensional time
V_0	Surface area in the contact face times the membrane thickness, [cm^3]
x	Length in x-direction, [cm]
ξ	Non-dimensional length

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1 Introduction

Given the importance of efficient and safe drug dispensation nowadays, drug delivery systems are moving away from simple pills towards controlled release and sophisticated programmable delivery systems. Controlled release systems are systems that release the drug in a controlled fashion to maintain an appropriate concentration for a long period of time. Delivery systems of this type will have an impact on the quality of life of patients as well as providing a potentially safer way of delivering correct dosages.

Mathematical modeling of the drug release process plays an important role in the design of controlled release systems as it can be used to study various design parameters and avoid excessive experimentation. Furthermore, given the significant advances in computer simulation technology, numerical modeling is increasingly becoming an integral part of research and development in this area. Although extensive experimental studies have been carried out in this field in the recent years, modeling of these systems is currently lacking. Numerical modeling relies on careful representation of the physical situation, and it requires a thorough understanding of drug release kinetics, as well as mathematical expressions and modeling tools.

Diffusion through matrices is one of the major mechanisms utilized for controlling drug release rate. Diffusion-controlled systems can be divided into two categories, depending on the relative magnitudes of drug concentration and solubility in the matrix. If the drug concentration is low enough, such that all drugs can be dissolved uniformly and the dissolution process proceeds rapidly, the release rate can be determined from the well-known Fick's second law. In the case of higher drug concentrations, or lower solubility, then both dispersed and dissolved drug exist in the matrix at the same time. Theoretical description of such system was first provided by Takeru Higuchi [1] and [2] almost 50 years ago.

Some efforts have been made in recent years to analyze the dissolution- and diffusion-controlled release systems. For example, Frenning [7], [8] and [9] proposed two models where he combined the Noyes-Whitney equation and the diffusion equation for slowly dissolving drug release.

Similar to the work of Frenning, Cabrera et al. [10] used Fick's second law and the Noyes-Whitney equation to model drug release from planar system where the drug dissolution is slow. Their model for the release process takes into account situations like non-uniform drug loading and non-uniform size distributions of dissolved particles at a finite rate. The model assumes a one-dimensional release direction. This model was later expanded to describe cylindrical and spherical multilayered systems. Recently, Blagoeva and Nedev [11] considered a nonlinear diffusion problem for drug release from two-dimensional polymeric systems with finite dissolution rate. Their numerical scheme was based on finite element approximation in space and time difference method. However, these models are all case

specific and have only limited experimental verification. Furthermore, they do not directly apply to silicone matrices.

In contrast to the previous work in the field of drug release modeling, the goal in this study is to have a generally applicable modeling system. It is important that engineers and pharmaceutical scientists work together to produce effective controlled release systems ensuring a step-by-step validation of models against experimental results. The focus of this work is on developing a numerical model that quantifies the controlled release of drugs from silicone elastomer matrices.

In this work, a numerical model is developed that describes the drug release from silicone matrices. The model is in the form of coupled nonlinear partial differential equations (PDEs) that are solved numerically by a second order difference scheme in space and a fully implicit first order difference scheme in time. This model has been implemented in Matlab [12]. Two types of drugs are considered: Ibuprofen and Diclofenac. A parametric study is carried out for various initial and boundary conditions.

This thesis is organized as follows:

Chapter 2 describes the mathematical background of what has been done in the field of drug delivery systems along with methods.

Chapter 3 describes the experimental work; how the measurements were carried out it the Pharmaceutical Department of the University of Iceland and what tools were used.

In Chapter 4 the mathematical model is described and the case studies are introduced for two drugs; Ibuprofen and Diclofenac.

Chapter 5 describes the numerical results and comparisons with measurements from experiments carried out by the Pharmaceutical Department.

In Chapter 6 the conclusions are summarized.

2 Mathematical background

This chapter describes the most common mathematical models that have been used in research of drug delivery systems. The models are the Higuchi model, Fick‘s second law, the Noyes-Whitney equation and a combination of the Noyes-Whitney equation and Fick‘s second law. All parameters used in this chapter are according to information from the Pharmaceutical Department.

2.1 Higuchi model

Takeru Higuchi was the first to publish a theoretical description of a model on drug release through a matrix system. Higuchi assumed that the amount of drug initially present in the matrix was substantially larger than drug solubility and that the dissolution rate was instantaneous. In his model he assumed that the drug was equally spread in the matrix. He divided the matrix into two regions. In one region (depletion zone) all drug is dissolved and a concentration gradient exists, and in the other region solid and dissolved drug coexist, making the dissolved drug concentration constant. Higuchi derived his square root of time law using a pseudo-steady state approximation for the drug concentration in the depletion zone and taking the movement of the border between the zones into account [1]. The Higuchi model is as follows:

$$Q = [D(2q_t - C_S)C_S t]^{1/2} \tag{2.1}$$

where Q is the total amount of drug released per unit area of the matrix [mg/cm^2], D is the diffusion coefficient for the drug in the matrix [cm^2/hour], q_t is the total amount of drug in a unit volume of matrix [mg/cm^3], C_S is the dimensional solubility of drug in the polymer matrix [mg/cm^3] and t is time [hours].

This simple model is commonly used for analysis of experimental data for matrix systems. However in Higuchi‘s work the system was simplified and some assumptions made in order to enable an exact solution assuming infinite size and drug content, instantaneous dissolution and uniform distribution of the drug. Furthermore, the model neither accounts for non-uniform drug distribution nor complex matrix shape. The Higuchi model is therefore of limited use for designing medicated silicone prosthetics, where the entire drug will be released. For example, in the case of permanent implants where the particle properties can affect the release and the device can have an irregular shape.

To show the limitation of Higuchi‘s law Figure 2.1 was plotted with parameters from the Pharmaceutical Department [14].

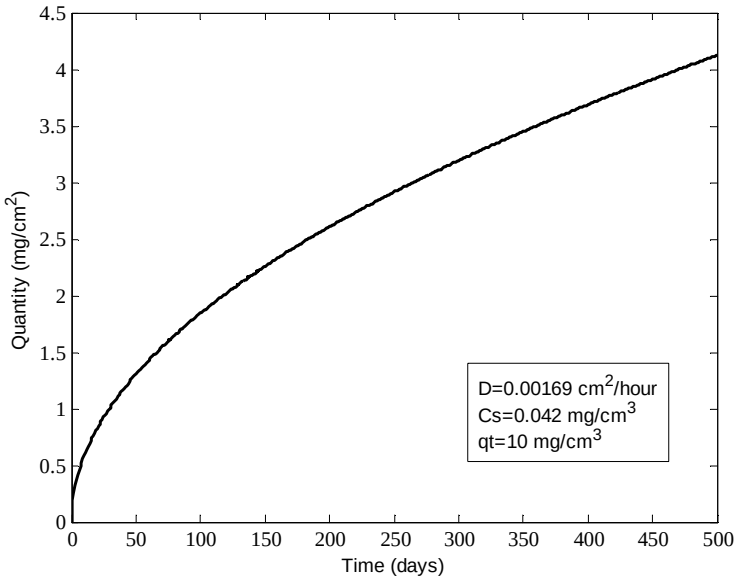

Figure 2.1: Q as a function of time with the Higuchi model.

As t approaches infinity, Q approaches infinity since the membrane does not have a finite size. Equation (2.1) is just an approximation and not all parameters are included in the model. The model is only valid when the initial quantity of drug per volume unit, q_t, is bigger than the drugs' initial solubility, C_S, or $q_t > C_S$. If $q_t >> C_S$ then the dissolution rate, k, starts to affect the result as well as the particle size of the drug, P, and geometric parameters describing the particles features, L_x, L_y and L_z. As was mentioned before Higuchi assumed that the amount of drug initially present in the matrix was substantially larger than drug solubility and that the dissolution rate was instantaneous. Therefore the dissolution rate and particle size are not needed in the model.

2.2 Fick’s second law

Another model to describe drug release is Fick’s second law. It predicts how diffusion causes the concentration field to change with time. Fick’s second law is different for the Higuchi model in the sense that it is valid when the amount of initial drug per unit volume (M_0/V_0) is smaller than the dimensional solubility of the drug (C_s) or $M_0/V_0<C_S$. The dissolution rate is also irrelevant. Fick’s second law is expressed as:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{2.2}$$

where the matrix is viewed as an infinite membrane of thickness L and x denotes the direction normal to the membrane. As before, D is the diffusion coefficient and C is the concentration for dissolved drug per unit volume. With the initial condition $C(0,x) = C_0$ and

the boundary conditions $\frac{\partial C}{\partial x}\Big|_{x=0} = 0$ and $C(t, L) = 0$ the solution can be expressed exactly as an infinite Fourier series, from which it can be deduced that [15]:

$$-D\frac{\partial C}{\partial x}\Big|_{x=L} = j(t) = \frac{2C_0 D}{L}\sum_{n=1,3,5,\ldots}^{\infty} e^{-\left(\frac{n\pi}{2L}\right)^2 (Dt)} \tag{2.3}$$

$$Q = \int_0^t j(t)\, dt \tag{2.4}$$

Here *j(t)* is the flux through the boundary of the matrix, $x = L$, as a function of time and Q is the quantity of released drug per unit area. C_0 is the initial concentration for dissolved drug per unit volume. These values were calculated numerically, using Matlab, taking 20 terms in the sum. The results are shown in Figures 2.2 and 2.3 for $n = 20$, $D = 0.00169$ cm^2/hour, $C_0 = 10$ mg/cm^3 and $L = 0.2$ cm [10]. Fick's second law assumes that all drug dissolves, but that does not apply in the real world, there are always some drug particles left behind.

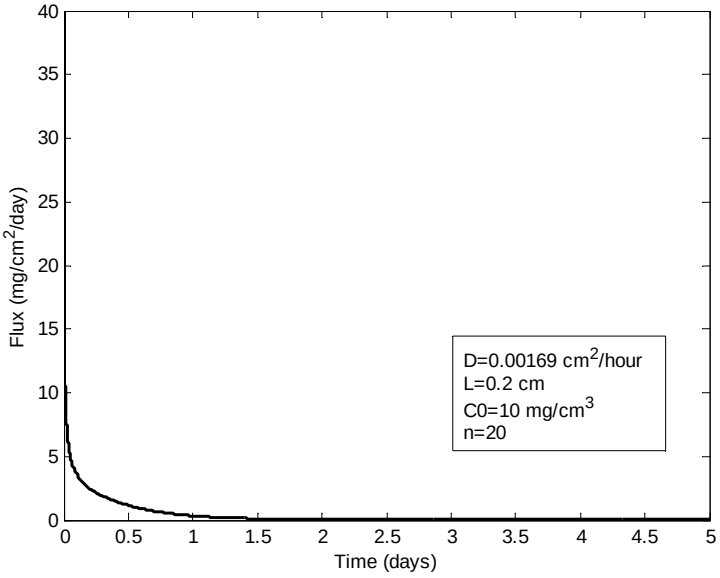

Figure 2.2: Flux through bottom boundary as function of time.

