Spring 2016

A computational model for transdermal diffusion of lidocaine and tetracaine topical patches

Qian Dong
New Jersey Institute of Technology

Follow this and additional works at: https://digitalcommons.njit.edu/theses

Part of the Materials Science and Engineering Commons

ABSTRACT

**A COMPUTATIONAL MODEL FOR TRANSDERMAL DIFFUSION
OF LIDOCAINE AND TETRACAINE TOPICAL PATCHES**

By
Qian Dong

In recent years, transdermal drug delivery patches (TDDP) have developed rapidly. This is because the TDD system has more advantages than traditional drug delivery systems such as oral medicine and intravenous injection. In order to reach the circulatory system of the human body, drug molecules have to pass through the epidermis (outer layer) of the skin. The barrier properties of epidermis originate from low permeability of stratum corneum (SC) which is the outermost layer of the human skin. The objective of this thesis is to build a Finite Element (FE) model, utilizing commercial FE software (ANSYS), that can be implemented to estimate parameters of diffusion as well as common diffusion cell experiments. Use of the regular geometry, "brick and mortar", to simulate tortuous intercellular route of SC is presented. It is assumed that diffusion occurs only within the SC lipids and the lipids are isotropic. The steady-state flux and lag time are solved and compared with the analytical results.

A COMPUTATIONAL MODEL FOR TRANSDERMAL DIFFUSION OF LIDOCAINE AND TETRACAINE TOPICAL PATCHES

By
Qian DongA Thesis

Submitted to the Faculty of
New Jersey Institute of Technology
In Partial Fulfillment of the Requirements for the Degree of
Master of Science in Materials Science & Engineering

Interdisciplinary Program in Materials Science and Engineering

May 2016

Blank Page

**A COMPUTATIONAL MODEL FOR TRANSDERMAL DIFFUSION
OF LIDOCAINE AND TETRACAINE TOPICAL PATCHES**

Qian Dong

Dr. N.M. Ravindra, Thesis Advisor   Date   Professor,
Department of Physics, NJIT
Director, Interdisciplinary Program in Materials Science and Engineering, NJIT

Dr. Costas G. Gogos, Committee Member   Date
Distinguished Research Professor, Chemical Biological and Pharmaceutical Engineering,
NJIT

Dr. Michael Jaffe, Committee Member   Date   Research
Professor, Department of Biomedical Engineering, NJIT

Dr. Nikolaos Loannidis, Committee Member   Date   Research
Engineer, Polymer Processing Institute, NJIT

BIOGRAPHICAL SKETCH

Author: Qian Dong

Degree: Master of Science

Place of Birth: Shi He Zi, The People's Republic of China

Undergraduate and Graduate Education:

Master of Science in Materials Science & Engineering,
New Jersey Institute of Technology, Newark, NJ, 2016

Bachelor of Science in Materials Science & Engineering
Tai Yuan University of Technology, Tai Yuan, PRC, 2013

Major: Materials Science & Engineering

This thesis is dedicated to my parents, Fu Xing and Yu Lin. I feel infinitely grateful every day of my life to have you two as my guidance. Thank you for all of the opportunities you have created for me, for putting my future above it all and giving me your unconditional and endless love. My achievements and qualities are all thanks to you, and I am so happy I could make you proud.

　　我将这篇论文献给我的父母。有你们相伴与我的左右我非常的开心。 感谢你们对我毫无保留的爱与奉献，感谢你们倾尽全力为我铺设出通往未来的道路。你们的认可与肯定是我向前最大的动力。

ACKNOWLEDGMENT

I would like to express my most sincere gratitude to Dr. N.M. Ravindra for his invaluable research guidance and thoughtful insights. My thanks to Professor Ravindra also for all the excellent study opportunities, including different international conferences on Materials Science, which gave me great opportunities to learn the most advanced technologies, theory and practice.

I would like to thank the thesis committee members, Drs. Costas G. Gogos, Michael Jaffe and Nikolaos Loannidis for their support and patience as I moved from an idea to a complete study. I express my gratitude to Dr. Max Roman for providing particular instruction on the FE model without which this work would not have been completed. I thank Dr. George Collins for his support.

TABLE OF CONTENTS

TABLE OF CONTENTS
(Continued)

Chapter   **Page**

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES
(Continued)

CHAPTER 1

INTRODUCTION

1.1 Objective

The transdermal drug delivery (TDD) system represents a new method to replace oral delivery of drugs and hypodermic injection. Although the TDD system is not a perfect alternative to traditional drug delivery methods (oral delivery or hypodermic injection), it has made an important contribution to medical practice. For thousands of years, people have already placed substances on the human skin for therapeutic effects such as traditional Chinese medicated bath [2], and, in the modern era, a variety of topical patches have been developed to treat chronic diseases. In ancient China, transdermal drug delivery system has been one of the ways for external treatment. Treatment of a variety of diseases includes dermatosis, rheumatism, joint pain, and others. The drug administered directly to the lesion site has less toxic side effects. In the modern era, the first transdermal system for systemic delivery consisted of a three-day patch that delivered scopolamine to treat motion sickness, and was approved for use in the United States in 1979. A decade later, nicotine patches became the first transdermal blockbuster, which raised the profile of transdermal delivery systems in medicine, in particular and for the public in general. With the development of transdermal drug delivery systems, TDD has already been developed for three generations [1-4]. Between 1979 and 2007, numerous transdermal drugs have been approved by the

FDA each year (Figure 1.1).
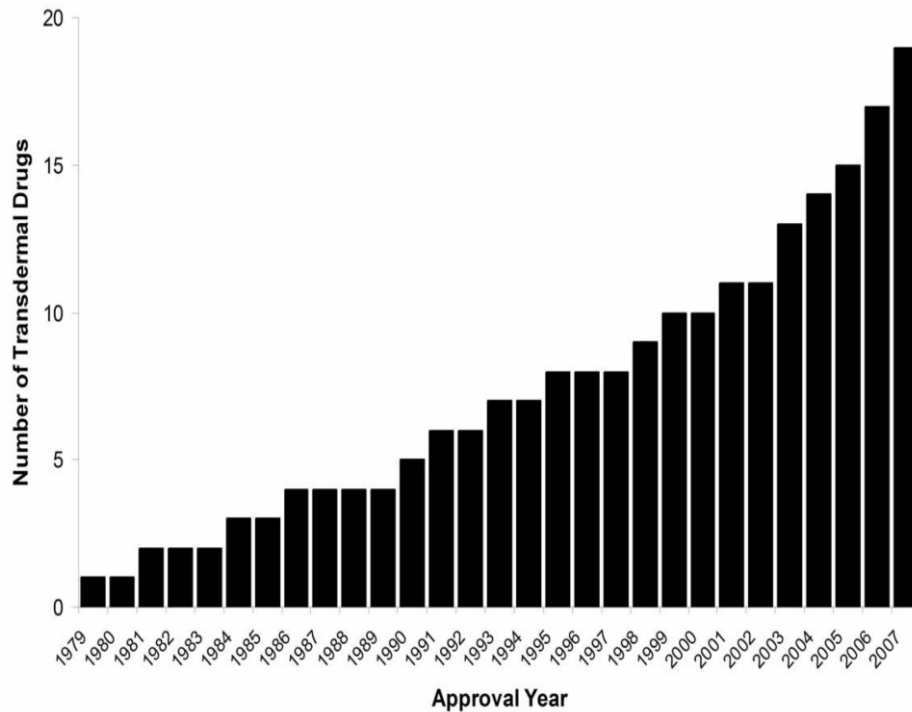
Figure 1.1 Cumulative number of transdermal drugs approved by the FDA since 1979.
Source: The FDA Orange Book.

Currently, in an effort to advance TDD systems, transdermal drug delivery patches

(TDDP) are being mainly fabricated. The nicotine patches have been mentioned widely in

the literature [4-6], but it is important to notice that these are typical first generation

transdermal patches with choice of special drugs. The use of TDDP significantly reduces

major drawbacks that are associated with oral medicine, intravenous injection and

intramuscular injection, such as viscera stimulation from oral medicine or increasing

infection risk by injection. It reduces pain and inflammation while propagating quicker

regeneration of tissues; and also it can avoid high percentage of protein related medicines

that can be influenced by the digestive system; moreover, unlike intravenous injection, optimal transdermal systems can slowly release medicine in the form of particles to the blood stream so as to avoid many undesired side effects.

Aside from these comparisons, the TDD still faces a big barrier of human skin. Thus, this study focuses on the use of commercial finite element analysis (FEA) software, ANSYS, to build a computational model for predicting diffusion in transdermal drug delivery patches. The FE results, which are much more conventional, are predicted by changing few parameters in the FEA model. This computational model can help the TDDP designers to choose ideal parameters for transdermal drug delivery experiments so that precious time and expense can be saved from performing long time experiments.

1.2 Background Information

1.2.1 Skin Structure

The skin is a remarkable organ of the body which is able to perform various functions. Skin is not only a protective barrier against mechanical, thermal and physical injury and potential exposure to hazardous substances, but also has many other functions such as absorption, permeability, secretion, excretion and immunity.

The skin is a variably lamellar structure, which not only includes three main components, epidermis, dermis and subcutaneous layer, but also includes several sub-structure at three main components as shown in Figure (1.2). Skin is constantly being

regenerated by new cell fission from the bottom layer of the skin to the top layer, because

the bottom layers have the blood supply. The main function of epidermis is to form a tough

barrier against the outside world, which has the primary obstacle to transdermal drug

delivery. The dermis is the middle layer of the skin located between the epidermis and the

subcutaneous layer, which is responsible for the structural integrity of the human skin. The

subcutaneous layer includes numerous fat cells for isolating cold and trauma from outside

to the underlying layer.
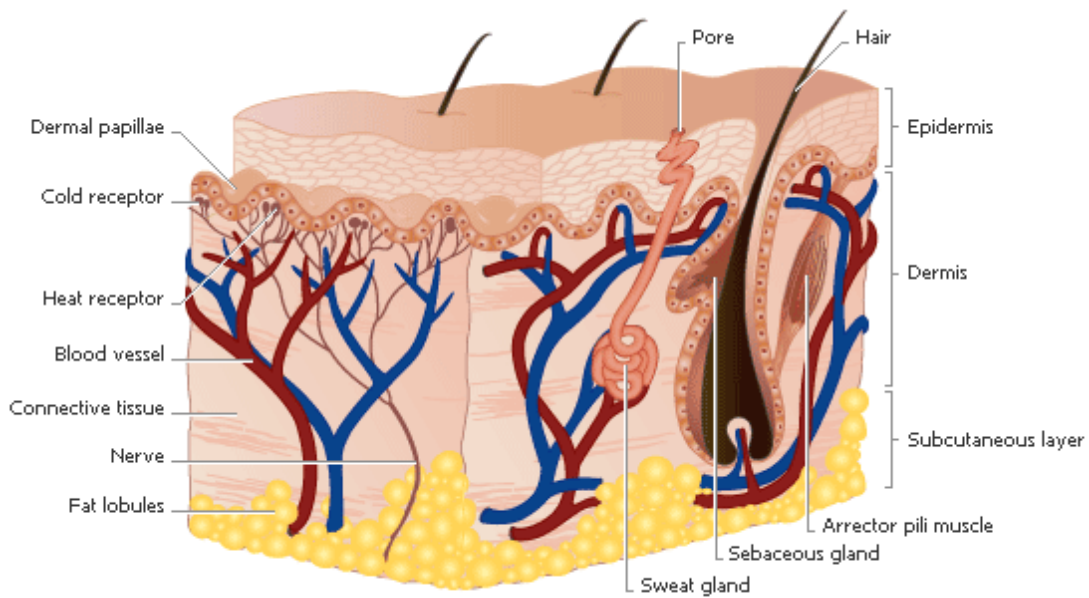
Figure 1.2 The structure of human skin which includes three main parts – epidermis,
dermis and subcutaneous layer. In each layer, they have different low-level structure.
Source: Falcone, R., Jaffe, M., Ravindra, N.M., New screening methodology for selection of polymeric
matrices for transdermal drug delivery devices, Bioinspired, Biomimetic and Nanobiomaterials, Volume 2
Issue BBN2, p. 65-75, 2013.

