Final Project

On

Modeling of drug penetration through skin in Transdermal drug delivery system

Ishan Jain

CIVIL AND ENVIRONMENTAL ENGINEERING,

VIRGINIA TECH, BLACKSBURG

Abstract

Today about 74% of drugs are taken orally and are found not to be as effective as desired [1]. Therefore, there is a dire demand to improve current oral drug delivery methods or produce alternate routes for effective drug delivery for better patient compliance and effective treatment.

To improve such characters transdermal drug delivery system was emerged [1]. In this report special focus is made on transdermal delivery system as an alternate drug delivery route.

Major focus of this report is to provide analytical and numerical solutions for predicting the model drug penetration concentration through skin in transdermal drug delivery system.

This report provides detailed discussion on the following two different models:

1) Steady state (simpler model that can be solved both analytically and numerically) analysis of drug concentration in the skin thickness and,
2) Unsteady state analysis (more robust model which will also provide the early drug penetration profile) of drug concentration in the skin thickness.

Galerkin Projections for both the methods are also provided which can be used for further finite element analysis. For each model error calculations and comparisons are also made for better understanding the accuracy of each model.

Table of Contents

Table of Figures

List of Tables

List of Equations

Section: 1 Introduction

1.1 Significance and Motivation

Drug discovery is a prolonged, onerous and costly process [2]. The average cost of scaling up the drug from laboratory setting is roughly $1-2 billion and the process takes up to 14-15 year [3]. Due to the high cost, there is tremendous weight to maximize efficiency and minimize the time it takes to discover and bring a drug to the market [4]. In order to do this, it is necessary to analyze the entire 'drug discovery and development processes' and make necessary changes to increase efficiency and minimize time of drug formulation and scale-up [2].

The goals to be met to commercialize a drug candidate are: therapeutic strategy, structure-activity relationship, dose form and regimen, scalability, cost of the starting materials, toxicity issues and clinical trials and approval [3, 4].

Most commercialized drugs can be administered by injection, oral, inhalation, and transdermal routes [5]. Almost 90% of all medicines are oral formulations because it is painless compared to injections, convenient compared to enemas, easy to use, and can be managed by the patient [6].

Many chronic diseases which required frequent treatment over a prolonged period of time are benefited by oral drug delivery. However, it is challenging to design oral delivery systems optimizing drug release and stability in the gastrointestinal (GI) tract and to achieve a desirable absorption rate, half-life in the bloodstream that is strongly affect by the rate of metabolism in the liver [7]. Oral drug delivery has low efficacy for extended drug release, and also has poor oral bioavailability for many drugs [8].

Today about 74% of drugs are taken orally and are found not to be as effective as desired [1]. Therefore, there is a dire demand to improve current oral drug delivery methods or produce alternate routes for effective drug delivery for better patient compliance and effective treatment.

To improve such characters transdermal drug delivery system was emerged [1]. In this report special focus is made on transdermal delivery system as an alternate drug delivery route.

1.2 Transdermal Drug Delivery Systems

Transdermal drug delivery systems are dosage forms designed to deliver a drug across a patient's skin [1]. Lotions, creams, and ointments have been used for local treatment of skin for many centuries. Controlled release technologies have widened the role of local delivery to skin [9].

This delivery system has many advantages: it is minimally painful, offers controlled release, has a lower rate of infection and higher rate of compliance compared to injections, and avoids first pass metabolism seen in oral drug delivery [9]. Bedsides above advantages, it also avoids harsh environment of GI tract which is a crucial issue for oral drug delivery [10].

However, only a narrow range of molecules can be delivered to transdermal drug delivery route [11]. This method allows systemic delivery of potent, lipid-soluble agents such as scopolamine for motion sickness, nicotine to aid in cessation of smoking, steroids for hormone replacement therapy or birth control, nitroglycerin for angina, and fentanyl for chronic pain [11].

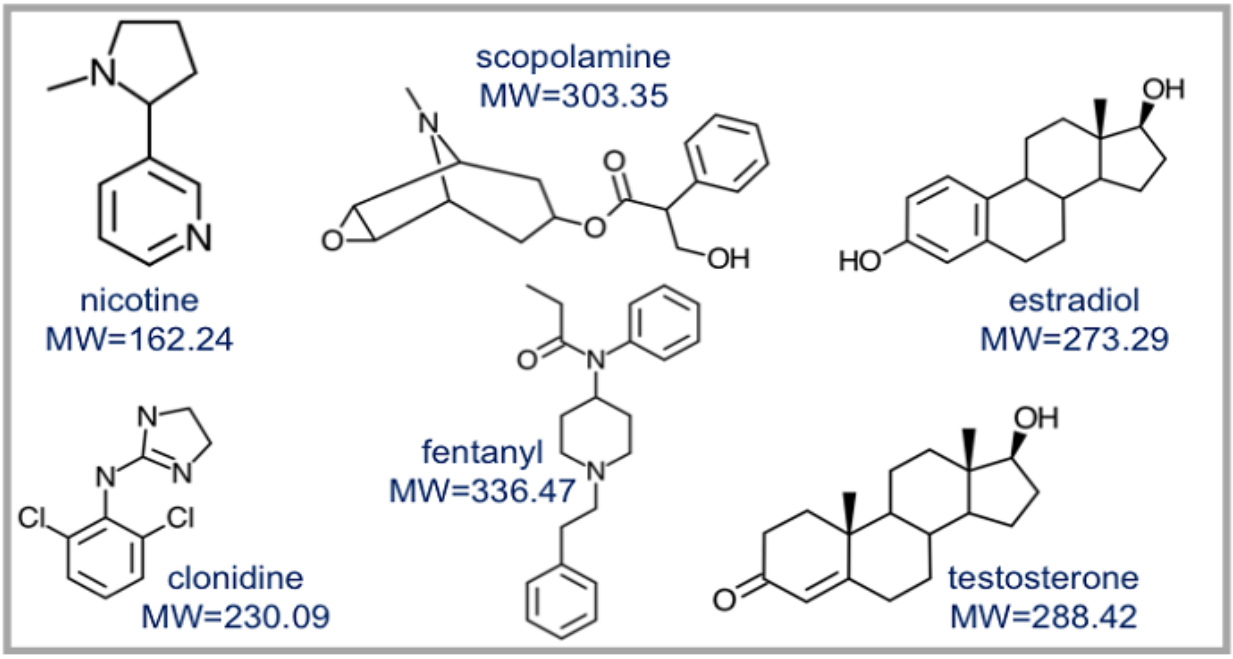

Figure 1 Low molecular weight, lipophilic organic drug molecules.[11]

Transdermal delivery systems often use a polymer membrane to control the rate of diffusion of agents from a reservoir through the surface of the skin and into the systemic circulation [11].

When transdermal delivery is used to provide systemic therapy, administration of the right dose depends on understanding the rate of drug penetration through the epidermis to the capillaries in the dermis [11].

