SIMULATION OF TRANSDERMAL DRUG DELIVERY SYSTEM FOR BREAST CANCER THERAPY USING COMSOL

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A thesis submitted in fulfillment
of the requirements for the award of the degree of
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SUPERVISOR'S DECLARATION

"I hereby declare that I have read this thesis and in my opinion, this thesis is adequate in terms of scope and quality for the award of the degree of Bachelor of Chemical Engineering (Biotechnology)"

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I hereby declare that the work in this thesis entitled "Simulation of Transdermal Drug Delivery System for Breast Cancer Therapy Using COMSOL" is my own except for quotations and summaries which have been duly acknowledged. The thesis has not been accepted for any degree and is not concurrently submitted for award of other degree.

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To my family and friends who are always there for me, through thick and thin.

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ABSTRACT

The objective of this paper is to study the effectiveness if the new method of breast cancer therapy, which is the application transdermal patch for the drug delivery system through the largest organ of human body, the skin. This study was done by simulating the process of drug diffusion using multiphysics software, COMSOL. For this study, we are using two types of drugs which have different physical and chemical properties as the subject, which is Paclitaxel and Doxorubicin. The simulation are done by obtaining the information such as the molecular weight and specific diffusivity of drugs through breast tissue until it reaches the targeted cancerous area. The simulation is computed using multiphysics software- COMSOL, to see how fast the drugs will be delivered to the targeted cancer cell. The effectiveness of this method of therapy by is studied by manipulating the properties of the type of drugs, the diffusivity of the drugs and the volume of the breast modeling. All of these parameters are manipulated by designing mathematical models governed by Fick's Law of diffusion. The differences of the concentration of drug on specific depth of breast tissue are shown by a color spectrum after the simulation was done. The application of transdermal patch in breast cancer therapy is the new type of drugs delivery system which lately has been the subjects of numerous researches, as it has been proven to be more advantageous than normal chemotherapy. The dosage of drug needs to be taken by the patients can be reduced significantly as this system is more topical and it is very specific, as the drugs applied to the skin will be absorbed and straightly attack the targeted cancer cell. Compared to normal chemotherapy, the drug pathway does not go through the vascular system or bloodstream, and it can reduce the side effects brought about by the strong drugs to the body of the patients. By doing this study, further development of this new type of breast cancer therapy can be done, so it can be creates more understanding and optimized as the primary type of breast cancer therapy.

ABSTRAK

Objektif utama kajian ini adalah untuk mengkaji keberkesanan cara terapi baru untuk pesakit barah payudara, iaitu dengan menggunakan pelekat transderma sebagai ejen penghantaran dadah melalui organ terbesar pada tubuh manusia, iaitu kulit. Kajian ini dijalankan dengan mensimulasikan proses resapan dadah dengan mengunakan perisian multi fizik, iaitu COMSOL. Kajian ini akan bertumpu kepada dua jenis dadah yang digunakan untuk terapi barah payudara, dengan sifiat kimia dan fizikal yang berbeza antara satu sama lain, iaitu Doxorubicin dan Paclitaxel. Bagi menjalankan simulasi ini, sifat fizikal yang penting untuk dadah tersebut, iaitu jisim molekular relatif dan juga kadar resapan dadah melalui tisu payudara ke kawasan kanser diperolehi dari dari kajian terdahulu. Simulasi yang dijalankan menggunakan perisian COMSOL ini adalah untuk mengkaji masa yang diambil oleh sesuatu dadah untuk tiba ke kawasan sel kanser. Kadar keberkesanan cara terapi ini dikaji dengan memanipulasikan ciri-ciri seprti jenis dadah yang digunakan, kadar resapan dadah serta isipadu model payudara. Ciri-ciri ini akan dimanipulasikan dengan merekabentuk model matematik berdasarkan *Fick's Law of Diffusion.* Kadar kepekatan dadah yang terdapat pada kedalaman spesifik didalam tisu payudara pada satu-satu masa akan diwakili oleh spektrum warna yang berbeza setelah melalui simulasi ini. Penggunaan pelekat transderma sebagai satu medium penghantaran dadah yang baru untuk terapi barah payudara akhir-akhir ini telah menjadi topik utama dalam kajian-kajian saintifik, kerana keupayaan dan keberkesanannya berbanding rawatan kemoterapi biasa. Dos ubat yang perlu diambil oleh pesakit-pesakit barah dapat dikurangkan, kerana sistem ini lebih bertumpu kepada kawasan kanser dan amat spesifik, kerana dadah yang dihantar menerusi kulit akan terus menuju ke kawasan yang telah dikenalpasti. Berbanding dengan rawatan kemoterapi, dadah itu tidak akan melalaui sistem vaskular mahupun sistem peredaran darah, dan akan mengurangkan kesan sampingan dadah tersebut kepada tubuh pesakit. Diharap dengan kajian ini, kajian bekenaan tentang sistem rawatan baru ini dapat diteruskan, agar ia lebih difahami dan dapat dioptimumkan keberkesanannya di masa akan datang.

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LIST OF SYMBOLS/ABBREVIATIONS

C	Concentration
cm	Centimetre
D	Diffusion constant (specific diffusivity)
Da	Dalton
d	Delta
g	Gram
h	height
mm	Millimetre
mol	Mole
r	Radius
s	Second
t	Time
µm	Micrometer
z	Z-axis
π	Pi
%	Percentage
>	More than/ followed by
AIs	Aromatase inhibitors
ALND	Axillary lymph node dissection
ER	Estrogen receptor
ER+	Estrogen receptor positive
IBIS	International Breast Cancer Intervention Study
PgR+	Progesteron receptor positive
SERMs	Selective estrogen receptor modulators
SLND	Sentinel lymph node dissection
USFDA	United States Food and Drugs Administration

CHAPTER 1

INTRODUCTION

This chapter will provide the brief overview of breast cancer, the conventional therapy of breast cancer, and also the application of transdermal patch as the method of breast cancer therapy. This chapter will also go through the background of the study, the statement of problem for this research, objectives that want to be achieved from this study, the scope of study and also the rational and significances of this study to the scientific and commercial development.