1.2.1.1 Components of Epidermis   The epidermis is the outermost layers of the human

skin [8]. The epidermis has 5 low-level layers which have different cell arrangement and

components. Figure 1.3 shows different cell arrangement in the epidermis layers. (1) Stratum basal is the bottom layer of epidermis. The cells in this layer can constantly reproduce so as to get constantly pushed up into the next layer. (2) Stratum spinosum layer can prevent bacteria from entering the cells and the moisture being lost. The cells of this layer can also reproduce. (3) Stratum granulosum can produce a protein, keratin, which is found in nail and hair. The cells, in this layer, cannot reproduce themselves. (4) Stratum lucidum layer plays the role of cushioning and protection and is found only on the palms of hands and soles of feet. (5) Stratum corneum is the outer-layer of skin which forms the primary barrier to drug transport.
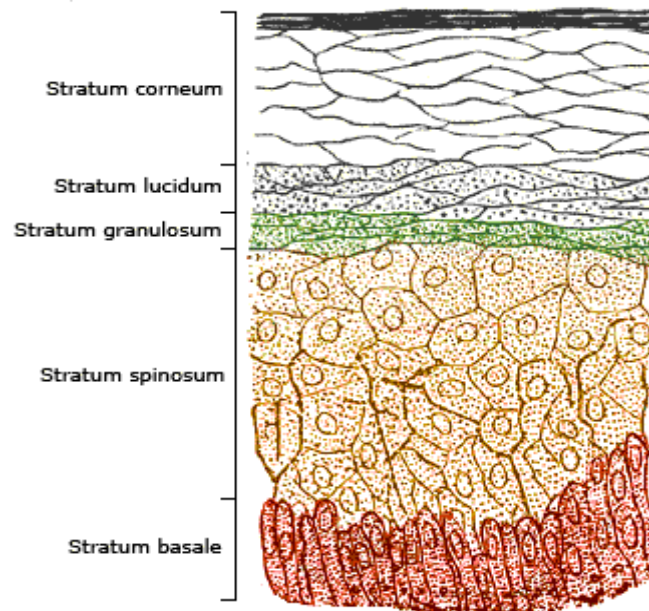
Figure 1.3 shows the schematic image of the epidermis with its sub structure such as the stratum basale layer, the stratum spinosum layer, the stratum granulosum layer, the stratum lucidum layer and the stratum corneum layer. The stratum corneum layer directly contacts with external environment.

1.2.1.2 Stratum Corneum (SC) The outer 10-15 micrometer of skin, called stratum corneum, is a dead tissue that forms primary barrier to drug transport, since stratum corneum is a composite material made of protein and lipids structurally organized as "brick and mortar", as shown in Figure 1.3. The hydrophobic lipid bi-layers fill all of extracellular spaces, where this lipid-enriched matrix is organized into lamellar membranes that surround the corneocytes. The lipid-enriched matrix of the stratum corneum includes not only the structure that limits transdermal delivery of hydrophobic drug, but also the so-called stratum corneum "reservoir", within which lipid soluble drugs, such as topical corticosteroids, can accumulate and be slowly released [6]. Therefore, once hydrophobic medicine can successfully pass through stratum corneum, they get into the viable epidermis layer which has live cells and nerves but not vessels; it can diffuse rapidly through deeper tissue and be taken up by the underlying capillaries for systemic administration [10].
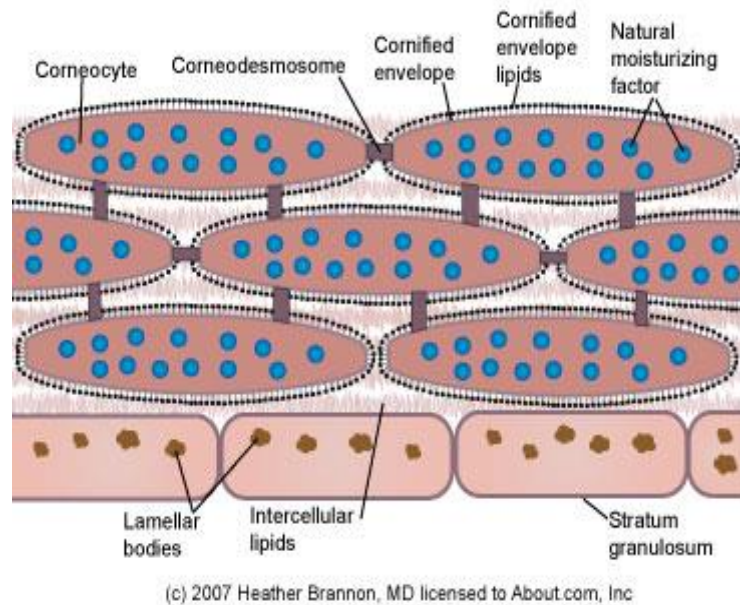
Figure 1.4 The SC layer consists by corneocytes which are like scaffold for SC structure, and extracellular hydrophobic matrix.
Source: Sebastien Henry, D., V.M., Mark, G.A. and Mark, R.P., Microfibricated Microneedles: A Novel Approach to Transdermal Drug Delivery, Journal of Pharmaceutical Sciences, Vol. 87, No. 8, August 1998.

Although the corneocytes (Figure 1.4) contribute volume to be a scaffold for the stratum corneum structure, modern transdermal delivery strategies focus primarily on manipulations of the extracellular lipid milieu. The reason why hydrophilic drugs have exceptional low permeability to cross stratum corneum is the consequence of several characteristics of the lipid-enriched, extracellular matrix, including its organization into a highly complicated and tortuous diffusion pathway, such as mortar between bricks, imposed by geometrically arrayed corneocyte "spacers" [6]. Furthermore, not only the stranger pathway of bilayers' extracellular lipids, but also the three extreme hydrophobic components, ceramide fatty acid and cholesterol, of lipid contribute to the barrier function, as shown in Figure 1.5.
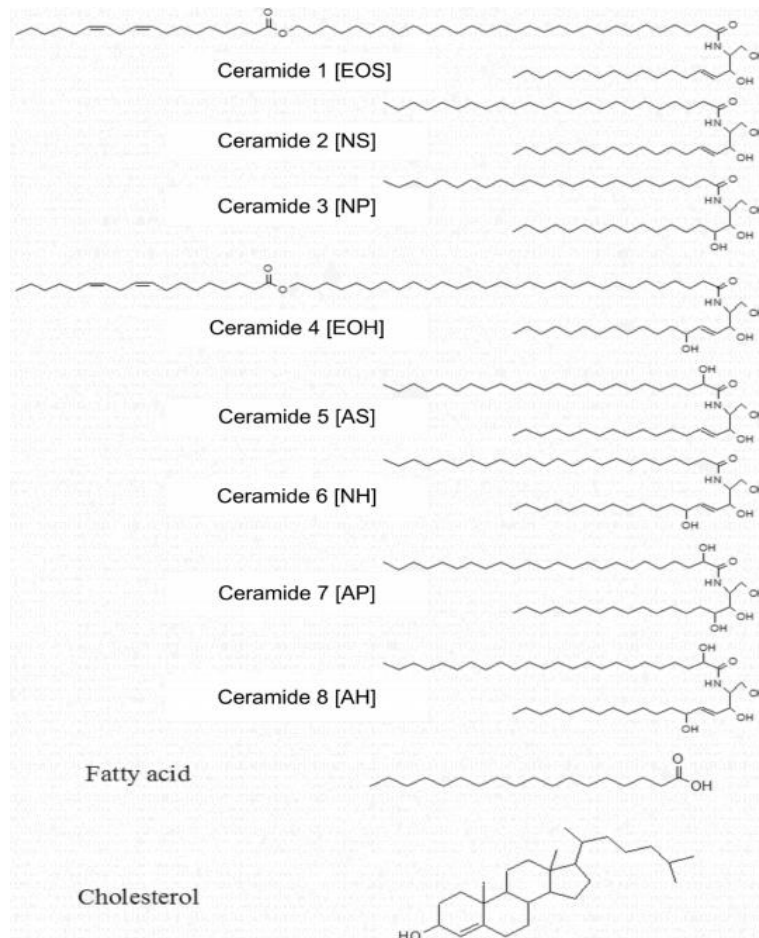
Figure 1.5 The structure of the major components of the stratum corneum intercellular lipids. Numbers 1 to 8 are ceramides and represent a thin layer with chromatographic mobility, with ceramide 1 being the least polar and ceramide 8, the most polar. The letters in square brackets are the structural classifications of the ceramide as suggested by Motta et al.

Source: Biochim Biophys Acta 1993;1182: 145-51.

1.2.2 Transdermal Patches

Transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. An advantage of transdermal patch over other types of delivery of medication is that the patch provides a controlled release of the medication into the patient. The main disadvantage to transdermal

delivery systems stems from the fact that the skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered by this method. Nowadays, there are three main generations of transdermal drug delivery systems. The first generation is a very simple patch which has specific medicinal properties such as low-molecular weight, lipophilic and efficacious at low doses. Base on Fick's law, the driving force of first generation TDD system is only the concentration gradient. The second generation of transdermal delivery systems already consider that skin permeability enhancement is needed to expand the scope of transdermal drugs. Thus the second generation of transdermal delivery systems add an enhancer layer to increase the skin permeability by reversibly disrupting stratum corneum structure or simply adding more driving force for transport into the skin such as chemical disruption, iontophoresis and non-cavitational ultrasound. The third generation transdermal delivery systems is poised to make significant impact on drug delivery because it targets its effects to the stratum corneum [5]. This targeting enables stronger disruption of stratum corneum layer of skin, while still protecting the deep tissue. For example, the micro-needles are conceptually a straightforward way to directly penetrate the stratum corneum layer.