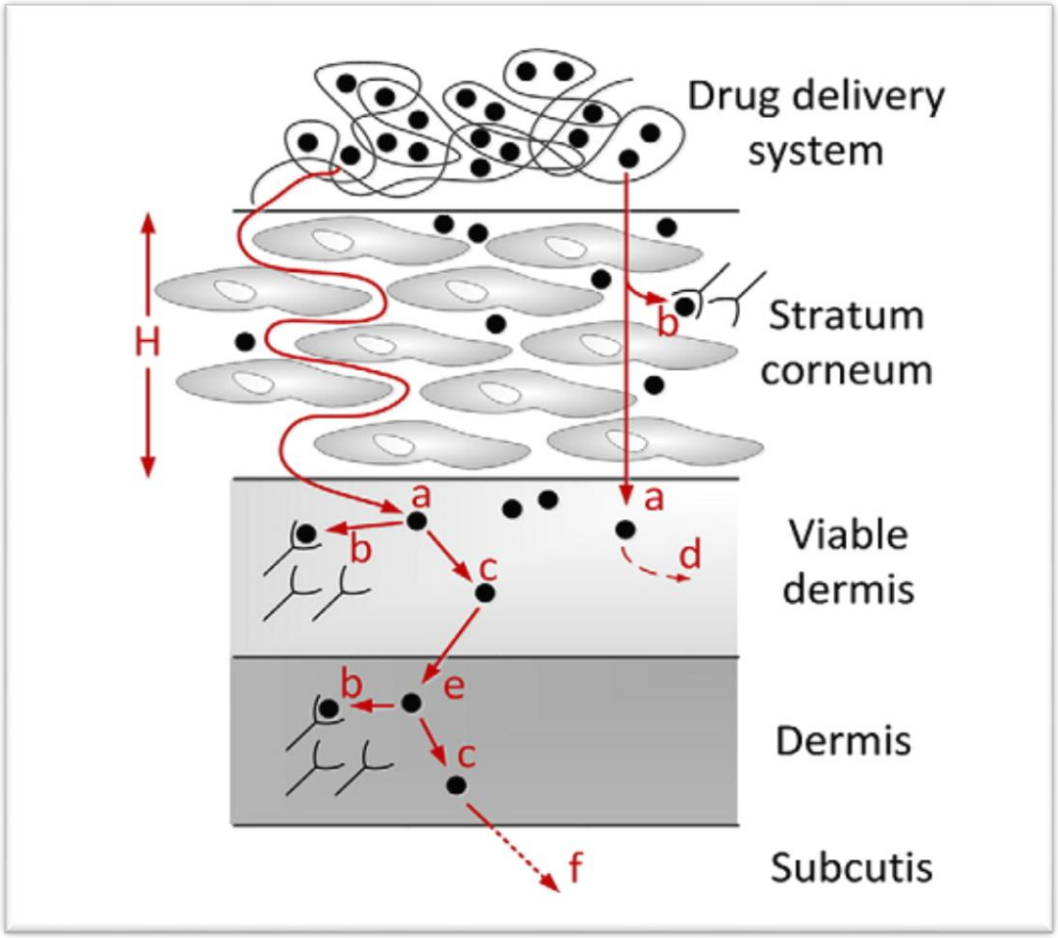

Figure 2. Mechanisms of drug transport and elimination during controlled release from a topical device on the skin. The solid circles represent the therapeutic agent and the arrows represent the modes of transport and reactions that occur after release from the device. Release and subsequent diffusion via transcellular, intercellular, or ollicular routes (arrow a) to the extracellular space (ECS), drug may be reversibly bound by protein binding (b), diffusion through the ECS due to concentration gradients or convective transport (c), metabolism within a cell (d), partition through tissue layers (e), and the subsequent systemic transport or elimination (f). The thickness of the stratum corneum is represented by H. [9]

1.3 Specific Objectives

Major focus of this report is to provide analytical and numerical solutions for predicting the model drug penetration concentration through skin in transdermal drug delivery system.

This report provides detailed discussion on the following two different models:

3) Steady state (simpler model that can be solved both analytically and numerically) analysis of drug concentration in the skin thickness and,
4) Unsteady state analysis (more robust model which will also provide the early drug penetration profile) of drug concentration in the skin thickness.

Galerkin Projections for both the methods are also provided which can be used for further finite element analysis. For each model error calculations and comparisons are also made for better understanding the accuracy of each model.

1.4 Specific Motivation

My research focus is to provide improved and controlled oral drug delivery methods for chronical diseases. My advisers (Dr. Rickey Davis and Dr. Kevin Edgar) have a huge focus on use of cellulose based polymeric drug nanoparticles for improving oral bioavailability of drugs [12, 13] and alternate topical routes (esp. drug delivery through eyes and skin) for drug delivery [5].

As my research project is directly related to drug delivery systems, therefore analysis of transdermal drug delivery system will be a great opportunity for me to study drug penetration concentration in the skin. This report's analysis may be further extended to compare oral drug delivery and transdermal system.

It is very interesting to me that people are using skin cream or cosmetic products for centuries, but transdermal delivery system came into picture since twenty century [1, 11]. In fact,

Merriam Webster dates the word “transdermal” to 1944 (Merriam-Webster 2011) highlighting that it is a relatively recent concept in medical and pharmaceutical practice [11]. Therefore, I believe that there are various opportunities to perform research in transdermal drug delivery route. It may hold expectations for future of drug delivery.

Section: 2 Model for drug penetration through skin in Transdermal drug delivery system

2.1 Transdermal Delivery System Designs

Currently, there are two types of simple patch design (Figure 3): The original patch design is a liquid reservoir system where the patch consists of a backing material that is both protective and adhesive, a liquid drug reservoir, and a release membrane [11].

A more recent design is the adhesive matrix system where the adhesive and the drug are combined in the same layer leaving only three layers to the patch; the backing layer, the drug and adhesive layer, and the protective layer that would be removed before applying the patch to the skin [11].

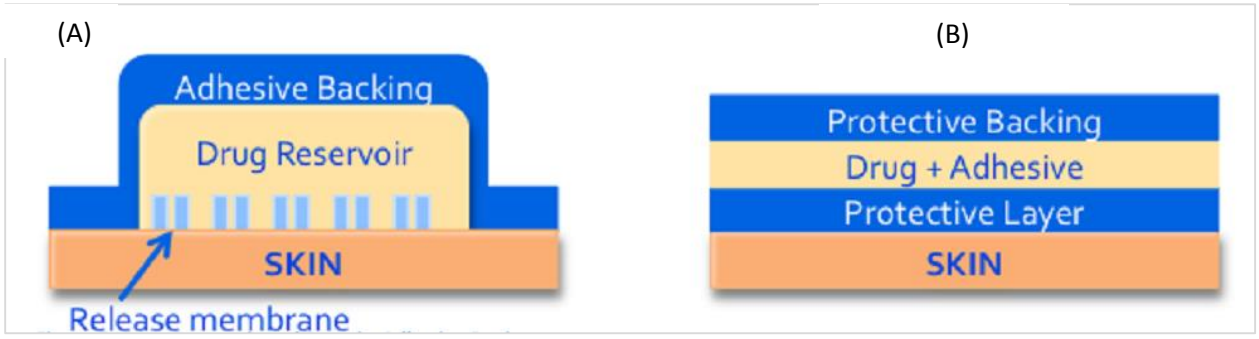

Figure 3: (A) Drug Reservoir (B) Drug-in-Adhesive Designs. [11]