The flux is greatest at the beginning which is logical as the drug amount in the matrix is at maximum at the beginning and then decreases as *t* gets bigger and the drug releases.

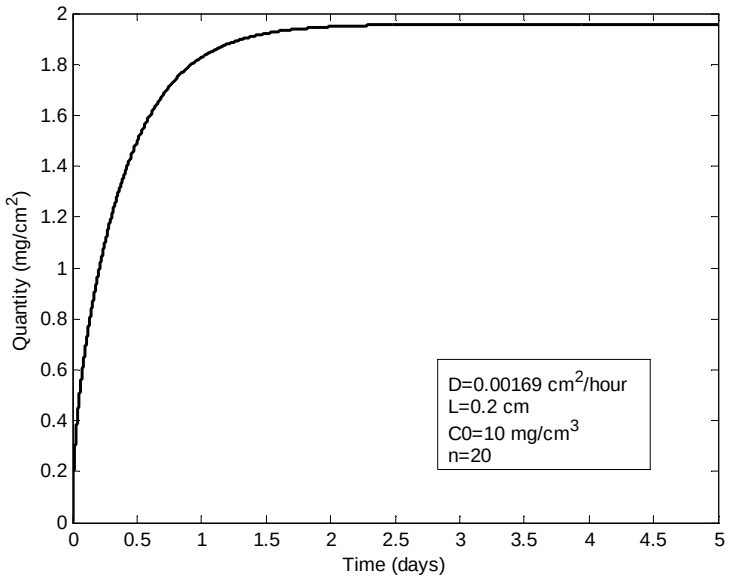

Figure 2.3: Quantity of drug release as a function of time with Fick's second law.

After 3 days the system has reached equilibrium. But as before Fick's second law does assume that all the drug dissolves and the matrix membrane will be "cleaned".

Figure 2.4 shows the Higuchi model compared to Fick's second law.

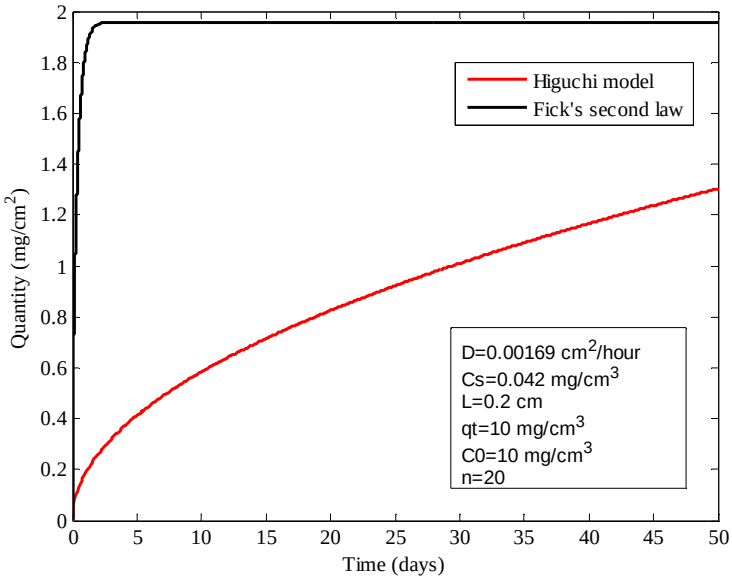

Figure 2.4: Comparison between the Higuchi model and Fick's second law.

As may be expected the results for the Higuchi model and Fick's second law do not agree well, since the model based on Fick's second law assumes that all the drug is effectively dissolved at time $t = 0$.

2.3 Noyes-Whitney equation

The two models above do not take into account the dissolution rate. The Noyes-Whitney equation [3] however does. This is a well-known equation in pharmaceutical science that relates the rate of dissolution of solids to the properties of the solid and the dissolution medium. The Noyes-Whitney relation gives the rate of dissolution, *dS/dt*, as:

$$\frac{dS}{dt} = -\frac{DA_{NW}(C_S - C)}{L} \tag{2.5}$$

Where *dS/dt* is the rate of dissolution, *D* is the diffusion coefficient, A_{NW} is the surface area of the solid per unit volume, *C* is the concentration of the solid in the bulk dissolution medium at time *t*, C_s is the concentration of the solid in the diffusion layer surrounding the solid and *L* is the diffusion layer thickness.

2.4 Combination of Fick's second law and Noyes-Whitney equation

When Fick's second law and the Noyes-Whitney equation are combined the result is a model containing drug release through a matrix system described by two coupled nonlinear partial differential equations (PDEs). Let us introduce:

$$A_{NW} = A_0 \left(\frac{S}{S_0}\right)^{2/3} \text{ and } \frac{D}{L} = k$$

By substituting for A_{NW} and $\frac{D}{L}$ into equations (2.2) and (2.5) the two coupled nonlinear partial differential equations (PDEs) are presented as:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} + kA_0 \left(\frac{S}{S_0}\right)^{2/3} (C_S - C) \tag{2.6a}$$

$$\frac{\partial S}{\partial t} = -kA_0 \left(\frac{S}{S_0}\right)^{2/3} (C_S - C) \tag{2.6b}$$

Here *C* is the concentration of dissolved drug [mg/cm^3], *S* is the concentration of solid drug per [mg/cm^3], *k* is a dissolution rate constant [cm/hour], A_0 is the initial surface area of the solid drug per volume unit matrix [cm^2/cm^3], C_S is the solubility of drug [mg/cm^3], *D* is the drug diffusions coefficient [cm^2/hour] and S_0 is the initial concentration of solid drug in the matrix [mg/cm^3]. These equations can also be expressed in non-dimensional form [7]:

$$\frac{\partial C'}{\partial \tau} = \frac{\partial^2 C'}{\partial \xi^2} + \kappa {S'}^{\frac{2}{3}}({C'}_S - C') \qquad (2.7a)$$

$$\frac{\partial S'}{\partial \tau} = -\kappa {S'}^{\frac{2}{3}}({C'}_S - C') \qquad (2.7b)$$

by setting $C' = \frac{C}{S_0}$, $S' = \frac{S}{S_0}$, ${C_S}' = \frac{C_S}{S_0}$, $\kappa = \frac{kL^2A_0}{D}$, $\tau = \frac{Dt}{L^2}$ and $\xi = \frac{x}{L}$.

Equation (2.6a) is basically a one-dimensional diffusion equation, with an additional term for drug dissolution. The model assumes a given type of nonlinear drug diffusion and adsorption isotherm. It further assumes a planar matrix with normal in the *x*-direction and the lateral dimensions to be much larger than its thickness *L*. The drug dissolution and release processes are described in terms of concentration *C(x,t)* of dissolved drug within the matrix and the concentration of solid drug *S(x,t)*, both have the dimension [mg/cm^3]. Equation (2.6b) is a reformulation of the Noyes-Whitney equation. The surface area of the solid drug is assumed to be proportional to its volume to the power of 2/3. This is found by the following relation of the surface area and volume of a sphere:

$$A = 4\pi r^2 \text{ and } V = \frac{4}{3}\pi r^3$$

The general relationship between A and V is then:

$$A = bV^{2/3} \text{ where } b \text{ is } 4.84 \qquad (2.8)$$

Thus if the solid drug consists of shrinking spheres whose original volume is S_0 with surface area A_0, the surface area when the volume of the drug has reduced to *S* will be:

$$A = A_0\left(\frac{S}{S_0}\right)^{2/3}$$

The model used to describe the problem in this thesis is based on the equations above and is described more fully in Chapter 4.1. It is very important to have real measurements to compare to when numerical models are designed. This is one of the strengths of the collaboration between the two departments. In next chapter it is illustrated how the measurements are carried out and what tools are used.

3 Experimental work

As has been pointed out this project was collaboration between the Mechanical Engineering and Pharmaceutical Departments of the University of Iceland. The Pharmaceutical Department has performed measurements on drug release through silicone matrices using equipment called Franz Diffusion Cell. The measurements are elaborated in Chapter 5. The Franz Diffusion Cell is illustrated in Figure 3.1.

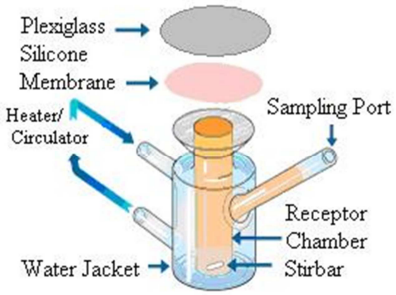

Figure 3.1: Franz Diffusion Cell [16]. Image modified and published with permission of PermeGear.

The drug is put into the silicone membrane which is then put between two flat ground joints. The silicone membrane is bigger than the joints circumference where the drug release takes place, therefore the drug can be released from that part of the membrane that is not in direct contact with the receiving phase. This is taken into account in the calculations. The released drug is then collected in the receptor chamber and measured after the experiment is over. Figure 3.2 shows an exact schematic of this process.

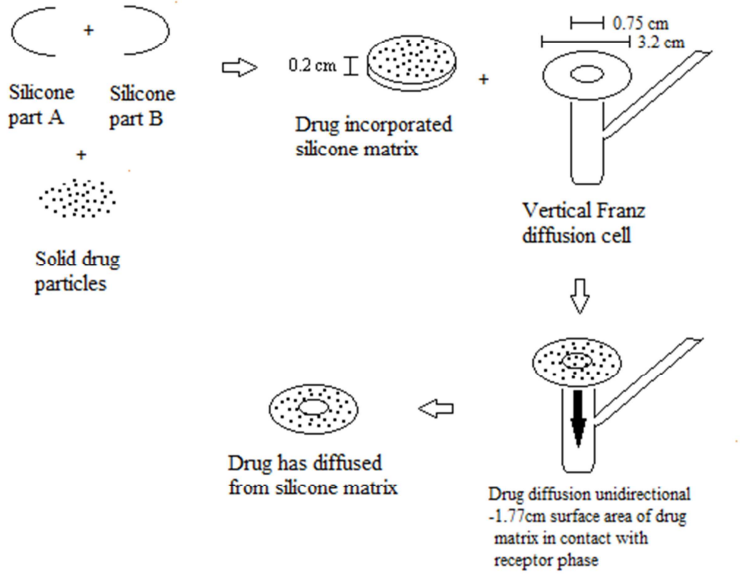

Figure 3.2: Schematic Figure of drug release from drug incorporated silicone matrix system.

Silicone is chosen because of its properties. It is an inorganic synthetic polymer, composed of repeated silicon-oxygen (Si-O) units in the polymer chain and organic groups linked to the silicon with C-Si bonds [4]. Silicone elastomers can be molded into different shapes and are commonly used in various types of medical devices and prosthetics. Specific advantages of silicone are its heat stability, chemical inertness, durability, biocompatibility and non-biodegradability [5, 6].

4 Problem description

In this chapter a more complete description of the mathematical model is presented along with a schematic figure. Case studies are explained along with parameters for each case.