Normally, transdermal patches have similar structures. There are four basic layers for the common transdermal patches as shown in Figure 1.6. Clear backing layer isolates other layers from contacting with natural environment. Drug reservoir layer stores the medicinal particles. Drug delivery membrane layer controls the ratio of drug actives in the

form medicinal particles. Contact adhesive layer directly attaches to the skin. Based on different patches, which have different enhancers to increase the diffusion of medicine into the skin, different layer for enhancers are added. In this study, the author uses SYNERA Lidocaine and Tetracaine topical patches. These patches have extra integrated heating component layer for increasing drug diffusion rate by additional temperature gradient, which can heat the patch and skin surface to 42 °C at room temperature. Therefore, the SYNERA patch has an additional enhancer layer between the clear backing layer and the drug reservoir.

Figure 1.6 Common transdermal patch structure which includes four basic layers such as (i) clear backing layer, (ii) drug reservoir layer, (iii) drug-release membrane layer and (iv) contact adhesive layer.
Source:(http://drugdelivery.chbe.gatech.edu/Papers/2012/Prausnitz%20Derm%20Book%20Chapter%20201 2.pdf) Accessed on March 15, 2016.

1.2.3 ADME/T Mechanism

ADME/T mechanism is abbreviation in pharmacokinetic and pharmacology for absorption, distribution, metabolism, excretion and toxicity, and describes the disposition of a pharmaceutical compound within an organism. The five criteria already describe all influences when particles of drug/drug actives touch and interact with human tissues. Nowadays, although drug designers can synthesize many different kinds of drugs which have different chemical components, 95% of them cannot be directly used in clinical trials, because of insufficient ADME/T properties.

1.2.3.1 Toxicity Arguably, drug toxicity is the most challenging drug property that remains one of the most significant reasons for many drugs failing to reach the market and for many drugs not approved to the market and withdrawal from the market during the late-stage of drug development [12]. Base on individual differences, drug toxicity may occur from any sources inside the human body such as receptor or enzyme and DNA interaction. In this study, the anesthetic agents, Lidocaine and Tetracaine, are high lipophilic particles whose concentrations need to be controlled below specific number in blood.

1.2.3.2 Excretion   Drug excretion is the process whereby a drug molecule is eliminated by human organs such as liver and kidney. Base on blood flow, protein binding and lipophilicity, scientists can roughly predict passive excretion [13]. For example, there is enzyme which can hydrolyze the Tetracaine in the circulatory system. But the renal

excretion process is more complex due to more than few processes of excretion.

1.2.3.3 Metabolism   Compounds begin to break down as soon as they enter the human body by some enzymes in the liver. As metabolism occurs, the initial (parent) compound is converted to new compounds called metabolites; and also metabolism can deactivate the administered dose of parent drug and this usually reduces the effects on the body; moreover, metabolism may also be pharmacologically active.

1.2.3.4 Distribution   Distribution is a transport process by bloodstream which is the main circulatory system in the human body. Bloodstream delivers drug molecules from areas of higher concentration to areas of lower concentration. Some factors affecting drug distribution include regional blood flow rates, drug molecular size, polarity and binding to serum proteins, forming complex. Sometimes, distribution will face some serious barriers such as blood brain-barrier.

1.2.3.5 Absorption   For a compound to reach a tissue, it usually must be taken into the bloodstream before being taken up by the target cell. In this study, drug particles/actives should pass through the stratum corneum layer so as to be taken up into systemic circulation. Different drug delivery systems have different mucous membranes which also have different absorption mechanism. Thus, for this study of transdermal drug delivery, the author will discuss percutaneous absorption.

1.2.4 Percutaneous Absorption Mechanism

Percutaneous absorption includes entire procedures of drugs delivery from the outermost layer of the skin to the systemic circulation. This process requires penetration into the layers of the skin with subsequent permeation across each layer of the skin and finally uptake to the capillary blood vessel in the upper region of the dermis [13]. In the percutaneous absorption system, different skin structure will give different routes for drug passives to diffuse into blood capillary. Thus, processes of passive diffusion of drug molecules are elaborated in the following model - Figure 1.7.
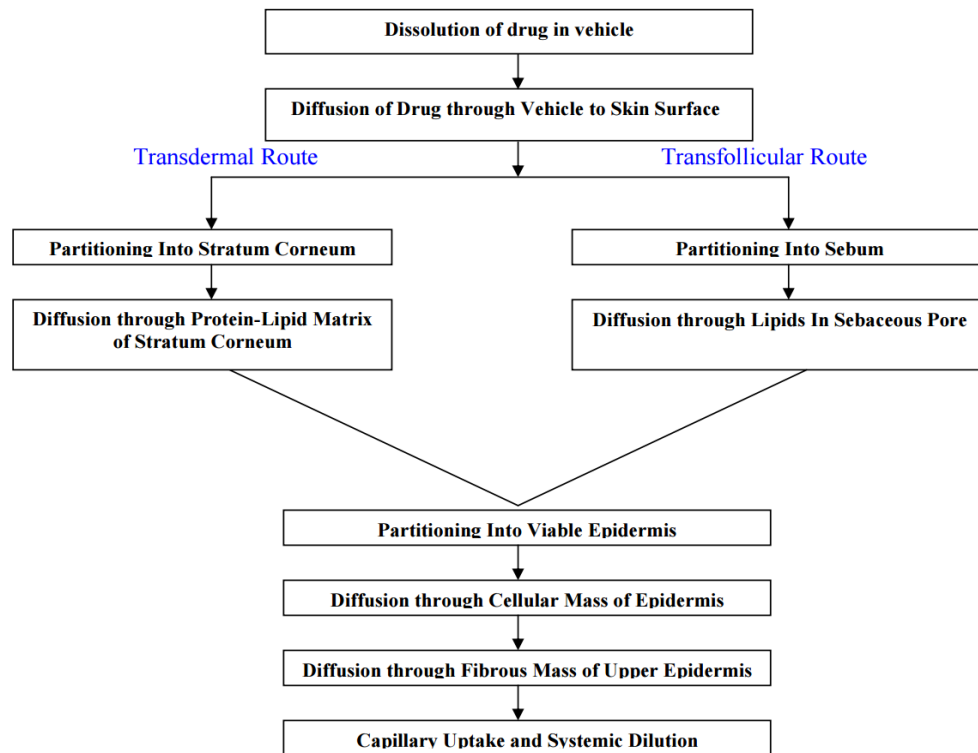

Figure 1.7 shows that before drug molecules reach systemic circulation, drug molecules first face partition phenomenon of the skin followed by diffusion through the epidermis layer.

Source: Alan, B., Ursula, G.R., Pierre, K., Panos, M. Olavi, P., In silico prediction of ADME and pharmacokinetics, European Journal of Pharmaceutical Sciences, 17, pp. 183-193, 2002.

1.2.4.1 Routes of Penetration   Absorption via the transdermal route primarily occurs by passive diffusion through the SC. The rate of diffusion depends on several properties such as: (1) diffusivity between drug molecules and the SC layer, applied concentration of drug, surface area of the skin exposed to the drug molecules and the length of diffusion pathway. Except for the same procedures as shown in Figure 1.7, there are two main routes: the trans-epidermal route and the trans-follicular route, to penetrate the SC layer. In the early time periods, chemical particles can penetrate the SC via skin appendages such as hair follicles, sebaceous glands or sweat glands with absorption through the squamous epithelial cell lining these structures into the deeper layers of the skin (Figure 1.8). However, due to large surface areas, trans-epidermal diffusion gradually increases until dominating penetration processes.

As shown in Figure 1.8, there are two other sub-pathways for the trans-epidermal route. The first, the transcellular is the diffusion pathway across corneocytes. The second, the intercellular contributes a tortuous pathway between corneocytes for lipophilic molecules. Hence, the permeability of the SC components, lipid protein matrix and corneocytes, are the most important properties of transdermal delivery systems. In this study, the anesthetic agents, Lidocaine and Tetracaine, are highly lipophilic. The octanol/water partition ratio (K_{ow}) of Tetracaine reaches 5370 at pH 7.3; and K_{ow} of Lidocaine also reaches 182 at pH 7.3. Based on the partition ratio, this study only focuses on intercellular pathway for anesthetic agent transport. Geometric structure of the

14

intercellular pathway is demonstrated in Figure 1.8.
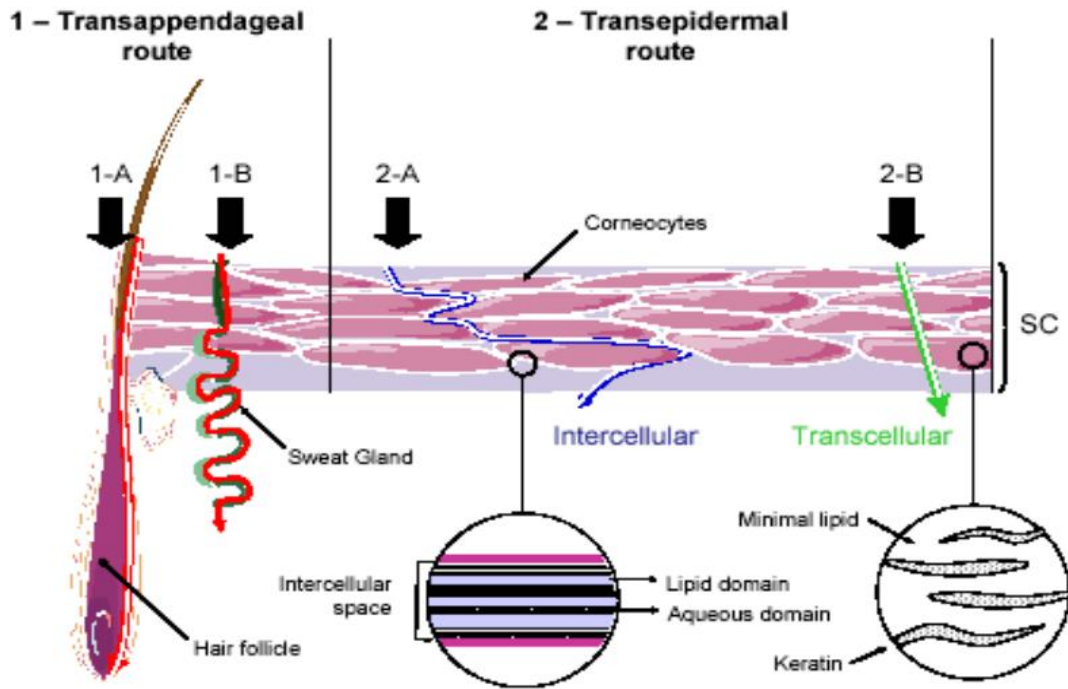
Figure 1.8 demonstrates two penetration routes for percutaneous absorption. (1) The trans-appendageal route dominates early when drug particles are put on the skin surface. (2) The trans-epidermal will gradually dominate instead of the trans-appendageal route.

Source: Alan, B., Ursula, G.R., Pierre, K., Panos, M. Olavi, P., In silico prediction of ADME and pharmacokinetics, European Journal of Pharmaceutical Sciences, 17, pp. 183-193, 2002.