2.2 Model for the analysis

Various current designs are the adhesive matrix system and it is widely used in commercialized transdermal delivery [11]. Therefore, Drug-in- adhesive design is selected with following assumptions for the purpose of this analysis:

1) The model drug is loosely attached with the adhesive and protective layer is taken off while applying drug patch on the skin.
2) Drug penetration is diffusion controlled (no convection/advection with in the drug patch). Diffusion controlled penetration can be modeled by one dimensional diffusional equation. Fick's law can be applied to model drug penetration concentration through skin. Lateral diffusion of drug is neglected; only longitudinal diffusion is considered.
3) Drug-adhesive can be irreversibly converted to drug and adhesive by applying pressure on the patch in room temperature condition. No additional activation energy is needed to separate drug from adhesive.
4) Barriers of hairs on skin is negligible and moisture & temperature doesn't degrade the drug.
5) As shown in Figure: 2, skin can be considered of three different layers of stratum corneum, epidermis, and dermis. These three layers have different barriers and diffusion rate. However, in this study skin is considered to be one homogeneously mixed layer to avoid various complications (Figure: 4).
6) Elimination of drug particles can occur in epidermis and dermis layer of skin via reversible protein binding (Figure: 2). Therefore, in simplified model of one homogeneously mixed layer of skin, first order elimination is also considered.
7) Length of patch applied is very small in term of skin length. Therefore, assumption of infinite slab can be used.
8) Mass transfer coefficient (D) is assumed to be constant.

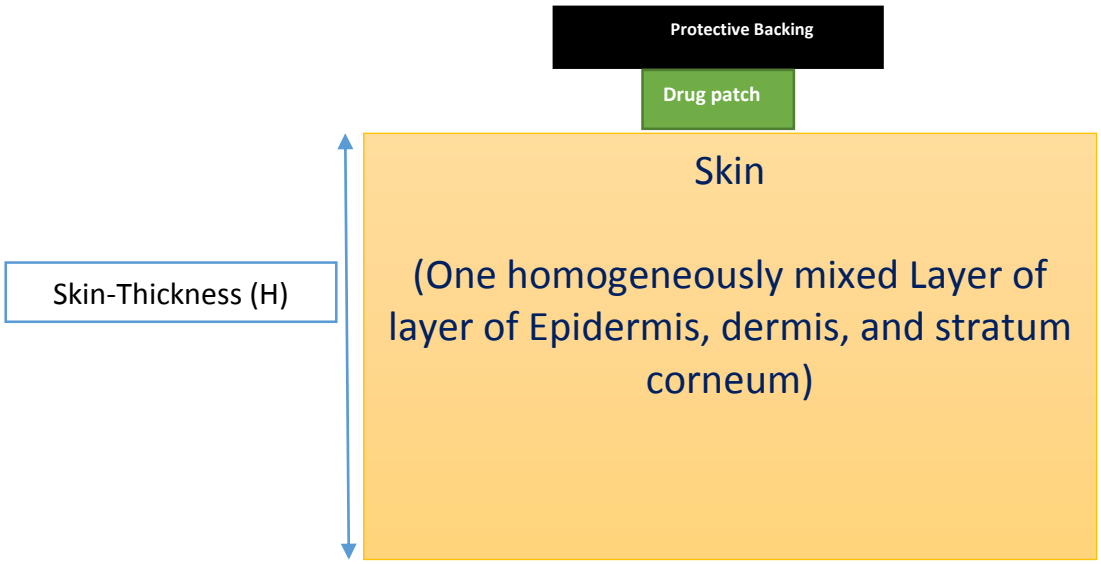

Figure 4 Simplified Drug-in-adhesive design for transdermal drug delivery

2.3 Mass transfer- Diffusion Equation

General diffusion equation [9] for mass transfer with advection and reaction (first order):

$$\frac{dC}{dt} + v * \nabla C = D * \nabla^2 C - k * C \qquad (1)$$

Where:

C= concentration of drug in the skin at any time t [hr]- (unit: mmol/L)

V = advection/convection velocity- (unit:mm/hr)

D= Diffusion coefficient for skin- (unit: mm^2/hr)

K= first order rate constant- (unit: hr^{-1}) and x= thickness of skin for diffusion (mm)

By neglecting convection term in $\frac{dC}{dt} + v * \nabla C = D * \nabla^2 C - k * C$ (1))

$$\frac{dC}{dt} = D * \nabla^2 C - k * C \qquad (2)$$

By neglecting lateral diffusion (i.e. only one dimensional diffusion of drug through skin)

$$\frac{dC}{dt} = D * \frac{d^2 C}{dx^2} - k * C \qquad (3)$$

Under steady state:

$$D * \frac{d^2 C}{dx^2} - k * C = 0 \qquad (4)$$

2.4 Initial and Boundary Conditions

Initial conditions:

At t=0 C(x=0) = Co and C(0< x <H) = 0

Boundary conditions Set-1:

For all time t, C(x=0) = Co and

dC/dx (x=0) = -1

Or, boundary condition Set 2:

For all time t, C(x=0) = Co and

C(x=inf)= 0

Where, H = skin thickness; C0= Initial drug concentration in patches.

As drug particles are usually of microparticles or nanoparticles size, therefore the thickness of skin (~1-2 mm) can be considered very large (infinity).

Once concentration of drug at the interface of blood/tissues with skin is calculated, Noyes-Whitney equation for drug dissolution can be used to predict the rate of drug dissolution [9].

$$\frac{dC_b}{dt} = h * (C_L - C_b) \quad (5)$$

Where,

h= constant for Noyes-Whitney equation which depends on surface area of drug molecules, length/ thickness of dissolution medium and diffusion coefficient of solid drug molecules through the medium.

C_L= concentration of drug at the interface of skin/blood

C_b= concentration of drug in blood/tissue after diffusion through skin.

It is also assumed that as soon as drug molecules come to the interface of skin/blood it is dissolved immediately. Therefore, rate of dissolution of drug in blood can be estimated by Noyes- Whitney Equation.

However, in this report we assumed sink conditions at the end of the skin thickness (L= 2mm). Sink condition means that C(x=inf) = 0.

Section: 3 Analytical Solution for the Steady State Model

3.1 Model assumptions

In addition to the assumptions listed in Section 2.2, some of the specific assumptions of values are made:

1) Drug loading is usually high in drug patches, therefore drug loading with concentration of 1 mmol/mm^3 is assumed. (C0= 1 mmol/mm^3 or 100 mol/L).
2) Usually thickness of skin is in the range on 1 mm-2.5 mm. On average, skin thickness (H) is assumed to be 2 mm.
3) Diffusion coefficient of a solute (solid) into a diffusion medium is usually in the range of 10^{-6} – 10^{-9} cm^2/sec. Diffusion coefficient of drug (liquid) in skin (which is made of lipids, and other lipophilic compounds) is assumed to be 1 mm^2/hr (~2.8*10^{-6} cm^2/sec).
4) Usually 1st order rate constant for elementary reaction is in the range of 10^{-4} – 10^{-12} sec^{-1}. But absorption/adsorption of drug molecules by protein is a complex reversible reaction, therefore rate constant of this diffusion controlled process is assumed to be 1 hr^{-1}.
5) As drug particles are usually of microparticles or nanoparticles size, therefore the thickness of skin (~1-2 mm) can be considered very large. Sink condition at x=H is assumed because as soon as drug particles cross the skin they are rapidly dissolved in blood or tissues.
6) In Noyes-Whitney Equation, for simplification value of constant ‘h’ is assumed to be 1 hr^{-1}.