4.1 Model conditions

It is assumed that the drug can only flow in one direction or in other words this is a semi-infinite problem. Figure 4.1 shows the direction of the flux and how drug release from silicone matrices is described. The lateral dimensions of the system are assumed to be much larger than its thickness *L*, so that the drug release process is effectively one-dimensional with a normal in *x*-direction. Flux and drug release can only occur at the lower boundary of the membrane or at $x = L$. Before measurements can start the membrane needs to reach equilibrium and it is assumed that the drug is uniformly distributed through the membrane at time $t = 0$. As time goes by the amount of solid drug in the matrix decreases as the drug travels further down the membrane until it has all transformed into dissolved drug. At $x = L$ the drug is collected in the receptor chamber.

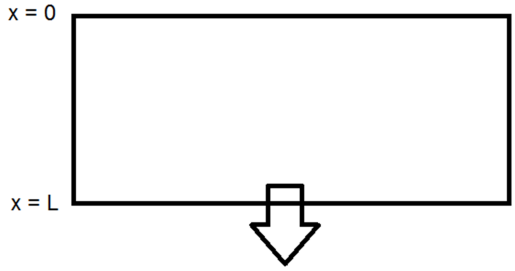

Figure 4.1: Schematic of the matrix system.

The change in concentration of dissolved drug, C, and of solid drug, S, is then given by the following equations.

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} + kA_0\left(\frac{S}{S_0}\right)^{2/3}(C_S - C) \qquad (4.1a)$$

$$\frac{\partial S}{\partial t} = -kA_0\left(\frac{S}{S_0}\right)^{2/3}(C_S - C) \qquad (4.1b)$$

Already introduced in equations (2.6 a and b). This is basically a one-dimensional diffusion equation with an additional term for drug dissolution.

The initial conditions for the model are expressed with:

$$IC: \begin{cases} C_0(0,x) = C_S \\ S_0(0,x) = \dfrac{M_0}{V_0} - C_S \end{cases} \tag{4.2}$$

Here M_0 is the initial amount of drug inserted in milligrams and V_0 is the initial volume that is, the surface area in the contact face times the membrane thickness. These conditions are used since the membrane is allowed to reach equilibrium before measurements start so there is concentration present at the very beginning.

The boundary conditions are expressed with:

$$BC: \begin{cases} \left.\dfrac{\partial C}{\partial x}\right|_{x=0} = 0 \\ C(t,L) = 0 \end{cases} \tag{4.3}$$

These conditions are known as perfect sink condition since it is assumed that there is no drug concentration present outside the matrix.

The amount of drug release is expressed by the following equation:

$$Q = S_0 L - \int_0^L (C + S)\, dx \tag{4.4}$$

The integral accounts for the entire drug remaining in the matrix. Q has the unit [mg/cm^2]. The PDEs are solved numerically by a second order difference scheme in space and a fully implicit first order difference scheme in time. This numerical scheme was implemented in Matlab. Two different drugs will be studied, Ibuprofen and Diclofenac. Since it is difficult to estimate the initial surface area of the drug per unit volume matrix we shall treat the product $k*A_0$ as a single parameter which is denoted by k' and is to be referred to as effective dissolution rate constant. It has dimension [1/day]. Different values of this effective dissolution rate constant, k', as well as the solubility, C_s, have great effect on how much drug is released through the silicon membrane. These effects are also viewed. In Chapters 4.2 and 4.3 three different cases for each drug will be represented along with the properties of the drugs.

4.2 Case studies for Ibuprofen

The silicone matrix is composed of 5 layers of equal thickness. The initial distributions of Ibuprofen with these layers in this study are:

Empty	5% Ibuprofen	5% Ibuprofen
Empty	5% Ibuprofen	5% Ibuprofen
Empty	5% Ibuprofen	5% Ibuprofen
Empty	5% Ibuprofen	5% Ibuprofen
5% Ibuprofen	5% Ibuprofen	Empty

Figure 4.2: Cases 1, 2 and 3 for Ibuprofen.

The specific cases in Figure 4.2 were chosen since the Pharmaceutical Department had carried out measurements for them. 5% Ibuprofen represents that in each layer there is 5% Ibuprofen and 95% silicone. The drug is put into each layer and then all five layers are put together. Case 1 was chosen since it is the simplest case possible. Case 2 was chosen to see if it has any effects on the results to make the drug go through many layers. Case 3 was chosen to see if it was possible to control the drug release with empty layers.

Ibuprofen is a non-steroidal anti-inflammatory drug. It is used for relief of symptoms of arthritis, primary dysmenorrhea, fever and as an analgesic especially where there is an inflammatory component. Ibuprofen is known to have an antiplatelet effect, though it is relatively mild and short-lived when compared with other better-known antiplatelet drugs such as aspirin. In general, Ibuprofen also acts as a vasodilator, having been shown to dilate coronary arteries and some other blood vessels. Ibuprofen is a core medicine in the World Health Organization's "WHO Model List of Essential Medicines", which is a list of minimum medical needs for a basic healthcare system.

Known parameters for Ibuprofen are presented in Table 4.1:

Table 4.1: Known parameters for Ibuprofen.

Description	Parameter	Ibuprofen
Dimensional solubility of drug in the polymer matrix	C_s	0.042 mg/cm^3
Diffusion coefficient for the drug in the matrix	D	
For Case 1:		0.00169 cm^2/hour
For Cases 2 and 3:		0.00138 cm^2/hour
Quantity of initial drug	M_0	
For Case 1:		2.75 mg
For Case 2:		14.94 mg
For Case 3:		13.82 mg
Membrane thickness	L	0.2 cm
Membrane surface area intact with contact face	A_M	1.77 cm^2

Membrane surface area intact with contact face, A_M, is calculated from the membrane radius which is 1.6 cm. However only 22% of the membrane is in contact with the contact face and therefore the area becomes 1.77 cm^2.

The measurements were carried out for two different types of silicone. That explains the two different values for the diffusion coefficient in Table 4.1.

4.3 Case studies for Diclofenac

The three cases of Diclofenac are shown in Figure 4.3. Cases 1, 2 and 3 were chosen do to same reasons are for the Ibuprofen.

Empty
Empty
Empty
Empty
5% Diclofenac

5% Diclofenac
5% Diclofenac
5% Diclofenac
5% Diclofenac
5% Diclofenac

1% Diclofenac
1% Diclofenac
Empty
1% Diclofenac
Empty

Figure 4.3: Cases 1, 2 and 3 for Diclofenac.

1% and 5% Diclofenac represent that in each layer there is 1% or 5% Diclofenac and 99% or 95% silicone, respectively.

Diclofenac is a non-steroidal anti-inflammatory drug taken to reduce inflammation and as an analgesic reducing pain in certain conditions. The drug is mainly used for musculoskeletal complaints, especially arthritis, rheumatoid arthritis, polymyositis, dental pain and pain

management in cases of kidney stones and gallstones. An additional indication is the treatment of acute migraines. Diclofenac is used commonly to treat mild to moderate post-operative or post-traumatic pain, particularly when inflammation is also present and is effective against menstrual pain and endometriosis.

Known parameters for Diclofenac are presented in Table 4.2:

Table 4.2: Known parameters for Diclofenac

Description	**Parameter**	**Diclofenac**
Dimensional solubility of drug in the polymer matrix	C_s	$0.6*10^{-3}$ mg/cm^3
Diffusion coefficient for the drug in the matrix	D	
For Case 1:		$0.52*10^{-3}$ cm^2/hour
For Cases 2 and 3:		0.00104 cm^2/hour
Quantity of initial drug:	M_o	
For Case 1:		3.63 mg
For Case 2:		16.95 mg
For Case 3:		2.12 mg
Membrane thickness	L	0.2 cm
Membrane surface area intact with contact face	A_M	1.77 cm^2

In next chapter all of these cases are studied and compared to measurements.

5 Results and comparison with data

With the model described in equations (4.1a) and (4.1b) six case studies were made. The model was run with parameters from the Pharmaceutical Department of the University of Iceland for the drugs Ibuprofen and Diclofenac [14]. The quantity of released drug, Q, was calculated for different values of solubility, C_s, and effective dissolution rate constant, k'. 3D graphs were made to show how solid and dissolved drug change with time and distance through the membrane and in a specific time point for different values of k'. The quantity of released drug was compared to measured data from the Pharmaceutical Department.

5.1 Results for Ibuprofen

5.1.1 Case 1 for Ibuprofen

As already was mentioned this is the simplest case possible. The drug only diffuses through the bottom layer so the thickness is now $L = 0.04$ cm.

Empty
Empty
Empty
Empty
5% Ibuprofen

Figure 5.1 shows the quantity of released drug as a function of time for different values of the drug solubility for Case 1:

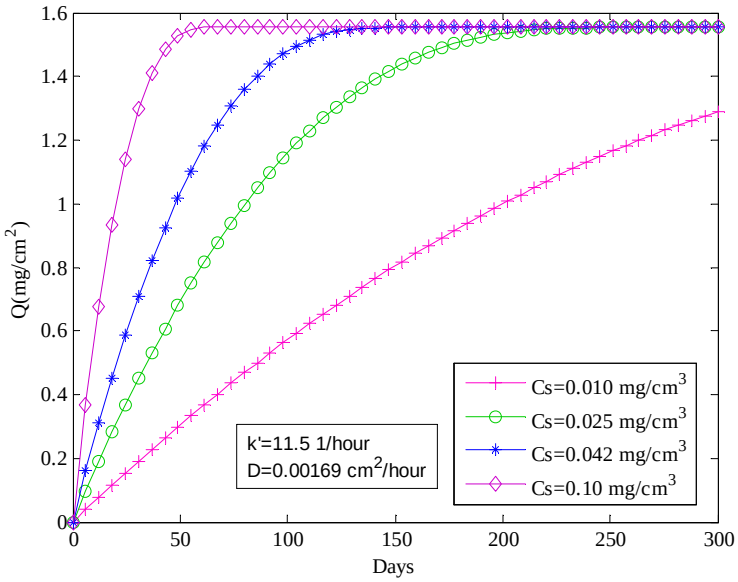

Figure 5.1: Quantity of drug release as a function of time for increasing values of C_s.

As the drug solubility increases the drug is released through the membrane in a shorter amount of time. This is to be expected since the higher the solubility the faster is the rate of drug dissolution according to equations (4.1a) and (4.1b).

Figure 5.2 shows the quantity of released drug as a function of time for different values of the effective dissolution rate.

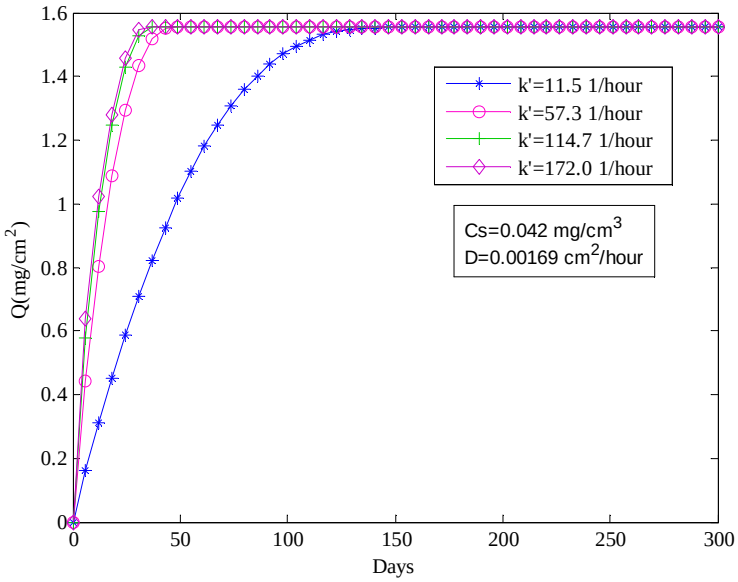

Figure 5.2: Quantity of drug release as a function of time for increasing values of k'.