1.2.4.2 Factors Affecting Drug Permeation   The stratum corneum layer and other epidermal layers are quite distinct structures [14]. Considering drug diffusion through epidermis, the drug solution must balance between lipid solubility and aqueous solubility to handle variable structures of the epidermis. The structure of the SC, brick and mortar, essentially provides a lipophilic milieu for drug transport whereas the other layers of epidermis provides a more hydrophilic domain. Therefore, the drug molecules which are balanced between lipid and water solubility can successfully reach systemic circulation

without excess partition in different solubility media. Based on partition character, the Potts & Guy equation (Equation 1.1) describes an empirical equation governing highly lipophilic compounds which use intercellular pathway to penetrate the SC barrier. Equation (1.1) shows that the permeability of highly lipophilic compounds mainly relate to the partition coefficient and molecular weight. Also, Table 1.1 demonstrates that additional factors will affect the permeability of diffusants.

$$\log k = 0.71\log \text{Kow} - 0.0061MW - 2.74 \qquad (1.1)$$

k is the permeability of the diffusant (m/s).

K_{ow} is the partition coefficient of the diffusant.

MW is the molecular weight of the diffusant (g/mol).

Table 1.1 Factors Affecting Drug Permeation

(a) Variations in skin structure
(b) Sites of application
(c) Hair follicles (effects of hair or shaving the site of application)
(d) Sweat glands
(e) Effect of age, blood supply, body temperature and composition (e.g. elevated body temperature, hyperthyroidism & inflammation etc.)
(f) First pass metabolism by the skin
(g) Ability of the skin to act as a reservoir for transdermal agents
(h) Physicochemical characteristics of the transdermal agents (the ideal compounds are low molecular weight, lipophilic, soluble in oil & water and have a high partition coefficient and melting point)
(i) Drug stability
(j) Use of solvent carriers or vehicles
(k) Use of penetration enhancers (nature & type)
(l) Use of delivery devices etc.

1.2.5 Diffusion

Diffusion refers to the process by which molecules intermingle as a result of their kinetic energy (In physics, the kinetic energy of an object is the energy that it possesses due to motion.) due to random motion. Therefore, the diffusion motion does not come from any outside force, but more as result of the random distribution of atoms being mixed. By definition, the atomic motion due to diffusion is random. However, a selective diffusion process, called osmosis, is driven by the internal energy of the solvent molecule so that the random diffusion has direction of molecule movement. This internal energy based driving force is the result from different gradients such as differences in concentration, temperature or magnetic field. This process was originally evaluated by Adolf Fick in the 19th century [15], who described this phenomenon by equation (1.2). There are two simple descriptions of Fick's law (Table 1.2).

Table 1.2 Description of Fick's Law

1, The molar flux due to diffusion is proportional to the concentration gradient.
2, The rate of change of concentration at a point in space is proportional to the second derivative of the concentration with space.

1.2.5.1 Fick's Laws of Diffusion The most common mathematical form of Fick's laws of diffusion makes the following assumptions: (i) The receptor phase is a perfect sink. (ii) Depletion of the donor phase is negligible. (iii) The membrane is homogenous.

$$J_i = -D_i \nabla C_i \tag{1.2}$$

The J_i is the molar flux (mol m^{2}s^{-1}) and the D_i is the diffusion coefficient (m^{2}s^{-1}).

The negative sign of equation (1.2) means that the transport direction of species i is reversed with concentration gradient, from higher concentration to lower concentration; moreover, the sign ∇ C_i means the gradient of difference of concentration with distance.

$$\nabla C_i = \frac{\partial c_i}{\partial x} \tag{1.3}$$

From the continuity equation for mass:

$$\frac{\partial c_i}{\partial t} + \nabla C_i = 0 \tag{1.4}$$

We can derive the Fick's second law directly:

$$\frac{\partial c_i}{\partial t} = D_i \nabla^2 C_i \tag{1.5}$$

Equation 1.4 shows a linear equation for the Fick's second law. Therefore, if this assumes that D_i is a constant, the relationship between diffusion concentration and time can be calculated from the Fick's second law. However, this assumption is only true in the dilute solution.

1.2.6 Diffusion Coefficient Prediction Theory

In the above sections, diffusion processes and modern mathematical equations, Fick's laws are introduced. In each equation of mass diffusion processes, the diffusion coefficient is the most important parameter. Therefore, understanding how to calculate the diffusion coefficient is very important for solving mass diffusion problems [16] [17].

1.2.6.1 Solid Media The diffusion coefficient in solids, at different temperatures, is generally found to be well predicted by the Arrhenius equation:

$$D = D_0 e^{-E_A/(kT)} \tag{1.6}$$

where

D is the diffusion coefficient (m^2/s).

D_0 is the maximum diffusion coefficient (at infinite temperature; m^2/s).

E_A is the activation energy for diffusion in dimensions of (J atom^{-1}).

T is the absolute temperature (K).

k is the Boltzmann constant.

1.2.6.2 Liquid Media The diffusion coefficient, as function of temperature, in liquids

can often be found using Stokes-Einstein equation, which predicts that:

$$\frac{D_{T1}}{D_{T2}} = \frac{T_1}{T_2} \frac{\mu_{T2}}{\mu_{T1}} \tag{1.7}$$

D is the diffusion coefficient (cm^2/s).

T is the absolute temperature (K).

T_1 and T_2 denote temperatures T$_1$ and T$_2$, respectively.

μ is the dynamic viscosity of the solvent (Pa s).

1.2.6.3 Gas Media The dependence of the diffusion coefficient on temperature for gases

can be expressed using Chapman- Enskog theory:

$$D = \frac{1.858 \cdot 10^{-3} T^{3/2} \sqrt{1/M_1 + 1/M_2}}{p \sigma_{12}^2 \Omega} \tag{1.8}$$

D is the diffusion coefficient, which is expressed in cm^2/s.

1 and 2 index the two kinds of molecules present in the gaseous mixture.

T is the absolute temperature (K).

M is the molar mass (g/mol).

p is the pressure (atm).

$\sigma_{12} = \frac{1}{2}(\sigma_1 + \sigma_2)$ is the average collision diameter (the values are tabulated) (Å).

Ω is a temperature-dependent collision integral (the values are tabulated but usually ~ 1)

(dimensionless).

1.2.6.4 Free Volume Theory In percutaneous drug delivery, if only the intercellular

pathway is considered, the drug molecules will migrate through the extracellular matrix of

the epidermal layer for reaching bloodstream or nerve cells located at the dermis layer. The

extracellular matrix is composed of macromolecular polymers such as proteins. Therefore,

the diffusion of drug molecules can be considered as mobility of small molecules in the

macromolecular matrix. Base on Equation (1.6), the mobility is considerably influenced by

temperature and concentration. However, the extracellular matrix is not common solid

media which can directly use Equation (1.6) for the determination of the diffusion

coefficient. In 1959, Cohen and Turnbull originally suggested an assumption [18] that there

were empty space, called free volume, between molecular sequences, which can be

migration pathways for small hard sphere molecules. In transdermal delivery systems, there

are many factors which will affect the mobility of the drug molecules. However, for

simplifying this case, only free volume concept need to be considered. Therefore, diffusion

coefficient can be assumed to be proportional to the probability of locating a vacancy of volume V* or larger and could be written [7].

$$D = A \, e^{\frac{\gamma V^*}{V}}$$ (1.9)

V^* is the critical volume for migrating molecule.

γ is the overlap factor of free volume.

A is the defined constant which is associated with kinetic energy.

V is the specific volume.

Although, Equation (1.9) already suggests a mathematical method for mobility based on free volume theory, this is not enough for dealing with problems of drug diffusion through the skin. Therefore, Vrentas and Duda [19] introduced the following relationship between more diffusion units and free volume:

$$V_{FH} = \frac{V^*}{\frac{w_1}{M_{1j}} + \frac{w_2}{M_{2j}}}$$ (1.10)

V_{FH} is the average hole of free volume.

w_1 and w_2 represent species 1 and 2.

M_{1j} and M_{2j} are diffusion units.

The above equations clearly indicate that the diffusion coefficient of small molecules is an exponential function related to free volume; and also the free volume is related with molecular shape and size. However, Vrentas and Duda [19] further simplified Equation (1.9) such as the Equation (1.11).

$$D = D_0 e^{-\frac{E}{KT}} e^{\frac{-\xi V^*}{V}}$$ (1.11)

D is diffusion coefficient.

D_0 is the pre-exponential factor.

E is the attraction energy between the molecules.

K and T are the Boltzmann's constant and absolute temperature.

ξ is the ratio of solvent to polymer jumping units.

V* is the critical space of free volume for molecule jump.

V is provided by polymer matrix for diffusion.

By using Equation (1.10) in Equation (1.11) to obtain Equation (1.12) about diffusion of a solute in a polymeric matrix.

$$D = D_0 e^{-\frac{E}{KT}} e^{-\frac{\gamma[W_s V_s + W_p \xi V_p]}{V_{FH}}}$$ (1.12)

W_s and W_p are the weight percentage of drug or polymer matrix.

V_p and V_s are the embedded volume of matrix and drug.

V_{FH} is average hole of free volume.

E is the attraction energy between the molecules.

K and T are the Boltzmann's constant and absolute temperature.

ξ is the ratio of solvent to polymer jumping units.

However, a modified equation, in copolymer media, of molecular migration in polymer matrix was suggested by Duda and Zelinsky at 1992 [20].

$$D = D_0 e^{-\frac{E}{KT}} e^{-\frac{\gamma[W_s V_s + W_p(W_{2a}\xi V_{2a} + W_{2b}\xi V_{2b})]}{V_{FH}}}$$ (1.13)

V_{2k} (k is for either a or b) is defined as the specific volume of block k in the copolymer at 0 K; and W_{2k} (k is for either a or b) is defined as the weight fraction of block k in the copolymer. When polymer matrix is homo-polymer, W_{2a} is equal to zero and W_{2b} is equal to equation 1.12. The Duda-Zelinsky equation reduces to Vrentas-Duda equation.

1.2.7 Partition Coefficient

The term, partition coefficient, is the ratio of a compound in a mixture of two immiscible phases in equilibrium so as to measure the different solubility of the compound in these two phases (Equation 1.14). K_{ow} is the ratio between solution of octanol and water.

$$\log K_{ow} = \log\{\frac{sloute_{octanol}^{un-ionized}}{sloute_{water}^{un-ionized}}\}$$ (1.14)

In pharmacology, the partition coefficient strongly affects how easily the drug can reach its intended target in the body, how strong an effect it will have once it reaches its target, and how long it will remain in the body in an active form [20]. Specifically, for a drug to be percutaneously absorbed, normally it must first pass through lipid bilayers of corneocytes in the outermost layer (SC) of the epidermis. Hence, the K_{ow} of diffusant cannot be too small to penetrate lipid bilayers.