3.2 Equation and Boundary Conditions

Under **steady state condition** (From Eq. 4)

$$D * \frac{d^2C}{dx^2} - k * C = 0$$

Initial conditions: (assume skin thickness (L)= 2 mm)

At t=0 $C(x=0) = 1\ mmol/mm^3$ and $C\ (0< x < 2\ mm) = 0$

Boundary conditions:

Set: 1 for all time t, $C(x=0) = 1\ mmol/mm^3$

$$\frac{dC}{dX}_{x=0} = -1$$

Or Set: 2 for all time t, $C(x=0) = 1\ mmol/mm^3$

$C(x=2mm\ or\ inf)= 0$

As drug particles are usually of microparticles or nanoparticles size, therefore the thickness of skin (~1-2 mm) can be considered very large. It can be assumed that as ‘x’ approaches to infinity (i.e x=2 mm) concentration of drug will be zero.

3.3 Analytical Solution

We have, $D * \frac{d^2C}{dx^2} - k * C = 0$ (second order linear ODE)

Therefore, characteristic equation: $\lambda^2 = \frac{k}{D}$ *(6)*

Therefore general solution of given steady state (second order linear ODE) will be:

$$C(x) = C1 * \exp(\sqrt{k/D} * x) + C2 * \exp(-\sqrt{k/D} * x) \quad (7)$$

From the boundary condition:

$$C(x) = C_2 * (\exp(-\sqrt{k/D} * x)) + C_1(\exp(\sqrt{k/D} * x)) \quad (8)$$

Therefore,

$$C(x) = C_0 * \exp(-x) \quad (9)$$

Hence, concentration of drug at the interface of skin and blood/tissues will be C(x=2 mm) = 0.135mmol/mm^3 (under steady state conditions). Surprisingly, both the boundary conditions (Set 1 and Set 2) gave the same solution.

Section 4: Numerical Solution for the Steady State Model

4.1 Geometric, strong form and Initial and Boundary conditions

Numerical Solution of steady state model

Second order ordinary differential equation (ODE)

Strong form

$$D \cdot \frac{\partial^2 C}{\partial x^2} - K C = 0$$

Geometric form: steady state, one dimensional, parabolic form

Neumann and Dirichlet boundary conditions

Neumann B.C. $\left.\frac{dC}{dx}\right|_{x=0} = -1$ & $\left.\frac{dC}{dx}\right|_{x=H} = 0$

Dirichlet B.C. (None needed)

However, $C(x=0) = 1 \ mmol/mm^2$

4.2 Galerkin Projection

weak formulation & Galerkin Projection

$$\frac{d^2C}{dx^2} - C = 0 \qquad \text{as } K/D = 1$$

$$\Rightarrow \int_0^L \left(\frac{d}{dx}\left(\phi_i \frac{dC}{dx}\right) - \frac{d\phi_i}{dx}\frac{dC}{dx} - \phi_i C \right) dx = 0$$

$$\Rightarrow \int_0^L \frac{d\phi_i}{dx}\frac{dC}{dx}\,dx + \int_0^L \phi_i C\,dx = 0$$

$$\Rightarrow \sum_{j=1}^{NE+1} \left[\int_0^L \frac{d\phi_i}{dx}\frac{d\phi_j}{dx}\,dx + \int_0^L \phi_i \phi_j\,dx \right] C_j$$

$$= -\delta_{i,1} \left.\frac{dC}{dx}\right|_{x=0} + \delta_{i,NE+1} \left.\frac{dC}{dx}\right|_{x=NE+1}$$

From B.C. $\left. dC/dx \right|_{x=0} = -1$ & $\left.\frac{dC}{dx}\right|_{x=NE+1} = 0$

$$\Rightarrow \sum_{j=1}^{NE+1} \left[\int_0^L \frac{d\phi_i}{dx}\frac{d\phi_j}{dx}\,dx + \int_0^L \phi_i \phi_j\,dx \right] C_j$$

$$= \delta_{i,1} \qquad \text{(Galerkin Projection)}$$

where, $i = 1, 2, 3 \ldots NE+1$

4.3 Assumptions

Assumptions are listed in Section 3.1.

4.4 Numerical solution

Second order linear differential equation for steady state is solved numerically using ODE45 solver. It is based on an explicit Runge-Kutta formula. In general, ode45 is the best function to apply as a "first try" for most problems (refer Appendix: A).

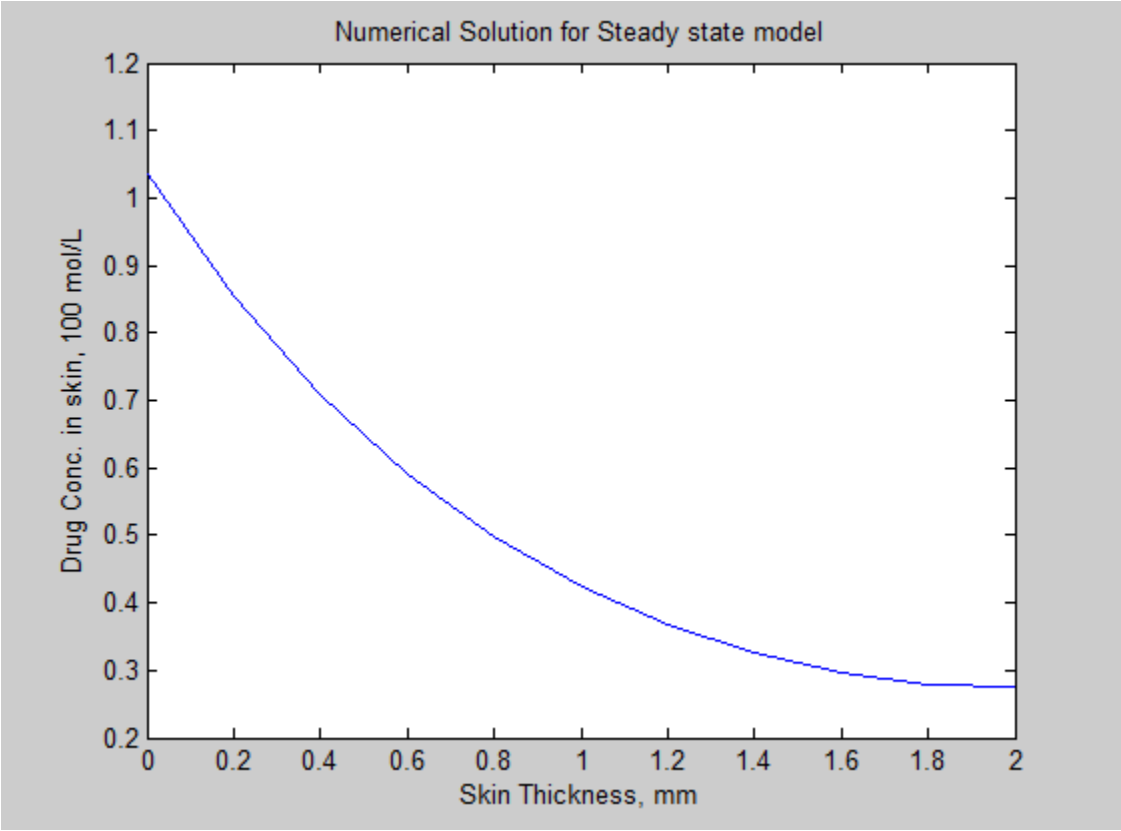

Figure 5 Numerical solution of steady state model for drug penetration in skin. Plot of drug conc. vs skin thickness.