As the effective dissolution rate increases the drug is released through the membrane in a shorter period of time. This was expected since the higher dissolution rate the faster the drug travels through the membrane. Figures 5.3 and 5.4 show how the quantity of solid and dissolved drug changes with time and distance through the membrane.

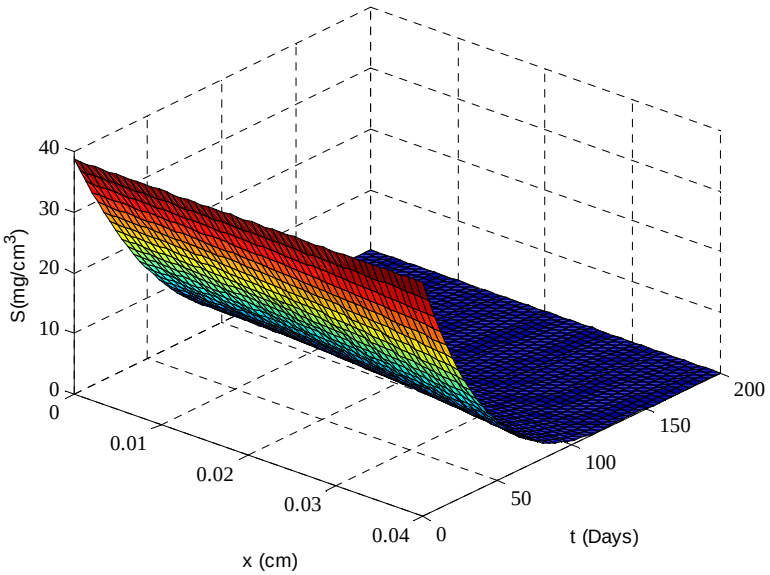

Figure 5.3: Solid drug as a function of time and distance with k' = 11.5 1/hour, C_s = 0.042 mg/cm^3 and D = 0.00169 cm^2/hour.

The amount of solid drug does not change much through the membrane for each time point. After t = 125 days there is no solid drug left in the membrane for given C_s, D and k'.

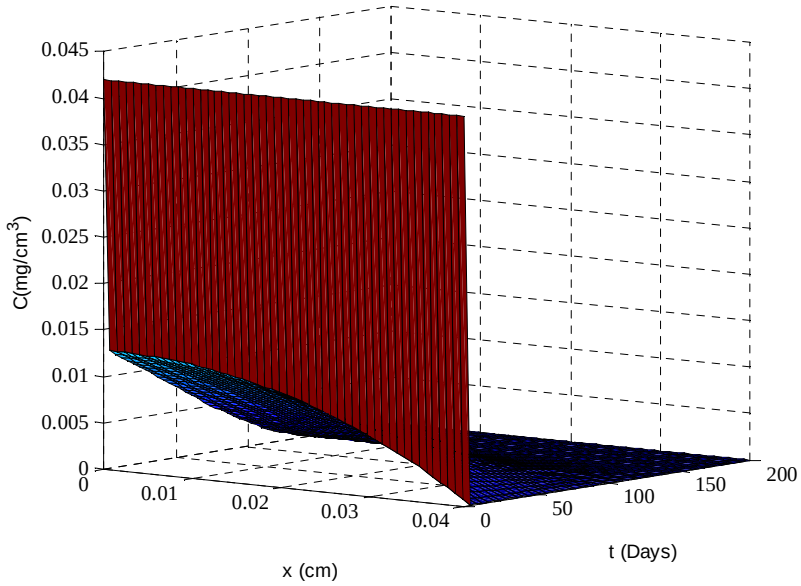

Figure 5.4: Dissolved drug as a function of time and distance with k' = 11.5 1/hour, C_s = 0.042 mg/cm^3 and D = 0.00169 cm^2/hour.

At $t = 0$ the values for dissolved drug start at $C = 0.042$ mg/cm^3 through the entire membrane according to the initial condition in equation (4.2). As time passes the values for dissolved drug decrease along the upper boarder or at $x = 0$. At $x = L$ there is no dissolved drug present according to perfect sink boundary condition (4.3), according to which there is no drug concentration outside the matrix.

Figure 5.5 shows how the amount of solid drug changes through the membrane when the effective dissolution rate changes at a specific point $t = 30$ days.

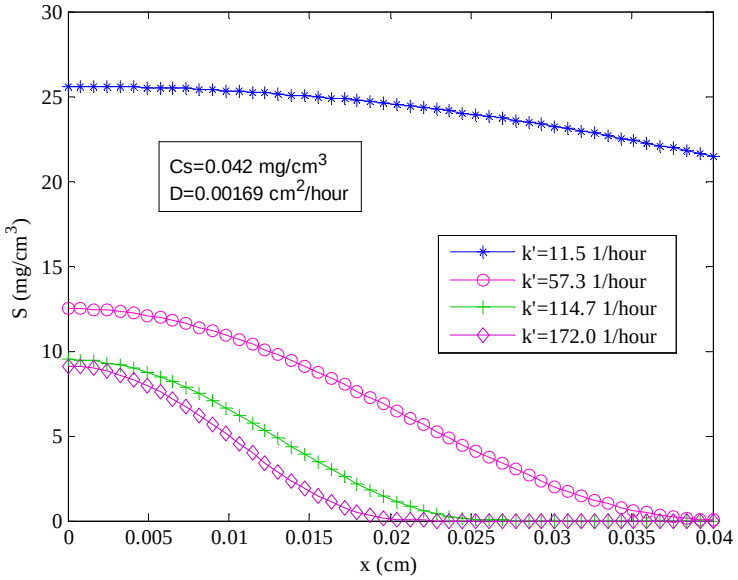

Figure 5.5*: Solid drug for different k' values at t = 30 days.*

As *k'* increases the less amount of solid drug is present at each point in the membrane. The drug dissolves more quickly and therefore the amount of solid drug decreases.

Figure 5.6 shows how the amount of dissolved drug changes through the membrane when the effective dissolution rate changes at the specific point t = 30 days.

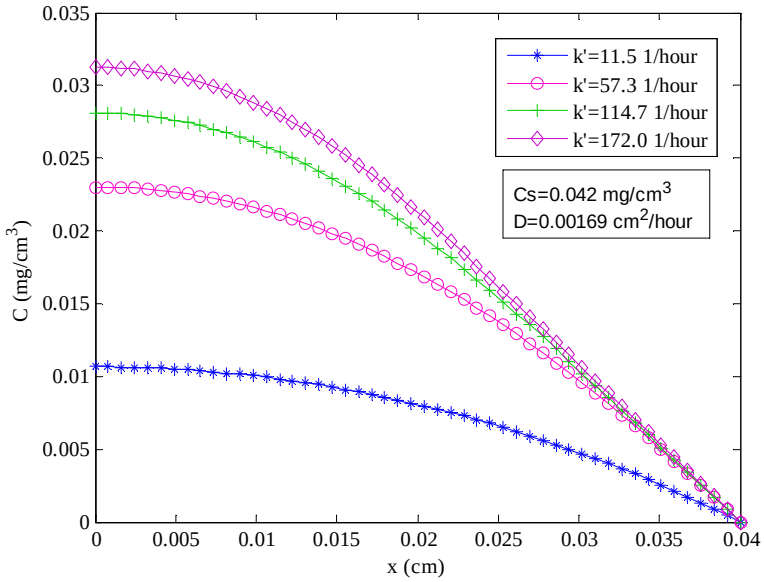

Figure 5.6: Dissolved drug for different k' values at t = 30 days.

As *k'* increases more amount of dissolved drug is present at point t = 30 days. The solid drug changes into dissolved drug before passing out of the membrane and therefore the quantity of dissolved drug increases with increasing effective dissolution rate.

Figure 5.7 shows the numerical model compared with the Higuchi model and measurements for Ibuprofen.

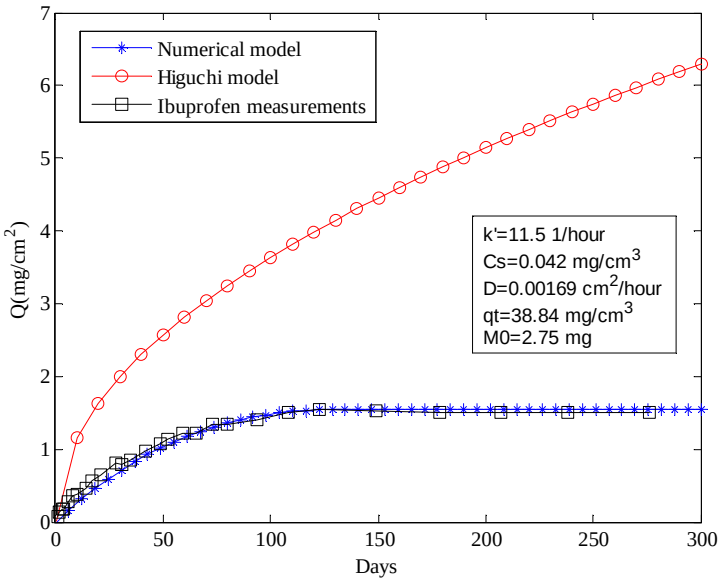

Figure 5.7*: Quantity of drug release as a function of time for the numerical and Higuchi models along with the data for Ibuprofen.*

The value for q_t is calculated from the initial drug (M_0) divided by the membrane area (A) and membrane thickness (L).

$$q_t = \frac{M_0}{A_M * L} = \frac{2.75\ mg}{1.77\ cm^2 * 0.04\ cm} = 38.84\ mg/cm^3$$

The two models do not compere well. Higuchi's model assumes that the membrane thickness is infinite and that the dissolution rate is instantaneous and therefore the curve will grow infinitely. The Higuchi model compares better with the numerical model as *k'* increases. The numerical model fits very well with the Ibuprofen data for this specific dissolution rate constant. According to the measurements all the Ibuprofen has been released through the membrane after approximately 120 days. The figure shows that Higuchi model is very limited and cannot be used to describe the drug release through a silicone membrane.

By changing the parameters C_s and *k'* it is possible to control the quantity of released drug. By running an optimizing routine in Matlab it was established that the best fit for the measurements for Case 1 is given with *k'* = 917.5 1/hour and C_s = 0.0080 mg/cm^2. The diffusion coefficient is the same as before. Figure 5.8 shows the quantity of released drug for these parameters along with the measurements for Ibuprofen and the numerical model with parameters from the Pharmaceutical Department as was shown in Figure 5.7.