CHAPTER 2

MATERIALS AND METHODS

2.1 Materials

The research material, considered in this study, is a commercial topical anesthetics patch, SYNERA, which combines amide (lidocaine) and ester (Tetracaine) local anesthetic for use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatological procedures such as excision, electrodessication and shave biopsy of skin lesion. The structure of SYNERA is shown in Figure 2.1. Table 2.1 presents the basic information of SYNERA.
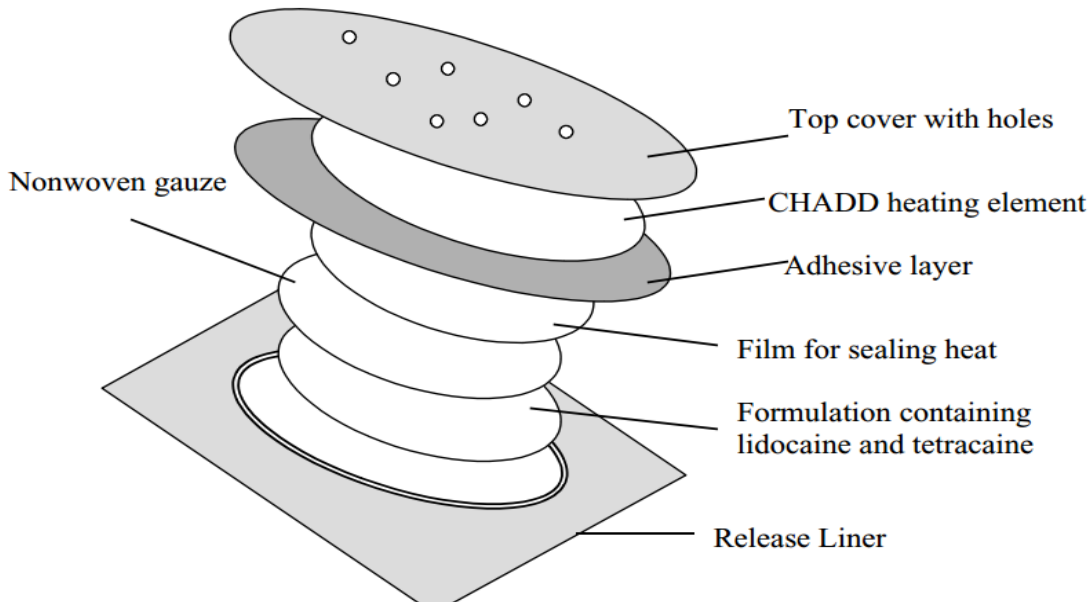
Figure 2.1 Synera patch not only includes drug reservoir and other common layers of transdermal delivery patches, but also includes CHADD heating element layer which uses chemical reaction to create extra temperature gradient instead of using drug vehicles for drug diffusion enhancement.
Source: Crank, J., The mathematics of diffusion (2nd Ed.). 2-12, 46-47, 1975.

Table 2. 1 Basic Information of SYNERA

Featured Indication	
Surface anesthetic for minor dermatological procedures in adults and needle punctures of the skin in adults and children ≥3 years of age	
Mechanism of Action	
Local anesthetic agent blocks voltage-gated sodium channels	
Dosage and Administration	
Doses per patch	70 mg/70 mg
Patch size	8.5cm x 6.0cm
Drug cover area	$10cm^2$
Route of administration	Dermal (topical application)
Application site	Normal intact skin
Application time	30 min
Number of simultaneous plasters (adults)	1–4 (maximum 4 per 24 h)
Number of simultaneous plasters (children)	1–2 (maximum 2 per 24 h)
Mean Peak Plasma Concentration Following Dermal Application for 30 min of Two Plasters Simultaneously	
Number of SYNERA Patches	1
Age Range (yr)	18- 65
Application Time (min)	30
Drug Content (mg)	Lidocaine 70 /Tetracaine 70
Estimated Amount Absorbed (mg)	Lidocaine/Tetracaine 1.7/1.6
C_{max} (ng/mL)	Lidocaine/ Tetracaine 1.7/0.9
Most Frequent Treatment-Related Adverse Events of Mild to Moderate Intensity in Clinical Trials	
Erythema, oedema, pruritus, burning sensation	
Partition Coefficient of Octanol/Water	
Lidocaine 182 at pH 7.3	Tetracaine 5370 at pH 7.3
Molecular Weight	
Lidocaine 234.34 g/mol	Tetracaine 264.363 g/mol

Although two local anesthesia agents, Lidocaine and Tetracaine, are formulated

by eutectic methods, eutectic mixture is not a crystal but a liquid. This is because the

melting point of this eutectic mixture is lower than room temperature. Hence, unlike other

solid forms of anesthetic agents, SYNERA does not need diffusion vehicle for transdermal

drug delivery in order for it to increase the drug concentration in the drug reservoir layer.

These two special factors, liquid eutectic mixture and thermal enhancer, remarkably

increase the drugs' absorption ability and minimize the action time of patches so as to avoid

many side effects, such as skin allergy, from drug delivery for long durations.

2.2 Methods

2.2.1 Parameters Switching

In the commercial FEA software, ANSYS 15.0, there is no mass diffusion package.

Therefore, the author has used thermal analysis package instead of mass diffusion. The

reasons for this implementation will be explained in the subsection.

2.2.1.1 Steady-State Diffusion　　Fick's first law introduces the theory of diffusion flux,

J (kg/m^2 s), which is the rate of mass concentration transfer through a given surface,

Equation (1.2), per unit time. Similarly, heat flux or thermal flux, q (J/ m^2 s) is the rate of

heat energy transfer through a given surface, per unit time, Equation (2.1). Comparing

Equation (1.2) with Equation (2.1), it is easily understood that mass flux and heat flux

separately relate to concentration or temperature gradient; and also, D and k are the

diffusion coefficient of different transfer equations.

$$q = -k\frac{dT}{dx} \qquad (2.1)$$

q is the heat flux (J/ m² s).

k is the thermal conductivity (J/m K s).

T is absolute temperature (K).

x is distance of temperature gradient (m).

2.2.1.1 Transient Diffusion In Fick's first law, flux is a constant which will not change

with time; it is called steady- state diffusion. In the same situation, heat flux is also constant.

However, to reach steady state will require some time. Therefore, Fick's second law,

Equation (1.5), was introduced to demonstrate the relationship between time and flux for

transient diffusion analysis. Also in the heat transfer analysis, there are similar equations

for energy transfer at transient situation, for example, Equation (2.2).

$$\frac{\partial T}{\partial t} = \frac{k}{\rho c_p}\nabla^2 T \qquad (2.2)$$

k is the thermal conductivity (J/m K s).

T is absolute temperature (K).

ρ is the density (kg/m³).

c_p is the specific heat capacity (J/(kg K).

Based on the above comparison, except for some differences between parameters,

the form of the two transfer equations are same. Therefore, the use of heat transfer analysis,

instead of mass diffusion analysis, is viable whether steady-state or transient situation. The

parameter switch is shown in Table 2.2.

Table 2.2 Parameter Switching

Thermal	Heat Flux	Conductivity	Temperature	Density	Heat Capacity
	J/ m^2 s	J/m K s	K	kg/m^3	J/kg K
Mass	Mass Flux	Diffusivity	Concentration	Density	Heat Capacity
	kg/m^2 s	m^2/s	kg/m^3	1	1

2.2.2 Finite Element Model

This study uses 10 layers in the form of brick and mortar geometry to simulate the two-

dimensional (2D) geometry of the SC (Figure 2.2). Element type is 4 nodes of two

dimension element, PLANE 55, for thermal analysis. Based on Table 2.2, the conductivity

can be directly replaced by diffusivity (D); and also for transient analysis, specific heat

capacity (C_p) and density (ρ) are equal to one; moreover, the initial concentration is equal

to 70 kg/m^3 for each anesthetic agents. For the shape of the finite element model, the lipid

layer between two corneocytes (S) is equal to 0.1 micrometer; and also the width (d) and

height (h) of corneocytes are 40 micrometer and 1 micrometer, respectively; moreover, the

length (l_s) of two lipid pathway in y direction is equal to 10 micrometer.
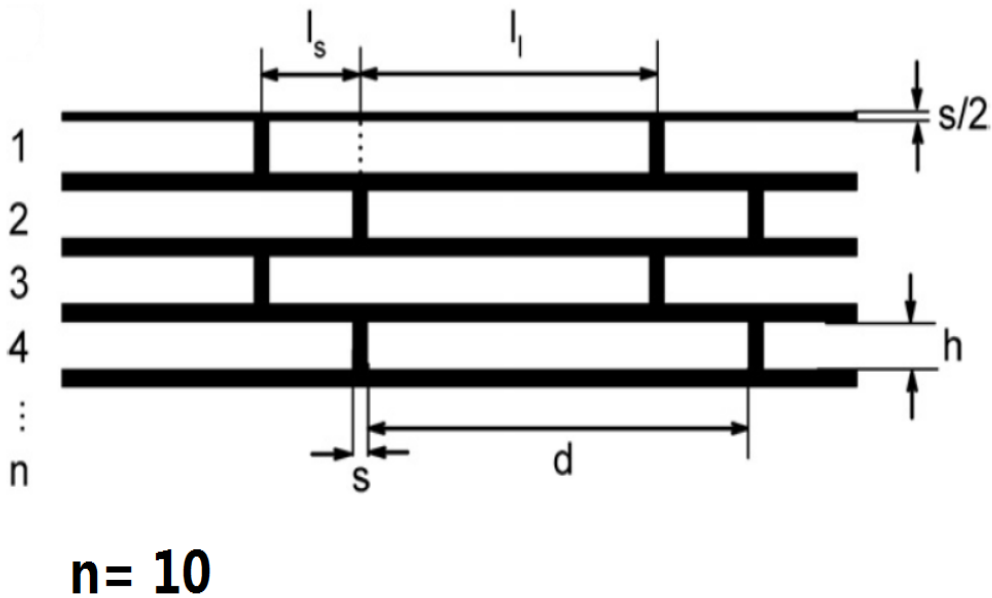
Figure 2.2 Geometric Shape of Brick and Mortar Model

2.2.3 Theoretical Calculations of Diffusion Parameters

Transdermal diffusion is not totally like simple mass diffusion, such as diffusion of hydrogen through metal. This is because, when drug molecules migrate between lipid media, molecular distribution should be considered first, which means some molecules will dissolve in liquid so that these molecules cannot pass through the SC even with enough diffusion time. Hence, the solubility between transfer media and drug will be considered (The partition ratio of octanol and water is to estimate distribution phenomenon).

2.2.3.1 Maximum Flux Determination   The steady-state diffusion of a drug across the skin may be described by Fick's first law, Equation (1.2). In this situation, Fick's first law can be manipulated by considering solubility between stratum corneum and drugs [21].

$$J_{max} = \left(\frac{D}{h}\right) \cdot K_{sc/v} \cdot C_{v,sat} = k_p \cdot C_{v,sat} \qquad (2.3)$$

J_{max} (kg/m^2 s) is the maximum drug flux when the system reaches steady- state. D (m^2/s) is

its diffusion coefficient in the stratum corneum (SC).

$K_{SC/v}$ is the drug's SC-vehicle partition coefficient.

h is the length of lipid pathway taken by the penetrant through the SC.