As shown in Figure 5, drug concentration through skin (in steady state) follows the same trend as analytical solution discussed in previous section. Drug concentration decreases from the surface value of 1 mmol/mm3 (at x=0) to ~0.28mmol/mm3 (at x=2).

4.6 Comparison with analytical solution

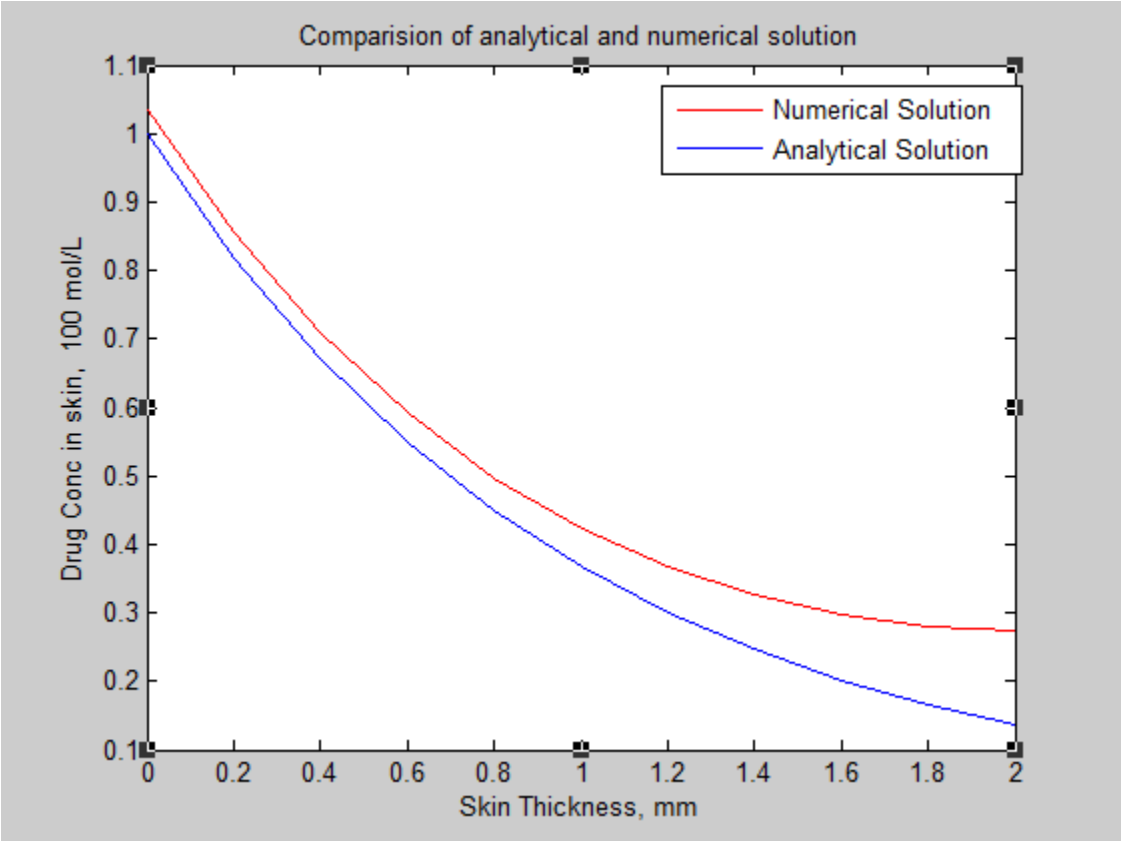

Figure 6 Comparison of numerical solution with analytical solution in steady state model

As compared in Figure 6, we can conclude that there is a difference in concentration calculated by analytical solution and numerical solution (FEM method). This difference was mainly due to the less number of element (NE= 10) were considered in FEM method. Also, numerical solution of this model also predict that drug concentration at skin (x=0) is slightly higher

than the analytical solution. However, it (numerical solution) provided a good estimation of diffused drug concentration through skin.

An error comparison in between analytical and numerical solution of this model is made in Table 1 and Figure 7.

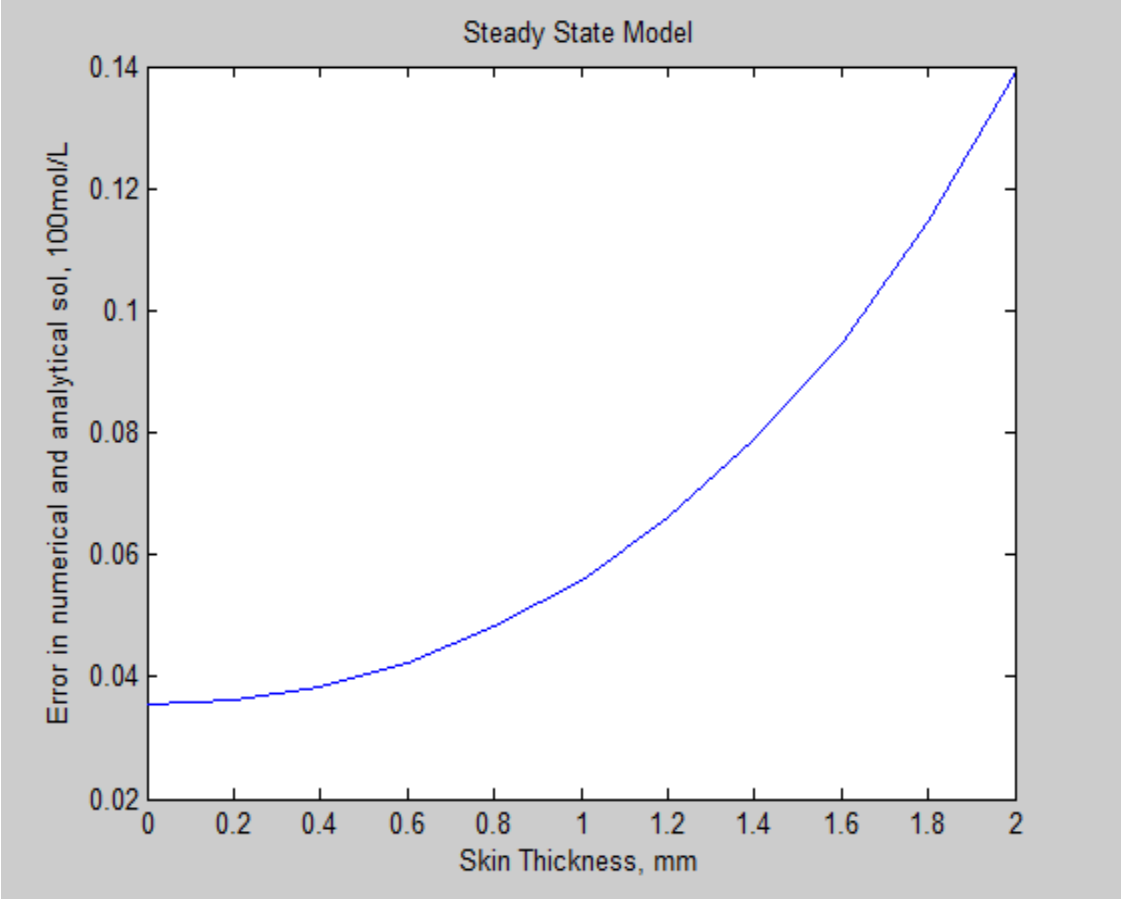

Figure 7 Plot of absolute error in analytical and numerical solution (using finite element method) of steady state