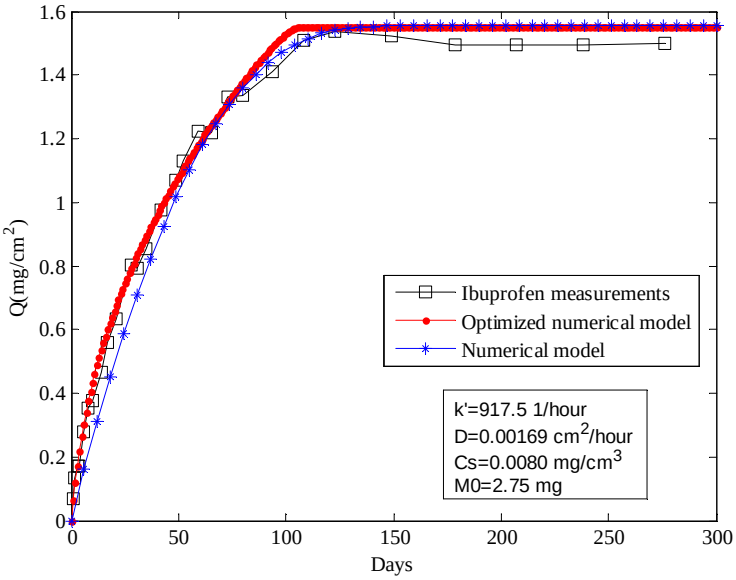

Figure 5.8: Quantity of drug release as a function of time for the numerical model with optimized parameters for C_s and k'.

The numerical model fits the measurements better than in Figure 5.7. Note that the value for k' is ~ 80 times larger whereas the value for Cs is ~ 50 times smaller. Such a correlation is to be expected since these parameters are strongly related and also indicates that it is difficult to estimate separate values of these parameters by a parametric fit.

Figure 5.9 shows a 3D plot of how the solid drug changes with time and distance.

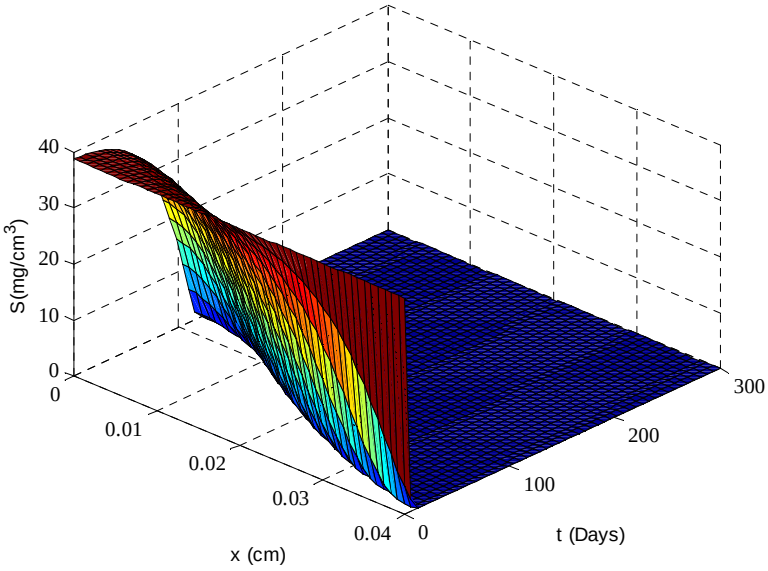

Figure 5.9: Solid drug as a function of time and distance with optimized parameters for C_s and k'.

Here an empty zone is formed that is, no drug is present. As the drug travels further down the membrane and as time passes the higher percentage of the drug is dissolved and passes out of the membrane. By increasing the dissolution rate constant the non-zero zone would decrease faster.

Figure 5.10 shows the values for solid drug at the specific point $t = 30$.

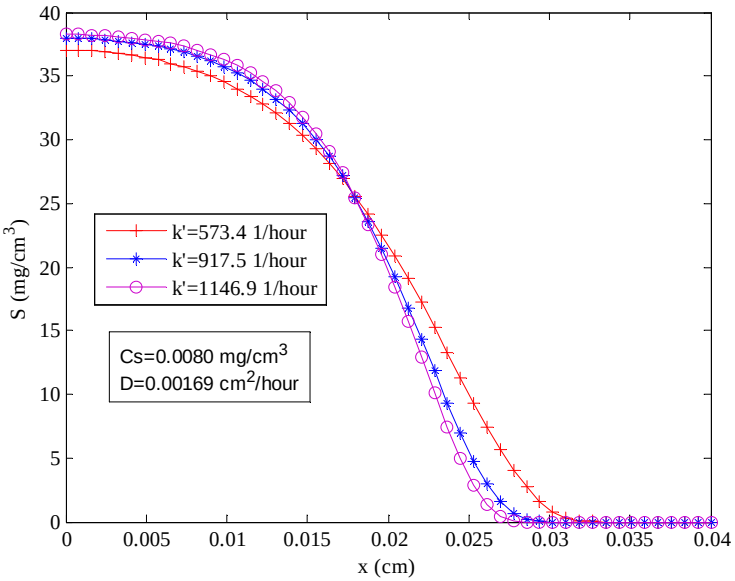

Figure 5.10: Solid drug for different k' values at t = 30 days.

As *k'* increases the less amount of solid drug is present at each point in the membrane and the zone boundaries gets more defined.

5.1.2 Case 2 for Ibuprofen

Now there is drug present in all five layers and therefore the drug needs to diffuse through five layers. The thickness of the membrane is now $L = 0.2$ cm.

5% Ibuprofen
5% Ibuprofen
5% Ibuprofen
5% Ibuprofen
5% Ibuprofen

Figure 5.11 shows the quantity of released drug as a function of time for Case 2 for Ibuprofen compared with measurements from the Pharmaceutical Department.

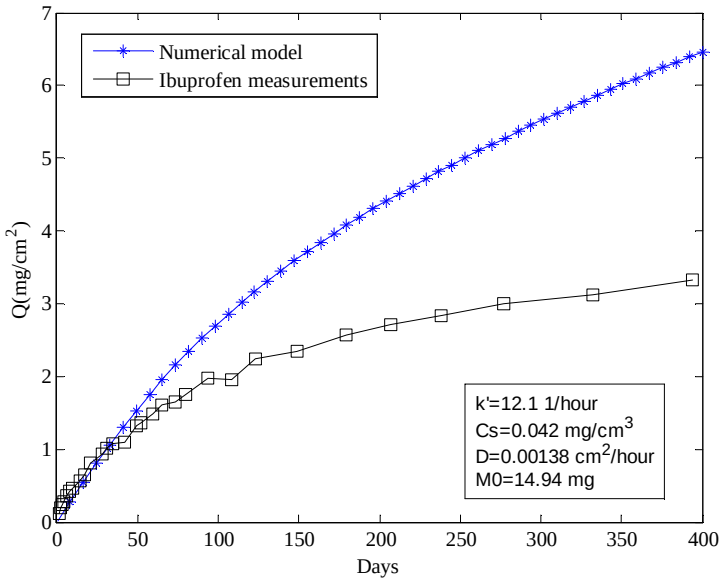

Figure 5.11: Quantity of drug release as a function of time for the numerical model and the data for Ibuprofen.

The numerical model and data compare well for the first 40 days. It seems like the silicone membrane saturates after a period of time and therefore drug remains in the membrane. According to measurements approximately 38% of the initial drug has been released through the membrane after 394 days. According to the numerical model, however, the entire drug will pass out of the membrane eventually.

Figure 5.12 shows when the entire drug has passed out through the membrane with Ibuprofen in all five layers.

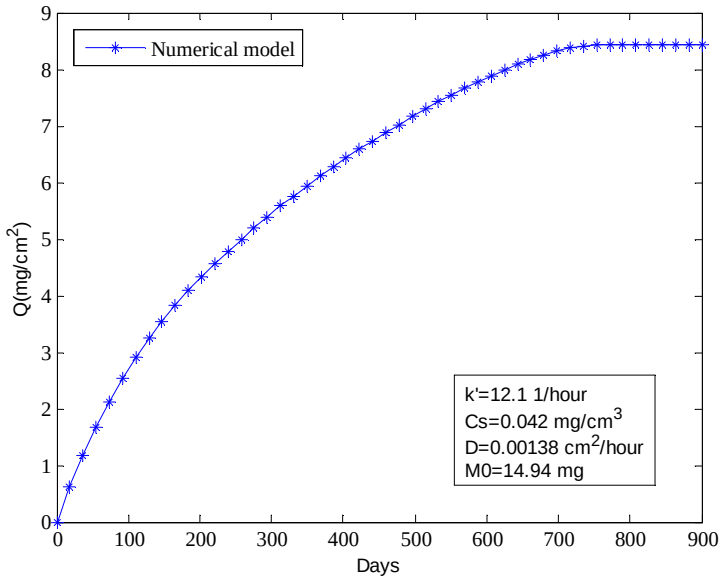

Figure 5.12: Quantity of drug release as a function of time for the numerical model.

After 750 days all the Ibuprofen has diffused out of the silicone membrane.

As before, by changing the parameters C_s and k' it is possible to control the quantity of released drug. Figure 5.13 shows the quantity of released drug when C_s = 0.0125mg/cm^3 and k' = 970 1/hour but with D = 0.00138 mg/cm^3 as before.

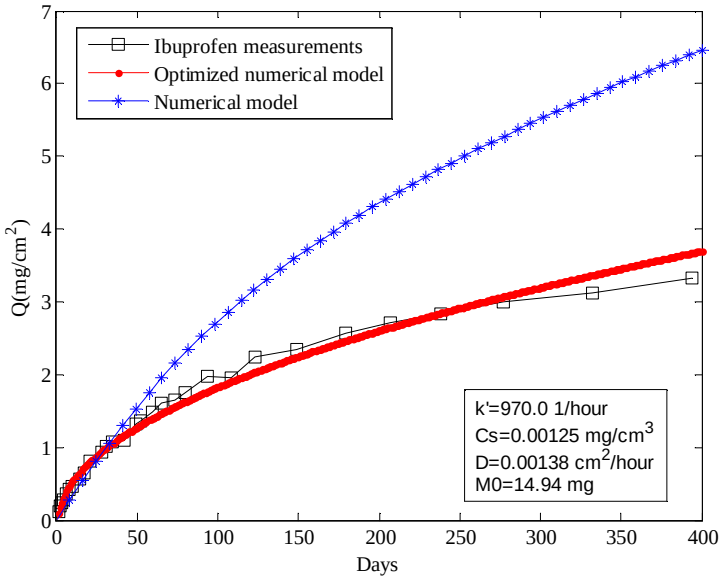

Figure 5.13: Quantity of drug release as a function of time for the numerical model.

The numerical model fits the measurements better than in Figure 5.11. After 300 days the curves split and more drug is released through the membrane according to the numerical model than happens in reality.

Figure 5.14 shows a 3D plot of how the solid drug changes with time and distance.