$C_{v,sat}$ (kg/m^3) is saturated concentration of the drug in the vehicle.

k_p (m/s) is the permeability of drug molecule (In this study, it can be directly calculated by

Equation (1.1)).

Comparing Equation (2.3) with Fick's first law, the diffusion coefficient of

transdermal diffusion is manipulated to $DK_{SC/v}$. By using permeability (k_p) in Equation

(2.3), the new diffusion coefficient will relate to permeability as in Equation (2.4). The new

diffusion coefficient *Ds* will be used for FE model.

$$D_s = K_p \cdot h \qquad (2.4)$$

2.2.3.2 Permeability Determination The author has already described Potts & Guy

equation, Equation (1.1), for permeability coefficient (k_p) of each drug across the skin from

aqueous solution. For calculating the corrected permeability coefficient (K_{pcorr}), the

following Cleek and Bunge Equation (2.5) will be used for highly lipophilic species for

which viable epidermis can contribute to rate-control [22].

$$k_p^{corr} \quad \frac{k_p}{1+\frac{k_p \cdot \sqrt{MW}}{2.6}} \tag{2.5}$$

MW is the drug's molecular weight. Therefore, if the diffusion pathway length (h) is calculated as in Figure 2.2, permeability and diffusion coefficient of each drug can be calculated. The results are shown at Table 2.3. The diffusion pathway length comes from 10 layers in the FE model (h=101μm).

Table 2.3 Diffusion Coefficient of FE Model

Permeability k_p (m/s)	
Lidocaine **8.3E-9(m/s)**	Tetracaine **6.02E-8(m/s)**
Diffusion Coefficient D_s (m^2/s)	
Lidocaine **8.383E-13(m^2/s)**	Tetracaine **6.08E-12(m^2/s)**

2.2.3.3 Lag Time   The term of time-lag is the period between closely related events. In this study, anesthetic agents, lidocaine and tetracaine, should transfer across the epidermis layer so as to reach the nerve cells of the dermis layer. Although, Fick's first law can be used to predict the maximum flux of diffusion, the value of flux always changes with diffusion time. This is because the concentration gradient between two sides of a membrane is not always constant (Figure 2.3). Based on Figure 2.3, the changing concentration with increasing time is not linear before the concentrate penetrates the entire thickness of the membrane. Hence, the time of concentration, or flux, required to reach stead state is called the lag time (t_L) [22]. The lag time for all FE model results are calculated by extrapolation

of the steady-state portion of the mass accumulation curve to the time axis. Lag time is related to the thickness of the skin, or length of diffusion pathway when geometry of media is irregular shape such as twist lipid pathway, and the diffusion coefficient. The equation for lag time is described by Equation (2.6).

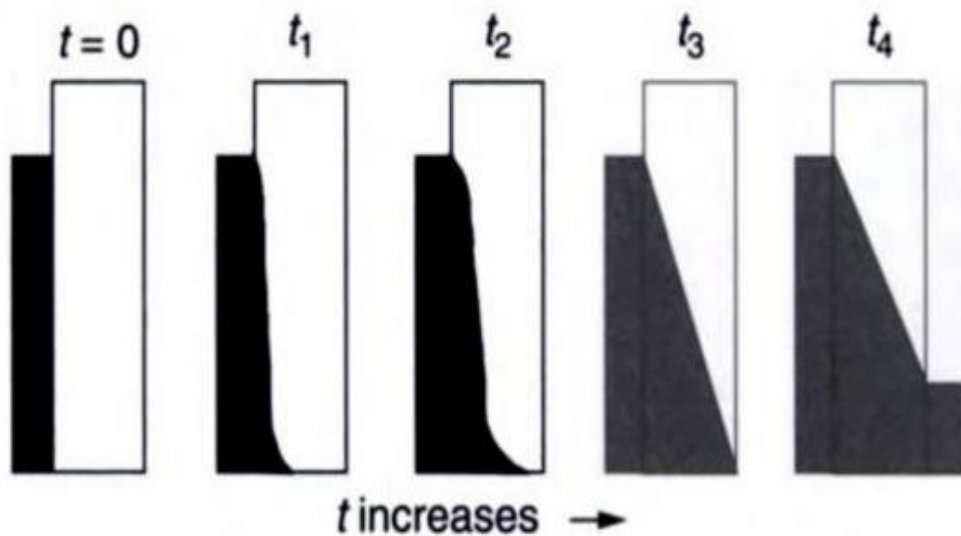$$t_L = \frac{h^2}{6D_s} \tag{2.6}$$

t increases →

Figure 2.3 shows the changing processes of the concentration gradient with increasing time. Concentration gradient is not linear before concentration reaches the other side of the membrane at t_3. After t_3, the concentration gradient is linearly decreasing.

2.2.3.4 Effect of Temperature   In the experimental transport of drugs through cell membrane, the temperature should be strictly controlled since temperature can increase the mobility of diffusion molecules. Also the permeability of drug increases significantly as the experimental temperature is increased in increments of approximately 7 ℃ [23]. It is observed that the apparent permeability and temperature are related by an exponential relationship that conforms to the Arrhenius equation. In this case, the permeability of

diffusant may be expressed as following equation.

$$P_{app} = \frac{D_T \times K}{h} \tag{2.7}$$

where P_{app} is the apparent permeability which is from Potts & Guy equation; K is the

partition coefficient between media and diffusants; h is the length of the pathway.

Combining Equation (2.7) and Arrhenius equation, the new equation will be obtained.

$$P_{app} = \frac{D_0 \times e^{-E_A/(kT)} \times K}{h} \tag{2.8}$$

Assuming that the partition coefficient and length of diffusion pathway remain

constant over the range of temperature studied, the following relationship can be derived

as in Equation (2.8) [23].

$$P_{app} \propto e^{\frac{-1}{T}} \tag{2.9}$$

This suggests that the apparent permeability of drugs increases exponentially with

temperature. A plot of logarithm of apparent permeability *versus* absolute temperature will

yield a linear relationship such as in Figure 2.4. In this study, a heating layer is also added

to topical patches to increase the skin temperature up to 40 ℃. Hence, the relationship

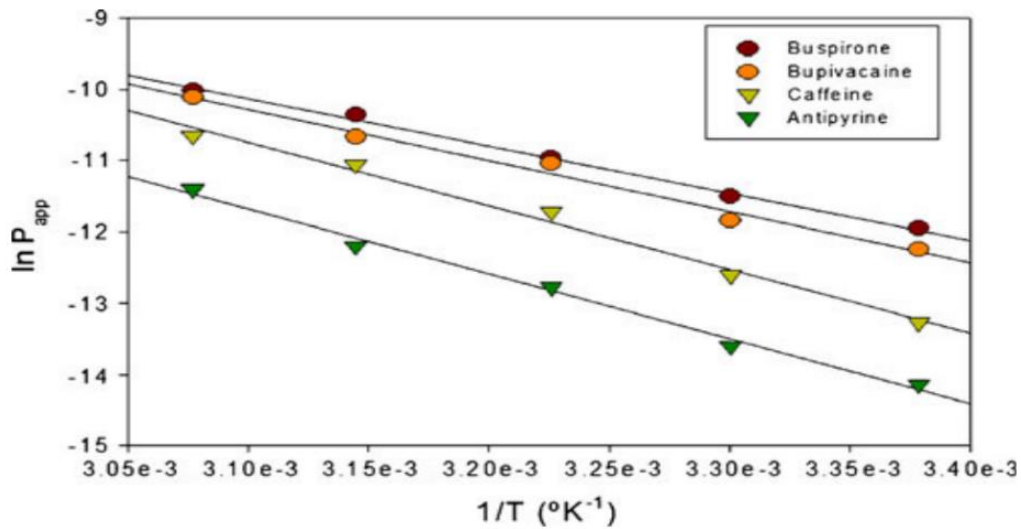between permeability of drugs, Lidocaine and Tetracaine, and temperature will be plotted.

Figure 2.4 A plot of lnP versus 1/T for five different temperatures, viz., 23 °C, 30 °C, 37 °C, 45 °C, and 52 °C, were utilized in individual permeation experiments. Four different diffusants transfer across porcine buccal mucosa.

2.2.3.5 Mass Absorbed. The flux and permeability coefficient allow an exposure assessment over time in steady-state condition [24]. When Fick's first law of diffusion is applied, K_p is constant over the range of concentration. Therefore, in order to characterize the quantity absorbed (M), some risk assessors have to be integrated over K_p by multiplying the chemical concentration (C) (i.e. the flux: $J = K_p \times C$), the exposed surface (S) and the exposure time (t):

$$dM = J \times S \times dt = Kp \times C \times S \times dt \qquad (2.10)$$

From Equation (2.9), the amount of absorbed mass increases with increasing permeability when the area and diffusion time are assumed to be constant. Hence, the quantities absorbed is directly dependent on $e^{\frac{-1}{T}}$.

However, in this study, the FE model is only a two dimensional model. Also the time-lag should be considered. Therefore, the new equation derived from Equation (2.9) is the following.

$$\frac{dM}{dS} = J \times (t - t_L) \qquad (2.11)$$

When active time is bigger than time-lag (t_L), Equation (2.10) can be used for prediction of permeation mass. This is because, after t_L, the diffusion process is going to be steady-state.

CHAPTER 3

RESULTS AND DISCUSSION

3.1 Maximum Flux and Lag Time

In steady-state, the maximum flux, J_{max}, should be first considered. FE results compared with analytical results for flux (Equation (2.4)) and for time lag (Equation (2.6)) are presented in Table 3.1. After lag time t_L, the diffusion system reaches steady state at the same location. For estimating the lag time across ten layers in the FE model, Equation (2.9) is used to plot the mass accumulation curve; and also, the ending time of diffusion process is 4000s (Figure 3.1) because analytical results of time-lag of lidocaine is 2028s. Hence, the processing time of Tetracaine is 500s (Figure 3.2) because analytical lag time is 280s.