Table 1 comparison of numerical and analytical solution in steady state model of drug conc. through skin

Skin Thickness(mm)	Conc. in skin (100, mol/L) Analytical Solution	Conc. in skin (100, mol/L) Numerical Sol	Absolute Error
0	1	1.035	0.035
0.2	0.818	0.858	0.036
0.4	0.670	0.708	0.038
0.6	0.548	0.591	0.042
0.8	0.449	0.497	.0481
1	0.367	0.423	0.055
1.2	0.301	0.367	0.066
1.4	0.246	0.325	0.078
1.6	0.201	0.296	0.094
1.8	0.165	0.279	0.1143
2	0.135	0.274	0.138

Section 5: Robust Model (Unsteady state model)

In section 3 and 4 we discussed analytical & numerical solution of steady state solution for drug penetration through skin to our bloodstream/tissue. However, understanding timely variation of drug penetration concentration through skin thickness is also important. Therefore, in this section unsteady state (transient state) model is considered.

From equation (3): (unsteady state, one dimensional diffusion-reaction model)

$$\frac{dC}{dt} = D * \frac{d^2C}{dx^2} - k * C$$

Concentration in the skin is function of time as well as of x. Therefore, by considering unsteady state equation prediction about time required for particular conc. level can be calculated. It is more robust model as, it provides change in concentration of drug with skin thickness as time changes, which is also important to consider in drug discovery or delivery. There are questions which need to be answered before making any drug commercialized such as, will it provide or achieve required concentration in skin rapidly? Or will this patch deliver the drug slower than the other delivery routes?

These questions are important to be answered for better patient compliance and drug efficacy. Therefore, unsteady state model analysis is considered a robust model.

Also, 2 dimensional steady state diffusion will be ignored in this robust model as drug diffusion will be targeted through only longitudinal direction (depth) in skin (one dimensional).

Section 6: Numerical solution for Robust Model

6.1 Geometric, strong, and boundary conditions

Numerical solution for Robust Model

Unsteady state One dimensional diffusion-reaction model:

Strong form of differential equation

$$\frac{\partial C}{\partial t} = D \cdot \frac{\partial^2 C}{\partial x^2} - K \cdot C$$

Geometric form: one dimensional parabolic partial differential equation)

Boundary conditions:

$$\left.\frac{\partial C}{\partial x}\right|_{x=0} = -1$$

$$\left.\frac{\partial C}{\partial x}\right|_{x=H} = 0$$

Initial condition

at $t=0$

$$C = \begin{cases} 0 & \forall x > 0 \\ 1 \ mmol/mm^3 & \forall x = 0 \end{cases}$$

6.2 Galerkin Projection and system of linear equations

Galerkin Projection

$$\int_0^L \phi_i \frac{\partial C}{\partial t}\, dx = -D\left(\phi_i \frac{\partial C}{\partial x}\right)_{x=0} + D\left(\phi_i \frac{\partial C}{\partial x}\right)_{x=L} - D\int_0^L \frac{\partial \phi_i}{\partial x}\frac{\partial C}{\partial x}\, dx - \int_0^L \phi_i C\, dx$$

$$C(x) = \sum_{j=1}^{N_G} C_j(t)\, \phi_j(x)$$

Where N_G is the number of unique global model.

Linear ordinary Equation:

$$\underline{M}\frac{\partial \underline{C}}{\partial t} + \underline{M}\cdot\underline{C} + D\left(\underline{D}^*\cdot\underline{C}\right) = D\,\underline{b}$$

$\underline{M}$ = global mass matrix

$\underline{D}^*$ = global square diffusion matrix

$\underline{C}$ = Unknown conc. matrix

$\underline{b}$ = Boundary condition matrix.

6.3 Assumptions

Assumptions are listed in Section 3.1.

6.4 Numerical solution

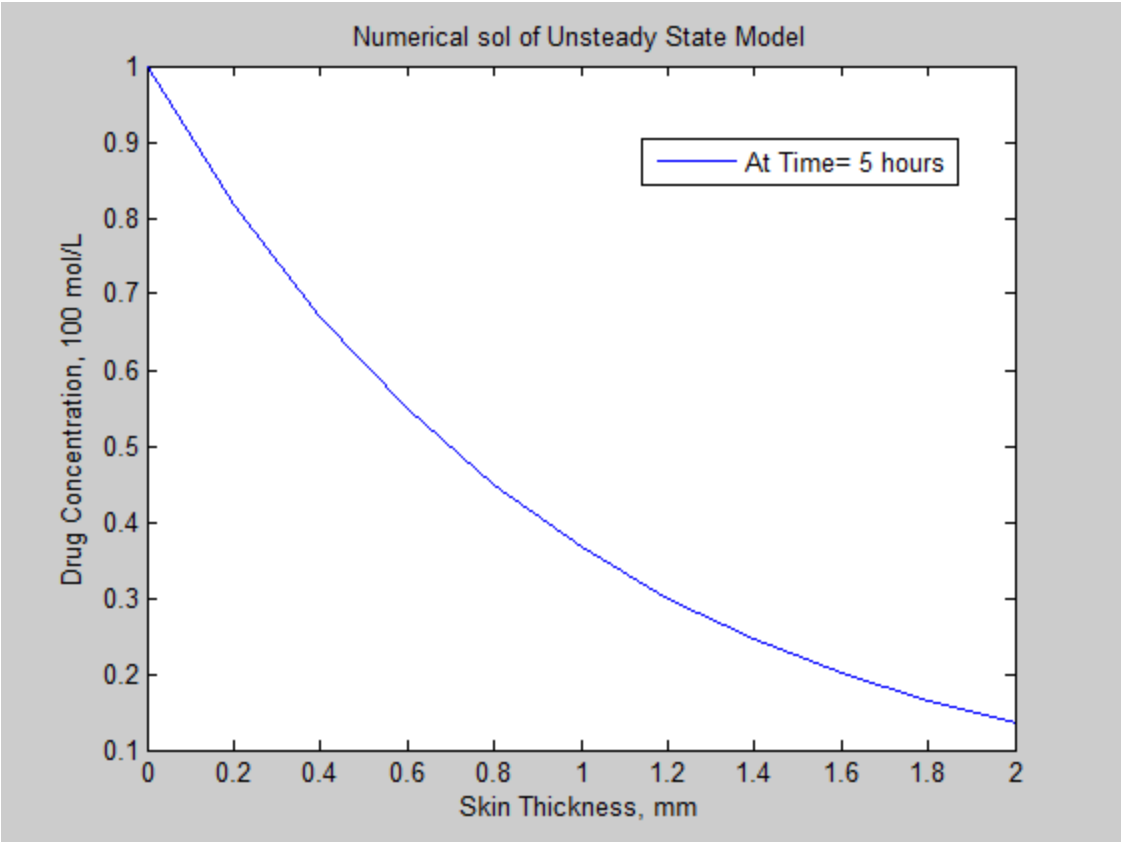

Figure 8 Steady state analysis (at time =5 hours) of drug penetration using Robust model.