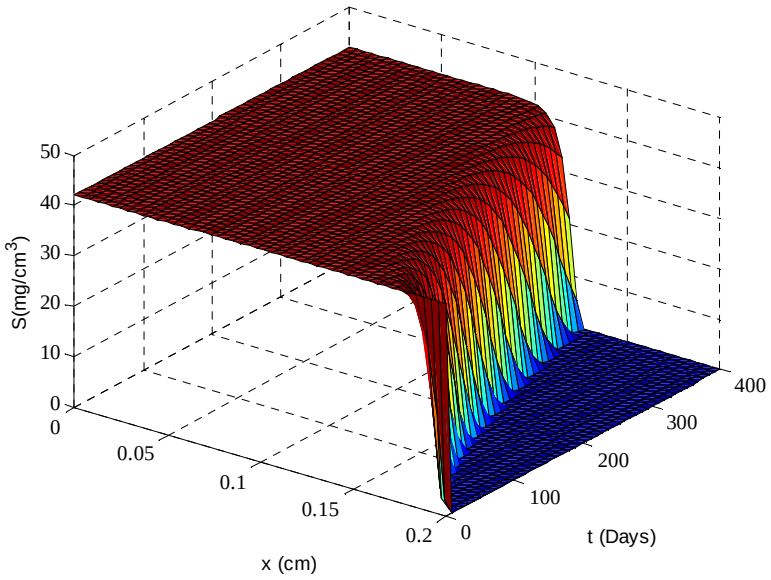

Figure 5.14: Solid drug as a function of time and distance with k' = 917 1/hour, C_s = 0.0125 mg/cm^3 and D = 0.00138 cm^2/hour.

As for Case 1 an empty zone is formed where no drug is present. As the drug travels further down the membrane and as time passes the higher percentage of the drug is dissolved and passes out of the membrane. By putting a higher value for the dissolution rate constant the non-zero zone would decrease faster.

Figure 5.15 shows the values for solid drug at the specific point t = 30.

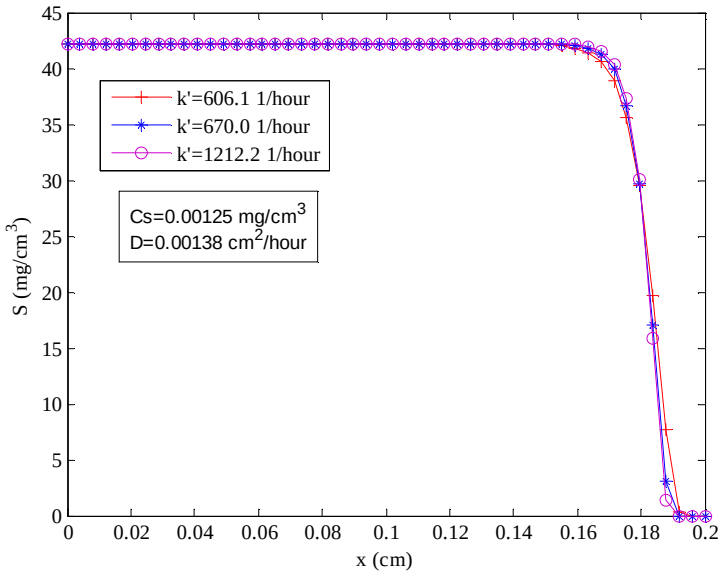

Figure 5.15: Solid drug for different k' values at t = 30 days.

According to the figure there is not much change, but as *k'* increases less amount of solid drug is present at each point in the membrane and the zone boundaries get more defined.

5.1.3 Case 3 for Ibuprofen

Now there is drug present in four top layers and the last layer is empty. As was mentioned before, this is done to see if it is possible to control the quantity of released drug. The thickness is still L = 0.2 cm.

5% Ibuprofen
5% Ibuprofen
5% Ibuprofen
5% Ibuprofen
Empty

Figure 5.16 shows the quantity of released drug as a function of time for Case 3 for Ibuprofen compared with data from the Pharmaceutical Department.

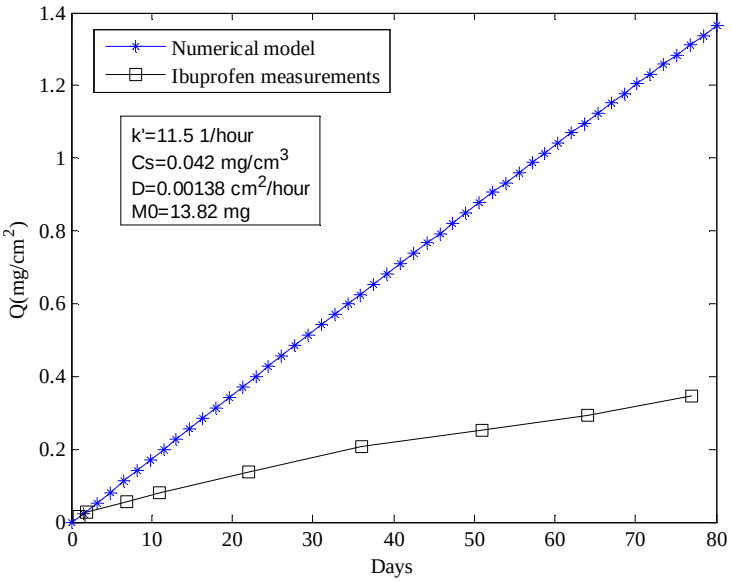

Figure 5.16: Quantity of drug release as a function of time for the numerical model and the data for Ibuprofen.

The numerical model and the measurements do not compare well at all. According to measurements approximately 4.5% of the initial drug has been released through the membrane after 77 days indicating that the diffusion coefficient in the bottom layer is in fact lower than that used in the numerical model. Such "blocking" by the bottom layer would lead to saturation in the remaining four layers that would slow down the drug dissolution.

Figure 5.17 shows when the entire Ibuprofen has passed out through the membrane with 4 layers of Ibuprofen.

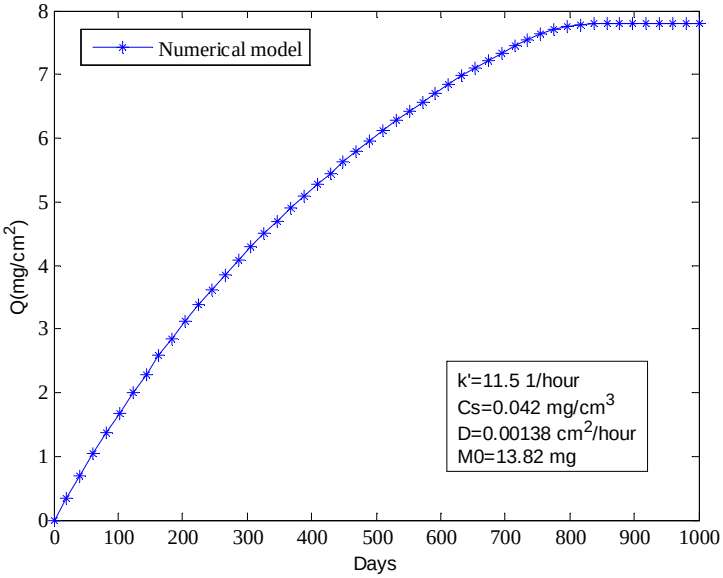

Figure 5.17: Quantity of drug release as a function of time for the numerical model.

After 800 days all the Ibuprofen has passed out of the silicone membrane.

5.2 Results for Diclofenac

5.2.1 Case 1 for Diclofenac

As for the Ibuprofen, we start with the simplest case and the thickness is L = 0.04 cm.

Empty
Empty
Empty
Empty
5% Diclofenac

Figure 5.18 shows the quantity of released drug as a function of time for different values of the drug solubility for Case 1 for Diclofenac.

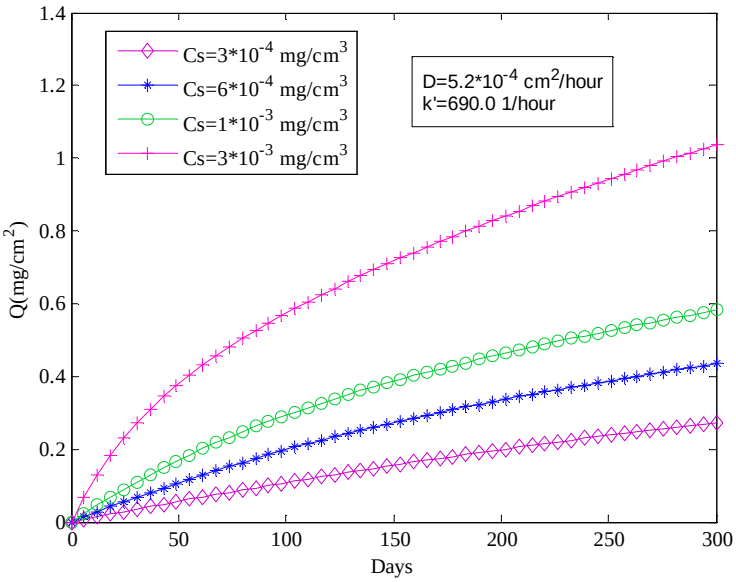

Figure 5.18: Quantity of drug release as a function of time for increasing values of C_s.

As C_s increases the drug is released through the membrane in a shorter amount of time. This is to be expected since the higher the solubility the faster is the rate of drug dissolution according to equations (4.1a) and (4.1b).

Figure 5.19 shows the quantity of released drug as a function of time for different values of the effective dissolution rate.

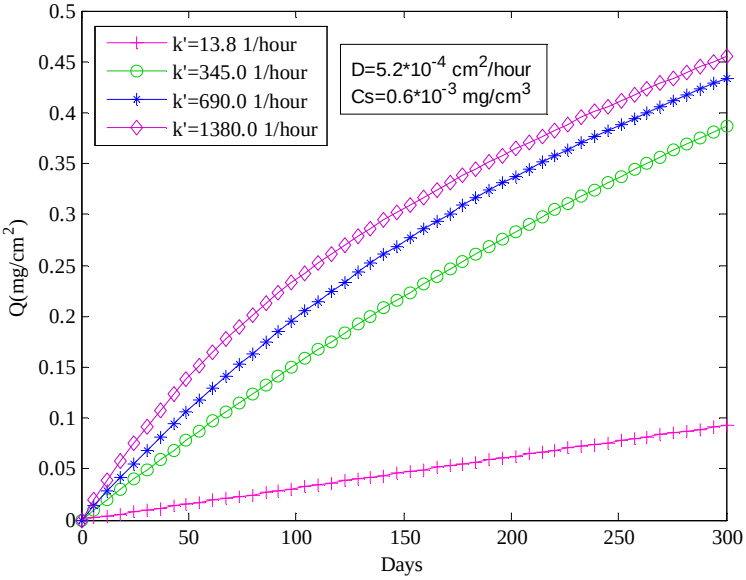

Figure 5.19: Quantity of drug release as a function of time for increasing values of k'.

As *k'* increases the drug is released through the membrane in a shorter amount of time and therefore the amount of released drug is higher for each time point.