Table 3.1 Analytical and FE Results (Flux and Lag Time)

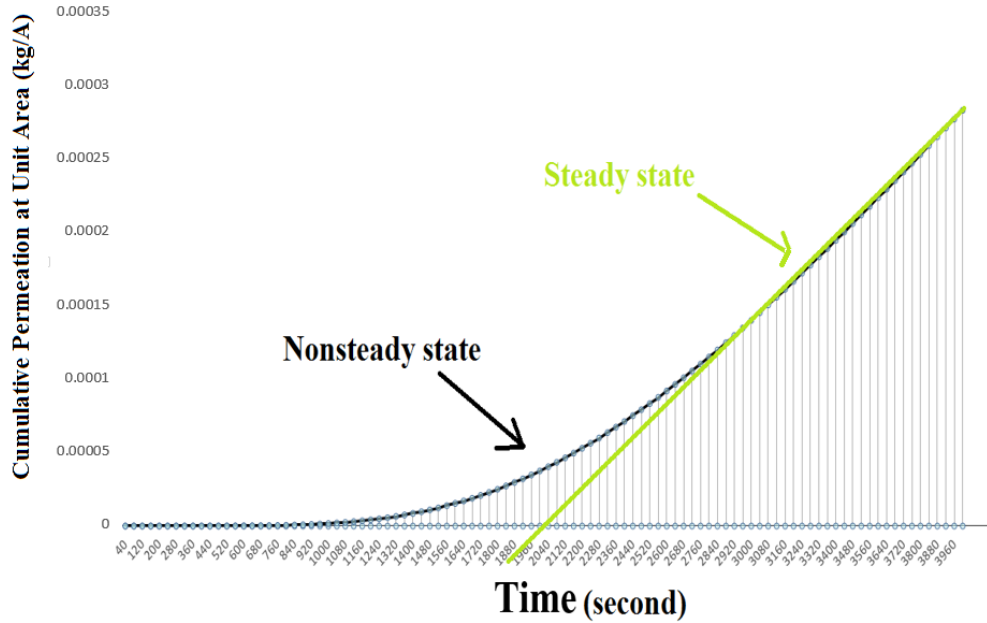|	**Analytical results**	**FE results**
Lidocaine		
SS Flux (kg/m^2 s)	0.581E-6	0.560E-6
Time lag (s)	2028	2020
Tetracaine		
SS Flux (kg/m^2 s)	4.214E-6	4.07 E-6
Time lag (s)	280	272.5

Figure 3.1 shows that the cumulative permeation curve of Lidocaine per unit area has two portions. The initial portion of the curve represents non-steady state diffusion, and linear portion corresponds to steady state diffusion. Therefore, if extending steady state line intersects with time axis, the lag time will be gained. The intersection point is between 2040s and 2000s.
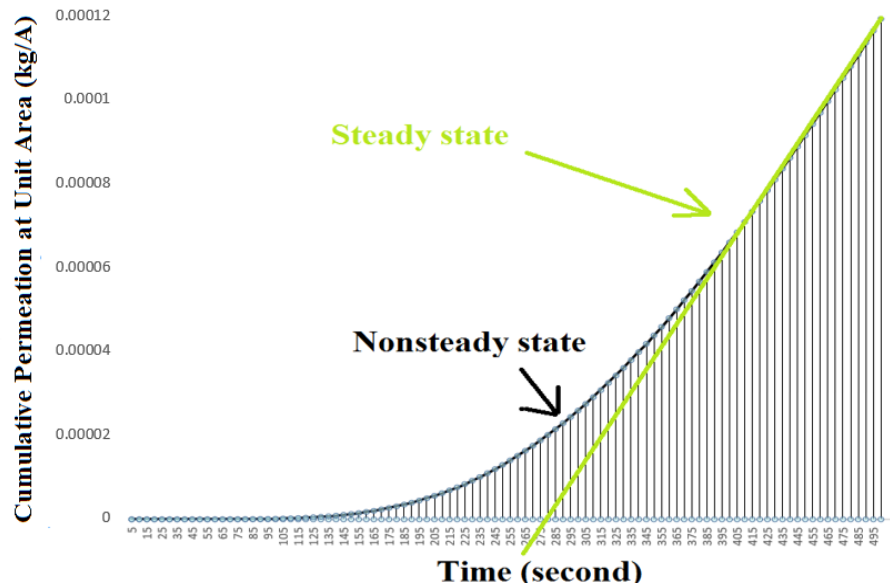

Figure 3.2 shows cumulative permeation curve of Tetracaine. This curve also has two portions, similar to the results for Lidocaine. Extending steady state line intersects with time axis to gain the intersection point which is between 275s and 280s. Hence, the FE result of lag time when Teracaine passes through ten layer-model is 272.5s.

3.2 Concentration Distribution

The concentration distribution in the lipid layers of the 10 layers stratum corneum model is depicted in Figure 3.3 at 1800s. The concentration of Lidocaine (Figure 3.3 (A)) in the bottom of the model is not steady state because diffusion time is smaller than lag time ($t_L=$ 2028s). However, Tetracaine (Figure 3.3(B)) is a good approximation for the steady state. A path was created at location 101 μm with the lipid diffusion pathway and the concentration distribution across the SC is shown in Figure 3.4.

A

.112408   15.643   31.1736   46.7041   62.2347
   7.8777   23.4083   38.9388   54.4694   70

B

27.0641   36.6054   46.1467   55.688   65.2293
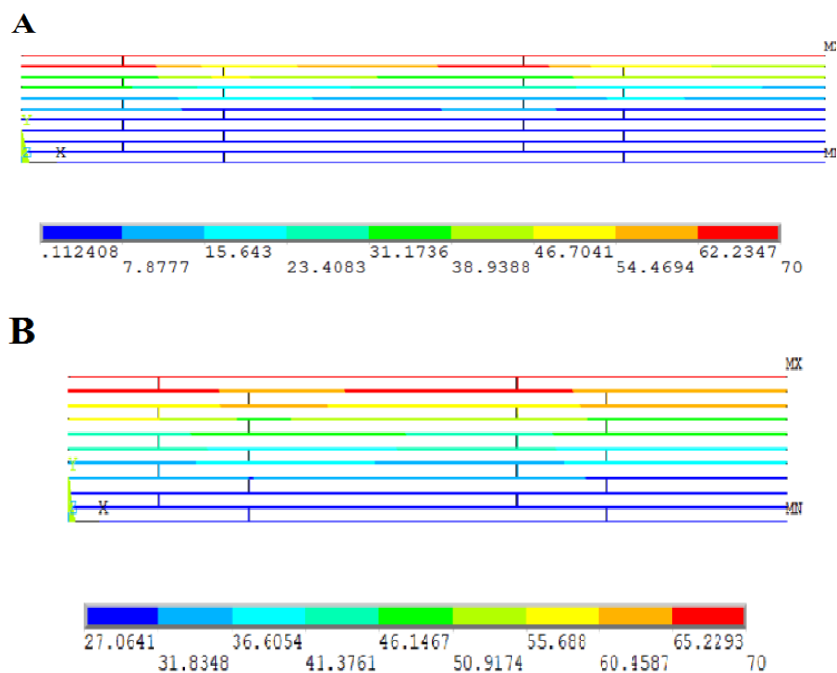   31.8348   41.3761   50.9174   60.4587   70

Figure 3.3 shows the contour plots of concentration distribution. (A) Contour plot of concentration distribution of Lidocaine. Color signifies concentration ranging from 0.1124 (blue) to 70 (red). Based on the differences between adjacent colors, the range of color (blue) is non-steady state. (B) Contour plot of concentration distribution of Tetracaine. Color signifies concentration ranging from 27.06 (blue) to 70 (red). Based on the differences between adjacent colors, diffusion of Tetracaine is a good approximation for steady state.
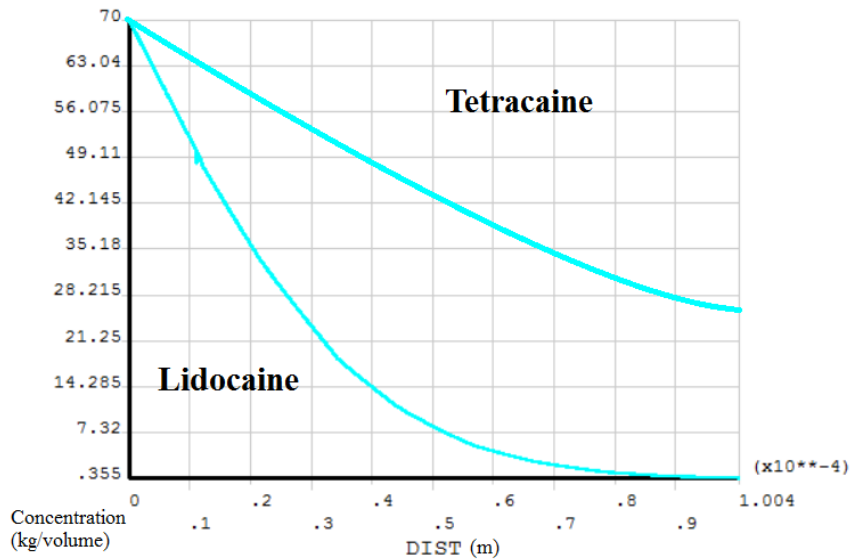
Figure 3.4 shows the concentration distribution along with the lipid pathway. The length of lipid pathway is 101 μm at ten layers FE model. After 1800s diffusion, concentration distribution of Tetracaine decreases with increasing distance and is almost a straight line. However, after 1800s, the concentration distribution of Lidocaine does not reach steady state.

3.3 Absorbed Mass

The SYNERA heating component generates a mild warming that is intended to increase the skin temperature from 37 ℃ to 40 ℃ so as to enhance the diffusion of the local anesthetic agents. However, the permeability is calculated by Equation (1.1), which is apparent permeability of diffusants at room temperature (25 ℃). Therefore, the permeability changes with temperature should be considered.

Clinical results show that 1.7 gram Lidocaine and 1.6 gram Tetracaine are absorbed by the skin after 30min (1800s) [**Highlights of Prescribing Information**]. In the FE model, the distance of diffusion pathway can be ignored. This is because the diffusion

depth will not be considered and the author is only interested in the number of molecules absorbed by the skin. Therefore, the time-lag can also be ignored. Equation (2.9) can be directly used for analytical results (shown in Table 3.2). The FE results are plotted in Figure 3.5 and Figure 3.6.

Table 3.2 Absorbed Mass per Unit Area

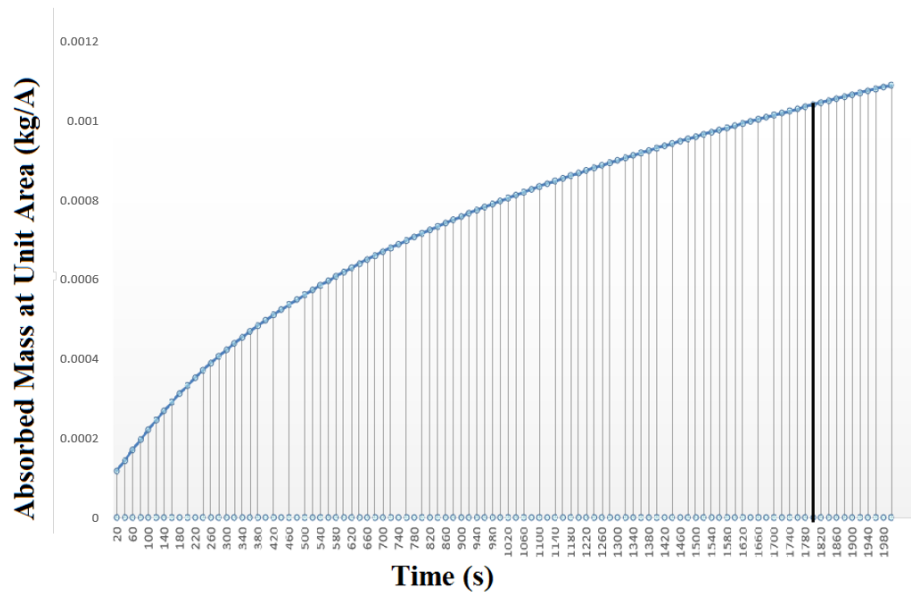|		Absorbed mass per unit area (kg/m^2)
Lidocaine	Analytical results	1.0458E-3
	FE results	1.14E-3
Tetracaine	Analytical results	7.578E-3
	FE results	6.52E-3