Unsteady analysis of one dimensional drug diffusion through is performed using MATLAB inbuilt function 'PDEPE' (Appendix: B) however, same analysis can also be performed using finite element method (performed for steady state model, refer Section 4).

It was found that drug concentration at skin thickness of 2 mm i.e. just before dissolving into blood/tissue was constant after ~4-5 hours (i.e. steady state is achieved at ~4-5 hours). As shown in the 2D surface plot (Figure 9) of drug concentration with skin thickness, we will be able

to observe and estimate what will be the diffused conc. of drug will be at any time after the patch is applied on skin.

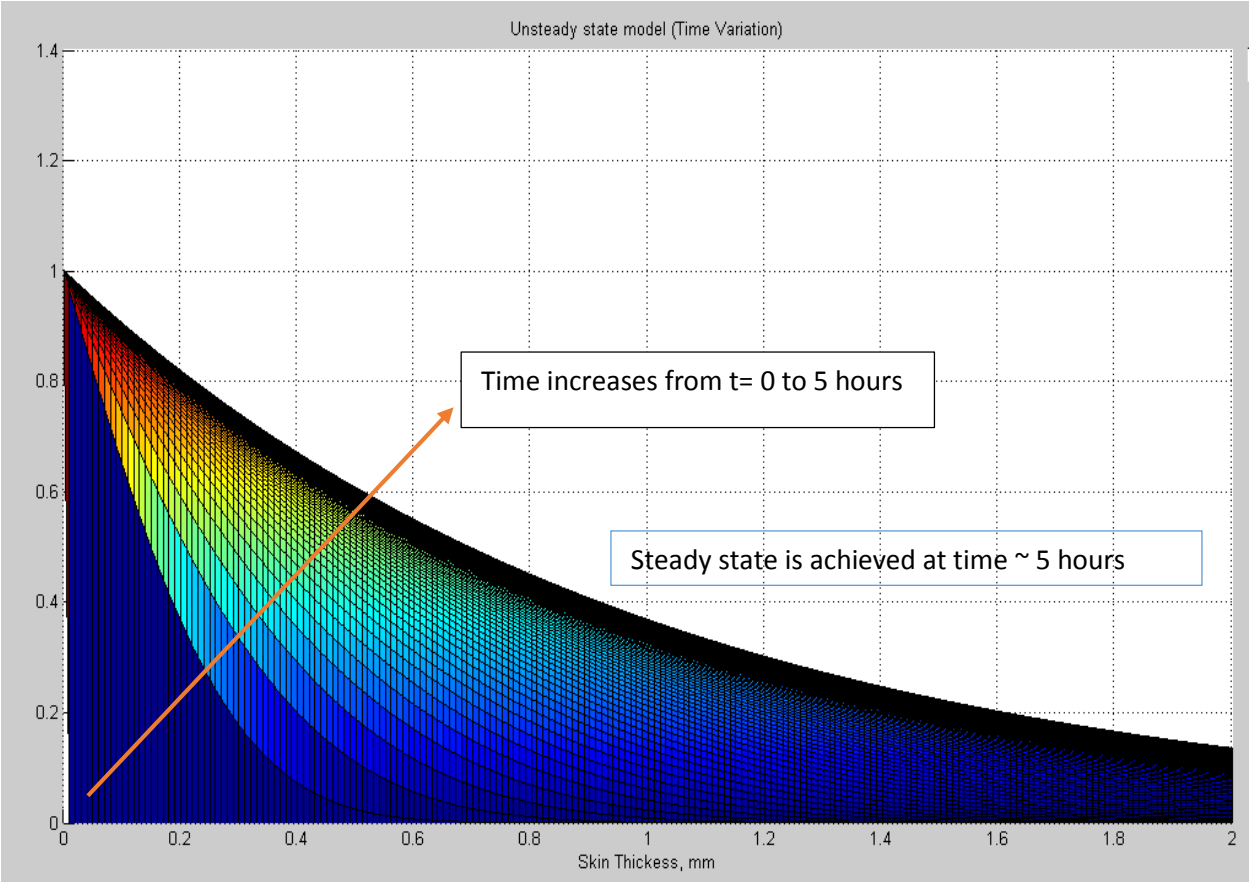

Figure 9: 2D surface plot of drug conc. (mmol/mm^3) with skin thickness (mm)

As time increase drug concentration at thickness ~ 2 mm continuously increases and after ~ 5 hours steady state concentration is achieved. As shown in Figure 9, drug concentration profile can be estimated and observed.

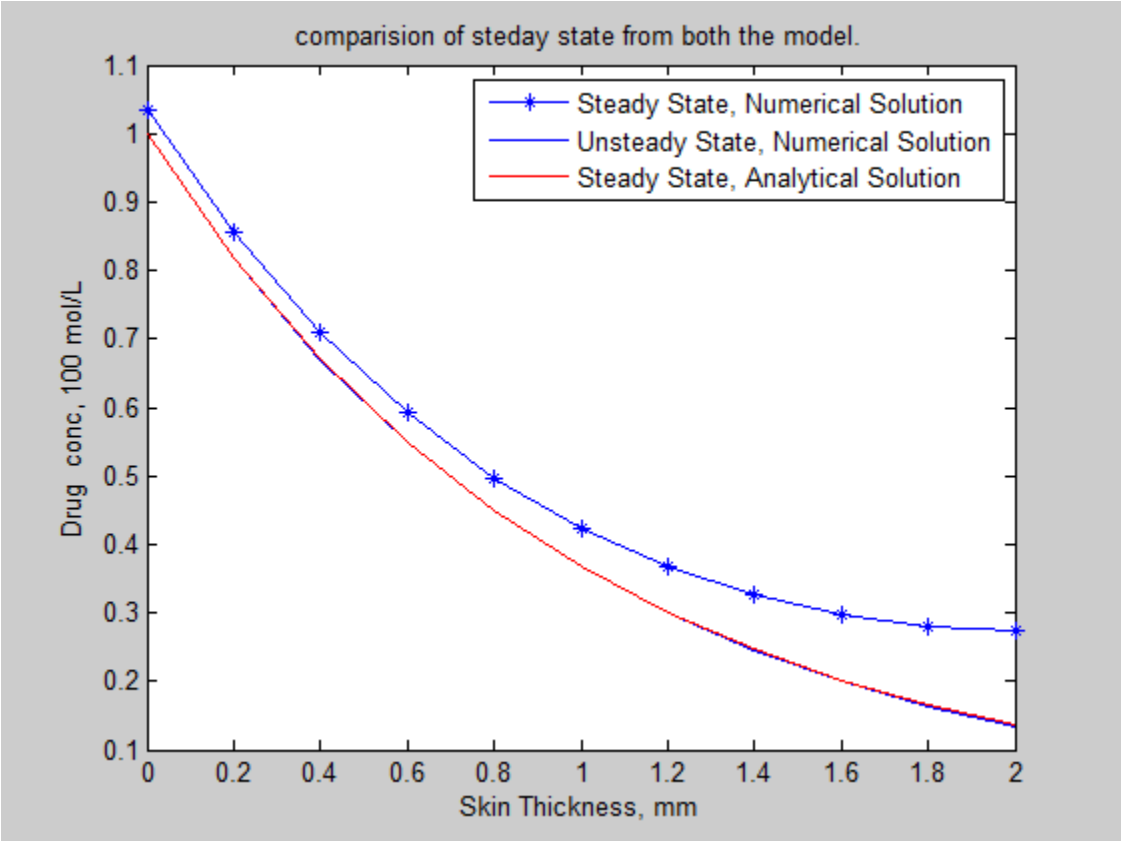

Figure 10 Comparison of steady state achieved by robust model (unsteady state), analytical solution and FEM method (steady state numerical model)