Figure 5.20 shows how the quantity of solid drug changes with time and distance through the membrane.

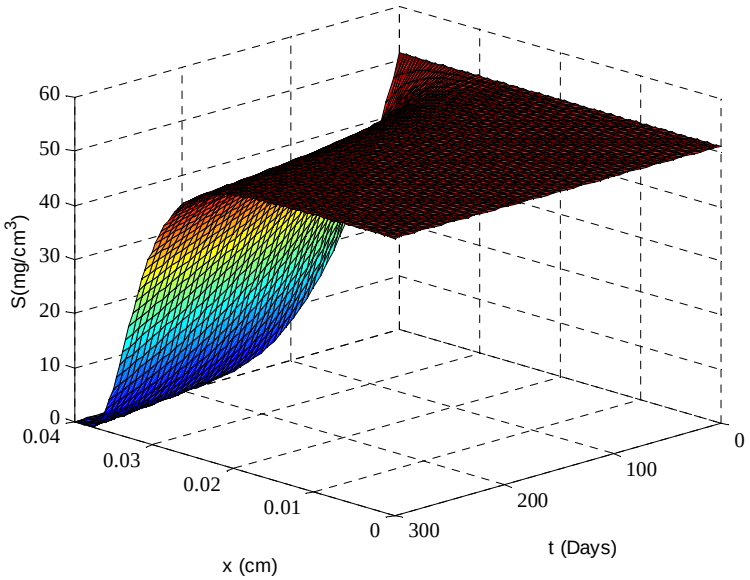

*Figure 5.20:Solid drug as a function of time and distance with k' = 690 1/hour, C_s = 0.6*10^{-3} mg/cm^3 and D = 5.2*10^{-3} cm^2/hour.*

For the first half of the membrane there is little as no change in the amount of solid drug present. After that the solid drug changes into dissolved drug and starts to pass out of the membrane. At t = 0 there is no change through the membrane according to the initial condition in equation (4.2). At t = 300 days and x = 0.04 cm there is no solid drug present in the membrane since it has all dissolved.

Figure 5.21 shows how the quantity of dissolved drug changes with time and distance through the membrane.

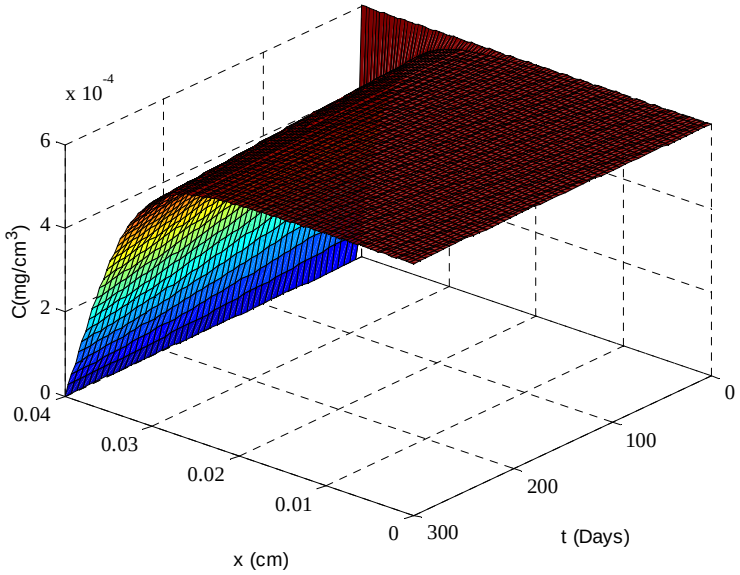

Figure 5.21: Dissolved drug as a function of time and distance with k' = 690 1/hour, $C_s = 0.6*10^{-3}$ mg/cm^3 and $D = 5.2*10^{-3}$ cm^2/hour.

According to the initial condition in equation (4.2) the values for dissolved drug is 0.0006 mg/cm^3 at the boundary $x = 0$ as well as for $t = 0$. The values for dissolved drug reach zero at the boundary $x = 0.04$ cm.

Figure 5.22 shows how the amount of solid drug changes through the membrane when the effective dissolution rate changes at the specific point t = 150 days.

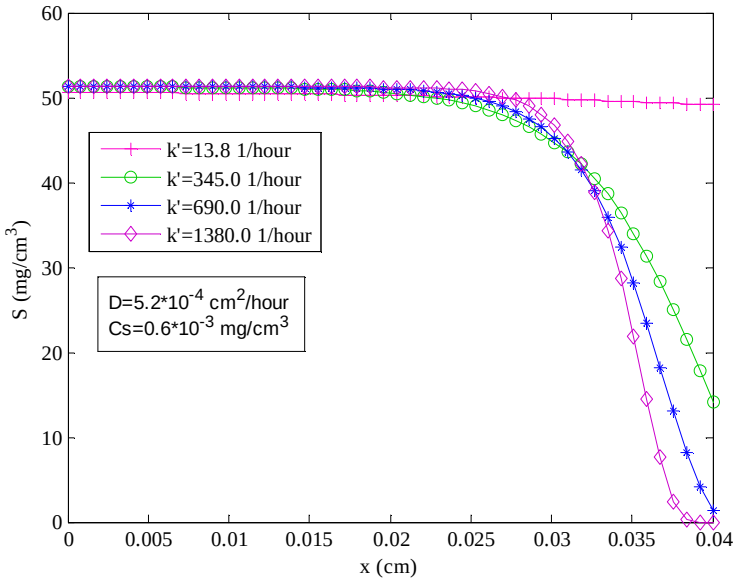

Figure 5.22: Solid drug for different k' values at t = 150 days.

As *k'* increases the less amount of solid drug is present at point t = 150 days. The drug passes out of the membrane more quickly and therefore the amount of drug decreases. Empty zones remain near the lower boundary layer.

Figure 5.23 shows how the amount of dissolved drug changes through the membrane when the effective dissolution rate changes at the specific point t = 150 days.

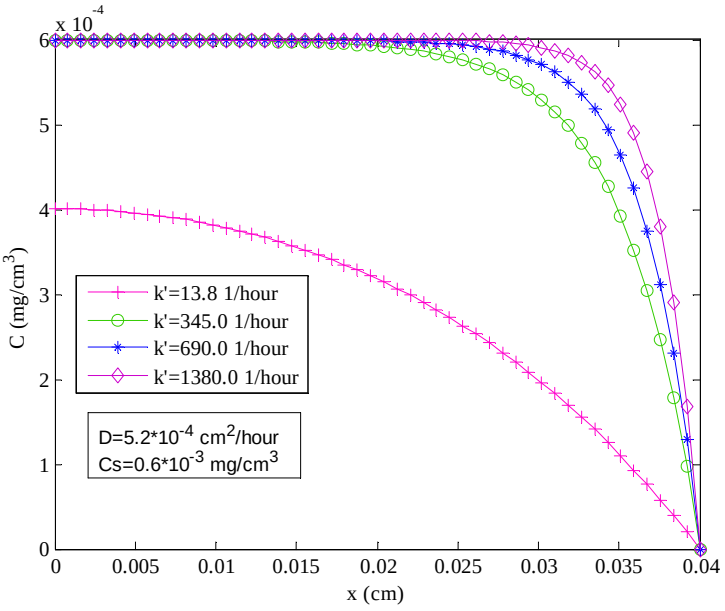

Figure 5.23: Dissolved drug for different k' values at t = 150 days.

As *k'* increases the more amount of dissolved drug is present at point *t* = 150 days. The solid drug changes into dissolved drug before passing out of the membrane and therefore the quantity of dissolved drug increases with increasing dissolution rate.

Figure 5.24 shows the comparison between the numerical model, Higuchi model and data for Diclofenac.

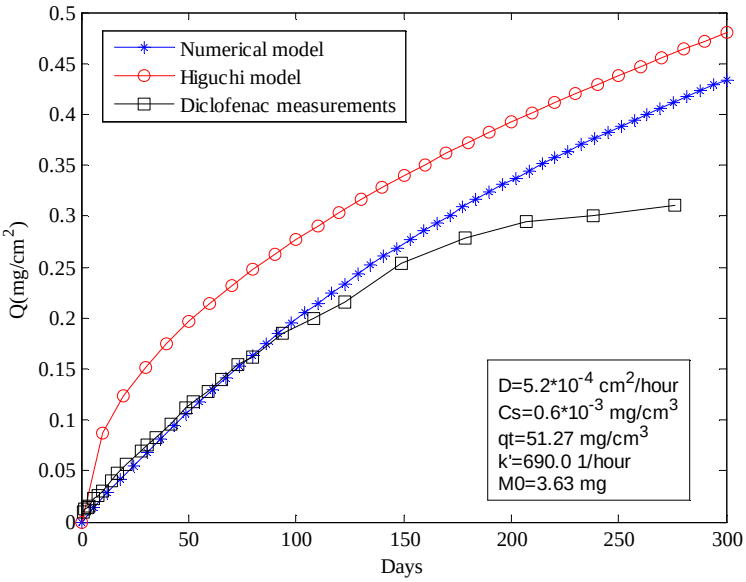

Figure 5.24: Quantity of drug release as a function of time for the numerical and Higuchi models along with the data for Diclofenac.

The numerical model fits very well to the Diclofenac data for the values of the dissolution rate constant equal to 690 1/hour for the first 100 days. After that more drug is released according to the model. However even more drug is released according to the Higuchi model. This is because in that model the membrane is assumed to be infinite. According to the measurements 15.1% of the initial Diclofenac has been released through the membrane after 277 days.

Figure 5.25 shows the numerical model compared with the Higuchi model for a longer period of time.

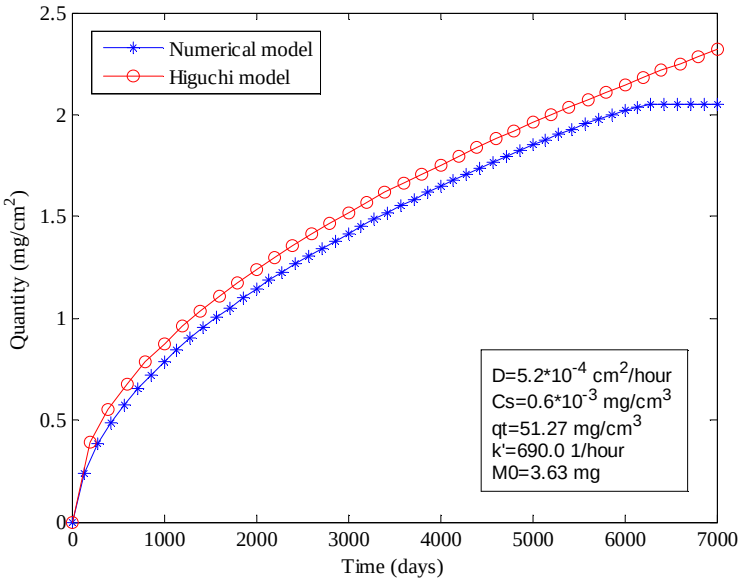

Figure 5.25: Quantity of drug release as a function of time for the numerical and Higuchi models.