Figure 3.5 shows the curve of absorbed mass of Lidocaine per unit area. The slope of this curve decreases with time since the concentration gradient decreases with processing time. The black line corresponds to 1.14E-3 kg/m^2 of Lidocaine going into skin after 30 min.
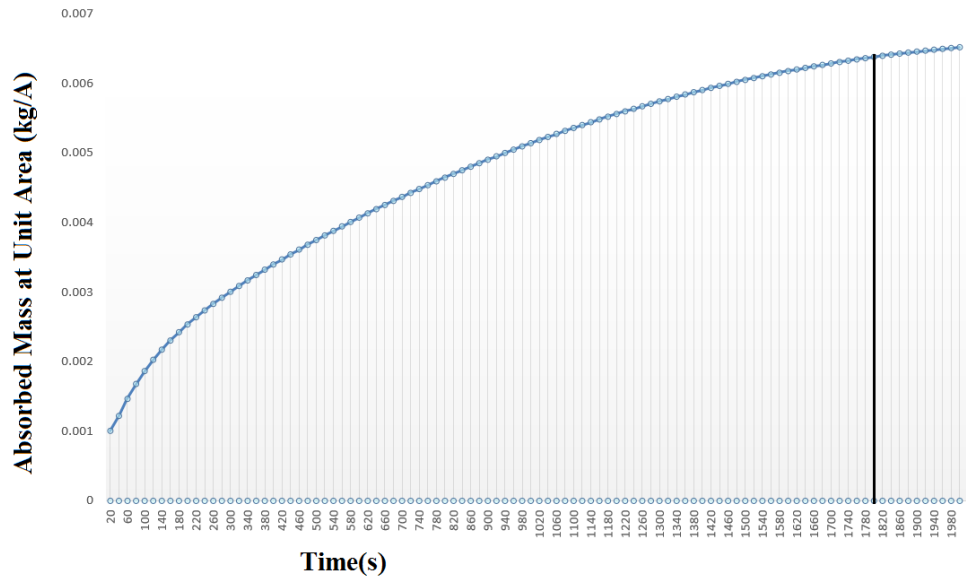
Figure 3.6 shows the curve of mass absorbed of Tetracaine per unit area. The slope of this curve decreases with time since the concentration gradient decreases with processing time. The black line shows 7.578kg/m^2 Tetracaine going into the skin after 30 min.

In this study, the effects of temperature are not considered since thermal analysis has been replaced by mass diffusion analysis. However, based on the results in Table 3.2, the absorbed mass of Lidocaine for 10cm^2, similar to the size of Synera drug, is 1.14mg which is smaller than 1.7mg. This is because the extra temperature from heating layer of the Synera patch increases the mobility of Lidocaine particles so as to increase the penetration rate of Lidocaine. However, the 7.578mg Tetracaine is absorbed by the skin, which is much bigger than clinical experiments. This may be because there is a layer between the skin and the drug reservoir for limiting the release of Tetracaine.

CHAPTER 4

CONCLUSIONS

The objective of this thesis was to build a transdermal finite element model which can estimate results of transdermal diffusion experiments. Since the common transdermal experiments needs long time to prepare, by mimicking the brick and mortar structure, a successful simulation of the stratum corneum lipid pathway accomplished the objective. FE model was used in mechanics and heat flow analysis. A method to use a commercial FE package (ANSYS) to solve a real transdermal diffusion problem is presented here. The method has been validated by comparing FE model results with results for real local transdermal patches for which analytical solutions exist. Although scientists believe that percutaneous penetration of polar and ionized compounds occurs not only through the lipid pathway route (intercellular) but also via a transcellular route that is through the corneocytes [25], the intercellular route is the main pathway for high lipophilic molecules. The permeability of the intercellular route can be easily calculated by Potts & Guy equation (Equation (1.1)) without experimental data, which correlates the skin permeability to solute molecular weight and octanol-water partition coefficient. However, the main disadvantage of using Potts & Guy equation is that the relationship between permeability and temperature (Equation (2.8)) cannot be represented by FE model. This is because in this study, parameters of the thermal transfer were replaced by mass diffusion parameters (Table

2.2). The stratum corneum model described here are two dimensional (2-D). Using three dimensional (3-D) will be a more realistic approach to represent the stratum corneum structure. Advantages of three dimensional model over two dimensional model are unknown. This is because although 3-D model uses more elements to increase realism, it always repeats same geometric structures of 2-D model. Wang [26] already compared 2-D and 3-D SC model topology. The same tortuosities of two models was found so that Wang argues that 2-D representation of the stratum corneum is adequate for the purpose of transdermal diffusion modeling.

For accuracy and realism, the use of a biological image is the best option to generate the SC topology, especially to observe the concentration distribution in any location and any time [27]. But in this study, good approximate flux and time lag results were estimated by a regular brick and mortar geometry. Therefore, regular brick and mortar geometry can be used instead of the more complicated but realistic irregular geometry.

For reducing computational time of 2-D stratum corneum model, different element types were used for different results. The element link 33 was used to replace element plane 55 for concentration distribution contour-plot. This is because using element link 33 can remarkably decrease the amount of elements. But link element can be calculated for flux.

The next step in this work is to utilize experimental results, time lags and permeability, to evaluate FE results with various sets of diffusivity. The transcellular route should be considered in situations when FE model deals with hydrophilic compounds.

REFERENCES

1. Prausnitz, M.R., Langer, R., Transdermal drug delivery, 26(11), 1261–1268, 2008.

2. Fang, W., Ma, X., Song, L., Summary on Application of Traditional Chinese Medicated Bath in the Treatment of Dermatosis (http://dx.doi.org/10.14725/gapr.v2n1a828) Published on Aug 30, 2015. Retrieved on December 7, 2015.

3. Hadgraft, J. and Guy, RH., Transdermal Drug Delivery, 2nd ed. New York: Marcel Dekker; 2003.

4. Williams, A., Transdermal and Topical Drug Delivery, Pharmaceutical Press, London, UK, 2003.

5. Scheindlin, S., Transdermal drug delivery: past, present, future. 4(6), 308–312, 2004.

6. (http://drugdelivery.chbe.gatech.edu/Papers/2012/Prausnitz%20Derm%20Book%20Chapter%202012.pdf) Accessed on March 15, 2016.

7. Falcone, R., Jaffe, M., Ravindra, N.M., New screening methodology for selection of polymeric matrices for transdermal drug delivery devices, Bioinspired, Biomimetic and Nanobiomaterials, Volume 2 Issue BBN2, p. 65-75, 2013.

8. James, W., Berger, T., Elston, D., Andrews' Diseases of the Skin: Clinical Dermatology (10th ed.), Saunders, p. 2-3, ISBN 0-7216-2921-0, 2005.

9. Marks, J.G. and Miller, J., Lookingbill and Marks' Principles of Dermatology (4th ed.), Elsevier, p. 1–7. ISBN 1-4160-3185-5, 2006.

10. Henry, H., Devin, V.M., Mark, G.A. and Mark, R.P., Microfibricated Microneedles: A Novel Approach to Transdermal Drug Delivery, Journal of Pharmaceutical Sciences, Vol. 87, No. 8, August 1998.

11. Lee, S.H., Jeong, SK., Ahn, S.K., An Update of the Defensive Barrier Function of Skin, Journal of Yonsei Medical, Vol. 47, No.3, pp. 293-306, 2006.

REFERENCES
(Continued)

12. Wei, Z., Yonghua, W., Aiping, L., Ge Z., Systems Pharmacology in Small Molecular Drug Discover, International Journal of Molecular Sciences, 17, p.246; doi:10.3390/ijms17020246, 2016.

13. Alan, B., Ursula, G.R., Pierre, K., Panos, M., Olavi, P., In silico prediction of ADME and pharmacokinetics, European Journal of Pharmaceutical Sciences, 17, pp. 183-193, 2002.

14. Mithun, B., Tamizharasi, S., Mechanisms, Kinetics and Mathematical Modelling of Transdermal Permeation-An Updated Review, International Journal Research and Development in Pharmacy and Life Science, Vol. 2, No. 6, pp. 636-641, ISSN: 2278-0238, 2013.

15. Fick, A., On liquid diffusion, Repinted in Journal of Membrane Science, Vol. 100, pp. 33-38, 1995.

16. Crank, J., The mathematics of diffusion (2nd Ed.). 2-12, 46-47, 1975.

17. Fick, A., Annals of Physics, 59, 170, 1855.

18. Cohen, M. H., Turnbull, D., Molecular transport in liquids and glasses. Journal of Chemical Physics, 31, 1164, 1959.

19. Vrentas, J. S., Duda, J. L., Hou, A. C., Evaluation of theories for diffusion in polymer–solvent systems, Journal of Applied Polymer Science, 23, 2469, 1985

20. Bodor, N., Buchwald, P., Drug Design and Targeting (secondary), John Wiley & Sons, Inc. ISBN 978-1-118-40776-9, 2012

21. Güngör, S., Begoña Delgado-Charro, M., Masini-Etévé Valérie, Potts, R.O., Guy, R.H., Transdermal flux predictions for selected selective oestrogen receptor modulators (SERMs): Comparison with experimental results, Journal of Controlled Release, 172, 601-606, 2013

REFERENCES
(Continued)

22. Cleek, R.L., Bunge A.L., A New Method for Estimating Dermal Absorption from Chemical Exposure, Pharm. Res., Vol. 10, No. 4, pp. 497-506, 1993.

23. Kulkarni, U.P., Mahalingam, R., Li, X., Pather, I., Jasti, B., Effect of Experimental Temperature on the Permeation of Model Diffusants Across Pocine Buccal Mucosa, AAPS PharmSciTech, Vol. 12, No. 2, DOI: 10.1208/s12249-011-9624-z, 2011.

24. Chevillotte, G., Ficheux, A.S., Ramirez-Martinez, A., Roudot, A.C., A new approach to characterize dermal systemic exposure by use of chemicals' permeability coefficient in finite dose- Application to ingredients of nail polish by skin and nail exposure routes, International Journal of Engineering Research & Science, Vol. 9, Issue. 9, December 2015.

25. Sznitowska, M., Janicki, S., Williams, A.C., Intracellular or intercellular localization of the polar pathway of penetration across stratum corneum. *J. Pharm. Sci.* 87–9:1109–1114, 1998.

26. Wang, T., Microscopic models for the structure and permeability of the stratum corneum barrier layer of skin. Ph.D. thesis, University at Buffalo, State University of New York, 2003.

27. Barbero, A. M., Frasch, H.F., Modeling of Diffusion with Partitioning in Stratum Corneum Using a Finite Element Modal, Annals of Biomedical Engineering, Vol. 33, No. 9, pp. 1281-1292, September 2005.