As observed in Figure 10, steady state solution from robust model is overlapping with analytical solution. Therefore, there is no observable error in the concentration profile achieved by these two methods. However, there is significant error in FEM method performed for steady state and steady state profile achieved through robust model. However, same analysis performed in Section 4, will be used to estimate the error in between robust model and steady state model (FEM method).

Section: 7 Summary

This model discussed how the concentration of drug (profile) changes through skin thickness. Steady state and unsteady state model analysis were performed and discussed in detail. It was observed that unsteady state analysis of one dimensional diffusion of drug through skin is useful to predict steady state time.

Some of the critical assumptions used in this model were: assumption of homogeneously mixed skin layer of thickness 2 mm and assumption of one dimensional drug diffusion. These models can be further improved by considering parameters related to actual drug [2] and considering different properties of Skin layers (Figure: 2).

In conclusion, this analysis will provide a better understanding of Transdermal route of drug administration as an alternate route of oral drug delivery.

References

1. A., K.J., *TRANSDERMAL DRUG DELIVERY SYSTEM: AN OVERVIEW.* International Journal of Pharmaceutical Sciences Review and Research, 2010. **3**(2).
2. Lipinski, C.A., et al., *Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings.* Advanced Drug Delivery Reviews, 2012. **64**: p. 4-17.
3. PWC, N., *Pharma 2005- An industrial revolution in R&D.* 1998(In Pharma 2005): p. 1-20.
4. Adams, C.P. and V.V. Brantner, *SPENDING ON NEW DRUG DEVELOPMENT.* Health Economics, 2010. **19**(2): p. 130-141.
5. Bierton, C., et al., *Route of drug administration may influence toxicological levels in the liver.* Journal of Clinical Pathology, 2013. **66**(7): p. 630-+.
6. Satish K. Patil, K.S.W., Venkatesh B. Parik, Anup M. Akarte, Dheeraj T. Baviskar, *STRATEGIES FOR SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE DRUGS.* 2011. **8**(2).
7. Lobenberg, R., J.S. Kim, and G.L. Amidon, *Pharmacokinetics of an immediate release, a controlled release and a two pulse dosage form in dogs.* European Journal of Pharmaceutics and Biopharmaceutics, 2005. **60**(1): p. 17-23.
8. Franz Gabor, C.F., Lukas Neutsch, Gerda Ratzinger, Michael Wirth, *Improving Oral Delivery.* Wiley, Ed., 2005: p. 345-397.
9. Weiser, J.R. and W.M. Saltzman, *Controlled release for local delivery of drugs: barriers and models.* Journal of controlled release : official journal of the Controlled Release Society, 2014. **190**: p. 664-73.
10. Pridgen, E.M., F. Alexis, and O.C. Farokhzad, *Polymeric Nanoparticle Technologies for Oral Drug Delivery.* Clinical Gastroenterology and Hepatology, 2014. **12**(10): p. 1605-1610.
11. E.J., W., *Three Generations: The Past, Present, and Future of Transdermal Drug Delivery Systems.* 2011.
12. Pereira, J.M., et al., *Interplay of Degradation, Dissolution and Stabilization of Clarithromycin and Its Amorphous Solid Dispersions.* Molecular Pharmaceutics, 2013. **10**(12): p. 4640-4653.
13. Marks, J.A., et al., *Pairwise Polymer Blends for Oral Drug Delivery.* Journal of Pharmaceutical Sciences, 2014. **103**(9): p. 2871-2883.

Appendixes

Appendix: A. Matlab code for numerical solution of steady state model

```
%% Define x values for nodes and # of elements
NE=10;
h= 2/NE;


%% Initialize matricies
% Equation takes the form: D*f + M*f = c
% D = zeros(NE+1, NE+1);      % NE x NE
% M = zeros(NE, NE+1);    % NE x NE+1
%u = zeros(NE, 1);       % NE x 1
%s = zeros(NE+1, 1);     % NE+1 x 1
c = zeros(NE+1, 1);       % NE x 1


%% Assemble the D matrix
for i = 1:NE+1
   for j = 1:NE+1
      if i == 1 && j == 1
         D(i, j) = 1/h;

      elseif i == j &&  i ~= 1 &&  i ~= NE+1
         D(i, j) = 2/h;

      elseif i == j + 1
         D(i, j) = -1/h;

      elseif i == j - 1
         D(i, j) = -1/h;

      elseif i == j && i == NE+1
        D(i, j) = 1/h;

      else
         D(i, j) = 0;
      end
   end
end
%% Assemble the M matrix
for i = 1:NE+1
   for j = 1:NE+1
      if i == 1 && j == 1
```

```
            M(i, j) = h/3;

        elseif i == j && i ~= 1 &&  i ~= NE+1
            M(i, j) = 2*h/3;

        elseif i == j + 1
            M(i, j) = h/6;

        elseif i == j - 1
            M(i, j) = h/6;

        elseif i == j && i == NE+1
           M(i, j) = h/3;
        else
            M(i, j) = 0;
        end
    end
end

%% Assemble c matrix
%p0=(-u(2)+1)/h;
c(1)= 1;

%% Solve for the u matrix
% Equation takes the form: D* u= b
% --> u = inv(D)*b
for i = 1:NE+1
    for j = 1:NE+1
w(i,j)=D(i,j)+M(i,j);
    end
end

%u(1) = 1;
%u(NE+1) = 0;

s=inv(w);
u=s*c;

%u(1) = 1;
%u(NE+1) = 0;

% %% Display u matrix
% disp('Finite Element Sol for U(x) =')
% disp(u)
```

Appendix: B Matlab code for numerical solution of unsteady state model

```
function [c,f,s]=expde(x,t,C,dCdx)
c=1;

D=1;
k=1;

f=D.*dCdx; %D=10^-8
s=-k.*C; %k=0.0001



function [pl,ql,pr,qr]=expdebc(xl,Cl,xr,Cr,t)
%C0=1;
pl=Cl-1;
ql=0;
pr=Cr;
qr=1;



function C0=expdeic(x)
if x==0
    C0=1;
else C0=0;
end


m=0

x=linespace(0,2,11);

t=linespace(0,5,11);

C=pdepe(m,@expde,@expdeic,@expdebc,x,t);

C;

Surf(x,t,C)

Plot(x,C(end, : );
```