The curves for the numerical model and the Higuchi model have the same form up to t = 6000 days when the entire drug has passed through the membrane according to the numerical model. After that the curve for the numerical model remains constant but the Higuchi curve continues to grow.

5.2.2 Case 2 for Diclofenac

Now there is drug present in all five layers so the drug needs to diffuse through five layers. The thickness of the membrane is now L = 0.2 cm.

5% Diclofenac
5% Diclofenac
5% Diclofenac
5% Diclofenac
5% Diclofenac

Figure 5.26 shows the quantity of released drug as a function of time for Case 2 for Diclofenac compared with data from the Pharmaceutical Department.

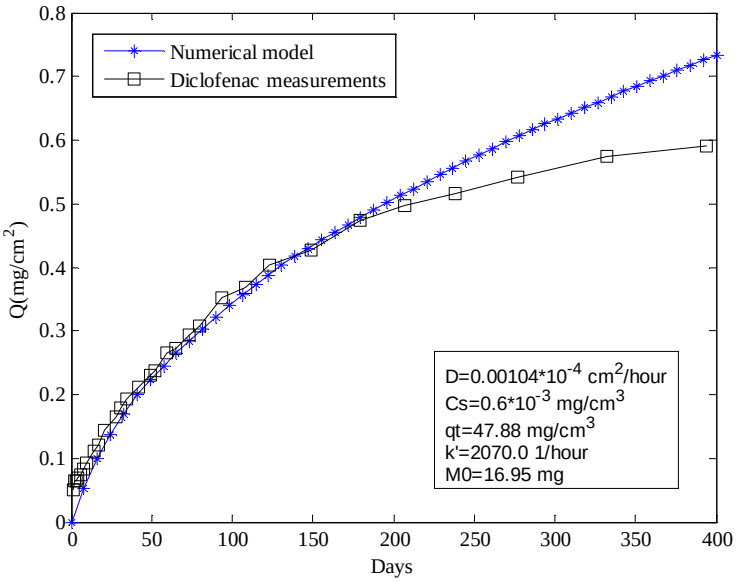

Figure 5.26: Quantity of drug release as a function of time for the numerical model compared with the data for Diclofenac.

The numerical model and the data compare very well for the first 200 days for the dissolution rate *k'* = 2070 1/hour. After that the model assumes more drug release. According to the measurements 5.8% of the initial Diclofenac has been released through the membrane after 394 days. As with the Ibuprofen it is likely that not all drug particles dissolve in the membrane and therefore the quantity of released drug is so little.

Figure 5.27 shows when the entire drug has passed through the membrane with 5 layers of Diclofenac.

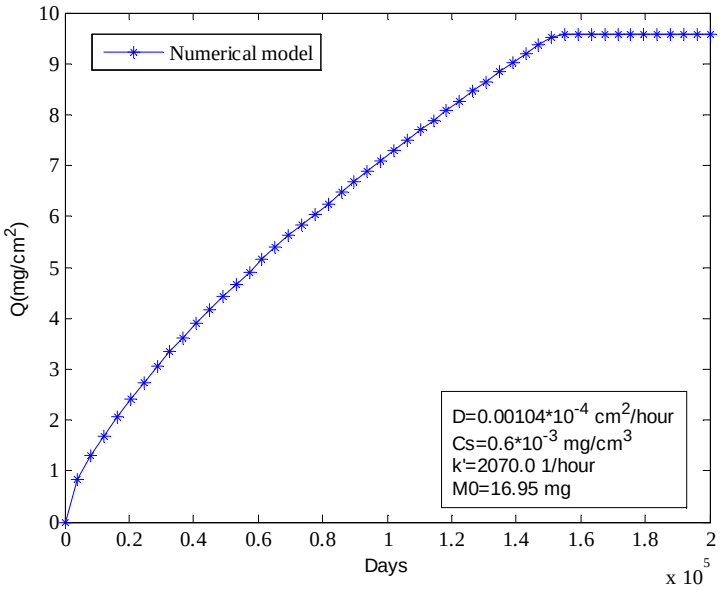

Figure 5.27: Quantity of drug release as a function of time for the numerical model.

It takes about 150.000 days for all the Diclofenac to pass through the membrane for given C_s, D and k'.

5.2.3 Case 3 for Diclofenac

Now there is Diclofenac present in three layers and two layers are empty. As was expressed before, this is done to see if it is possible to control the quantity of released drug. The thickness is still L = 0.2 cm.

1% Diclofenac
1% Diclofenac
Empty
1% Diclofenac
Empty

Figure 5.28 shows the quantity of released drug as a function of time for Case 3 for Diclofenac compared with data from the Pharmaceutical Department.

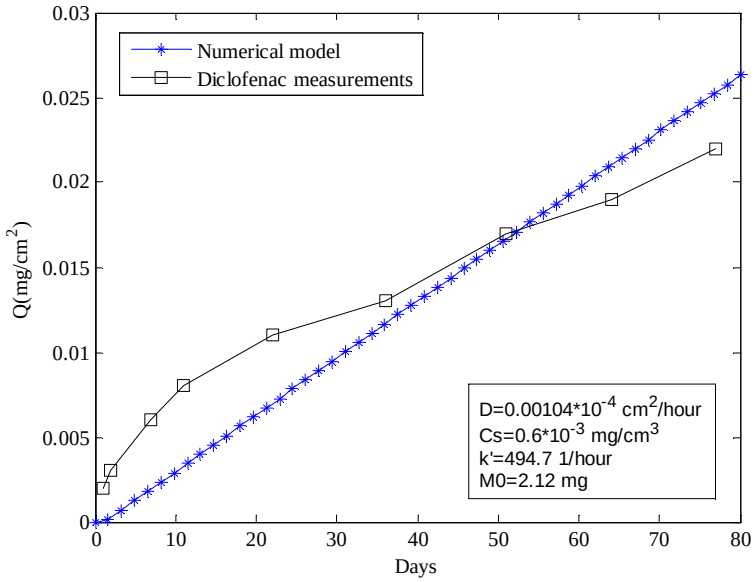

Figure 5.28: Quantity of drug release as a function of time for the numerical model compared with the data for Diclofenac.

According to the figure more drug seems to pass through the membrane in real life for the first 50 days then is accounted for by the numerical model. However this measurement was carried out for a shorter period of time than in the other two cases for Diclofenac so it remains to be seen what will have happen in real life after 300 days. But as before the membrane is assumed to saturate and after 50 days more drug has passed out of the membrane according to the numerical model then in the measurements. According to the measurements only 1.8% of the initial drug gets passed out of the membrane.

Figure 5.29 shows when the entire drug has passed through the membrane with 2 empty layers and 3 layers of Diclofenac.

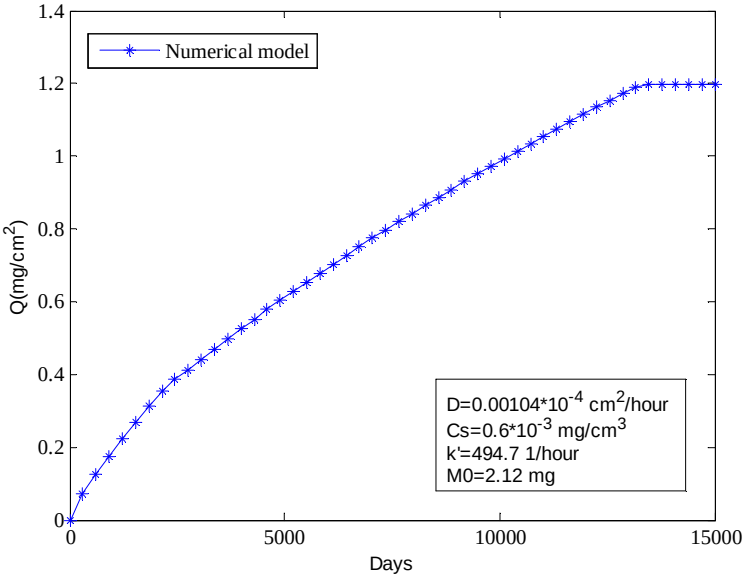

Figure 5.29: Quantity of drug release as a function of time for the numerical model.

It takes about 14000 days for the entire quantity of Diclofenac to diffuse out of the membrane with those specific values for *k'*, C_s and *D*.

6 Conclusions

The focus of this study was to develop a numerical model that describes the control of release for drugs through silicone matrices. So far the model works well for some multi-layered cases that have semi-infinite geometry. Since there is no easy way to measure the dissolution rate constant, the values used in this project were chosen to achieve the best fit for the measurements.

The numerical model seems to describe the drug release with k' = 11.5 1/hour for Case 1 of Ibuprofen when the entire drug passes through the membrane. As the layers were added up to five for Case 2, the model compared well to the data for up to 40 days. After that more drug is released according to the numerical model. The only obvious explanation for this is that the membrane saturates so that not all drug particles dissolve in the membrane and therefore the drug release is not as high as it is according to the numerical model. When an empty layer is put at the bottom of the membrane as in Case 3 the drug release decreases even more. Now the entire drug needs to diffuse through an empty layer before passing out of the membrane. If it would be possible to put a stimulus substance in the empty silicone layer, the diffusion would without a doubt be faster. As Figures 5.8-5.10 show it is very easy to control the drug release by changing the parameters of the effective dissolution rate constant and the solubility of the drug. If it is possible to control the concentration of the drug in each layer the numerical model can foretell with much accuracy the amount of drug released through a silicone membrane as well as the solid drug concentration in the material at each time point.

For Diclofenac the numerical model did not work as well as for the Ibuprofen. For Case 1 the model fits the data well for the first 50 days, after that it assumes more drug release. The most likely reason for this is that the values of the dimensional solubility of drug, C_s, and the diffusion coefficient, D are assumed to be too low. The membrane seems to saturate and the drug release becomes only a few percent of the amount of drug that was initially put in to the membrane. The changes in silicone for Cases 2 and 3 seems to be better for the drug release, since the new diffusion coefficient is two times larger than the first one. Case 2 fits the measurements well for 200 days if k' = 2070 1/hour. If the effective dissolution rate constant is set to a lower value, the calculated released drug amount would be smaller. For Case 3 the measurements were only done for 77 days and there were 2 empty layers in the membrane. Due to this only 1.8% of the initial drug diffuses out of the membrane.

From this we can draw the conclusion that the numerical model works well for drugs with rather high values for drug solubility and diffusion coefficient. As these parameters decrease the effective dissolution rate constant needs to increase. For drugs similar to Diclofenac, that have very low drug solubility as well as low diffusion coefficient the model compares well only at the early stages. After that the membrane seems to saturate and since the concentration is almost constant throughout the membrane the effect of the diffusion is limited. When empty layers have been added to the membrane the model does not fit as well to the measurements. As a result from that the drug release decreases. The effective

dissolution rate constant, k', dimensional solubility of drug, C_s, and the diffusion coefficient, D, have a big influence on the model. It is easy to control the drug release by changing these parameters.

The future work for this project would be to have the numerical model work for any type of geometry with different drug concentration in the layers of the membrane and combine the use of it with more accurate estimates of the relevant values.

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