1.1 Background of study

Breast cancer is one of the leading causes of death among women in the world. From the research done by The National Cancer Institute of United States of America, by the age of 50 years old, 1 out of 5 women will develop breast cancer. In Malaysia, the number of women affected by this disease increases from time to time. Although this disease is very dangerous, it is actually a highly treatable if it is detected in the early stage of the cancer.

There are numerous ways that has been developed in order to treat the breast cancer patients, and some of the treatment are surgical treatment, therapy of very strong drugs, or is known as chemotherapy, and also hormonal therapy. The most drastic treatment for breast cancer is through mastectomy, or breast surgery. This approach is considered as the most efficient as it directly discard the tumor, but risk of the cancer to

return is still present and the procedure could leave physical trauma and effect to the patient.

The most widely used method of therapy for breast cancer is using strong drug or chemotherapy. Traditionally, this method is done either by using shot injection, or by using oral drugs. The newest development in chemotherapy is application of transdermal patch, which is an adhesive patch containing the drugs that are applied to the skin, near the targeted breast cancer cell. The drugs will be absorbed by the skin, through the layers of breast tissue, until it reaches the specific region where the cancer cells lies. This study will simulate the effectiveness of different type of drugs used on the transdermal patch to the breast cancer by analyzing its concentration on different depth of breast for a specific time.

1.2 Problem Statement

The efficiency of the used of transdermal patch on the skin for breast cancer treatment rely upon the diffusivity of the drugs through layer of breast tissue, and also the chemical and physical properties of the drugs. The transportation of drugs through the skin is more effective than when it is taken orally or through injection, as the action is more topical and site specific. This study will focus on the use of two different types of drugs, which are Doxorubicin and Paclitaxel. These two drugs have different molecular weight and standard diffusivity, and this study will simulate the diffusion of these drugs in order to analyze its effectiveness. The drug diffusivity factors will also be examined in the simulation, where the drugs diffusivity will be manipulated to obtain the most effective drug diffusivity. Furthermore, the relationship between the breast volume and the efficiency of the treatment is studied. In order to analyze the effectiveness of the drug diffusion, we will simulates the diffusion process using, a multiphysics software, called COMSOL.

1.3 Research Objectives

The main aim of this study is investigating the effectiveness of different type of drugs used on the transdermal patch to the targeted cancer cell. We also want to see how different type parameter affected this type of treatment. This can be achieved by fulfilling these objectives:

1. To compare the effect of diffusivity of different type of drug used on the transdermal patch to the targeted cancer cell.
2. To investigate the effect of the specific drug diffusivity to the efficiency of transdermal drug delivery system.
3. To investigate the relationship between the breast volume and the concentration of drugs on the tissue

1.4 Scope of Studies

This study will focus on the effect of the diffusivity of two different kinds of drugs- Doxorubicin and Paclitaxel- and their efficiency on the treatment of breast cancer. The other parameter that we want to investigate in this study is the effectiveness of the usage of transdermal patch analyzing the specific diffusivity of the drugs used, in order to obtain the most efficient drugs diffusivity. The different breast model with different volume will also be designed in order to obtain the relationship between the breast volume and the efficiency of the treatment. To start this study, we will first obtain the data of the respective drugs, which are the specific diffusivity and the molecular weight of the drugs. The size of the breast will also be calculated to determine the placement of the patch on the breast and also to determine the volume of the breast. When all of this data was obtained, the mathematical model of the simulation will be constructed, and the simulation was run using multi-physics software- COMSOL. By using this software, the graph of the concentration of drugs through the breast on specific time will be obtained and analyzed.

1.5 Rational and Significance of Studies

The rational of this study is provide additional insight to the treatment of breast cancer using transdermal patch as it is still considered a new development in healthcare. This method has been proven to be advantageous, comparing to the traditional chemotherapy method. This technology has been proven safer to the body because it did not affect the other tissue of the body aside from the targeted cancer cell, compared to oral drugs or shot injection, as it diffuse through the skin and did not go through the vascular system. The better understanding of transdermal patch can optimize the concentration of the drugs used and the efficiency of the patch itself. This optimization can decrease the dosage of drugs for cancer treatment, thus reducing the cost of the treatment and making it more affordable.

CHAPTER 2

LITERATURE REVIEW

This chapter will cover about the overview of the statistics of the global and local breast cancer cases, the conventional treatment of breast cancer which includes physical surgery, the chemotherapy using strong drugs and hormonal therapy, and also the general principal of the application of transdermal patch for breast cancer therapy.

2.1 Overview of Breast Cancer Cases

Cancer has become one of most prominent cause of death to globally, especially in the developed nation. The main reason on why cancer continues to develop such a dangerous reputation as the big killer is because of the aging and growth of the world population alongside an increasing adoption of cancer-causing behaviors, particularly smoking, in economically developing countries.

Based on the GLOBOCAN 2008 estimates, about 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in 2008; of these, 56% of the cases and 64% of the deaths occurred in the economically developing world. Based on these data, it was also found that the leading cancer that affects women in the world is breast cancer.

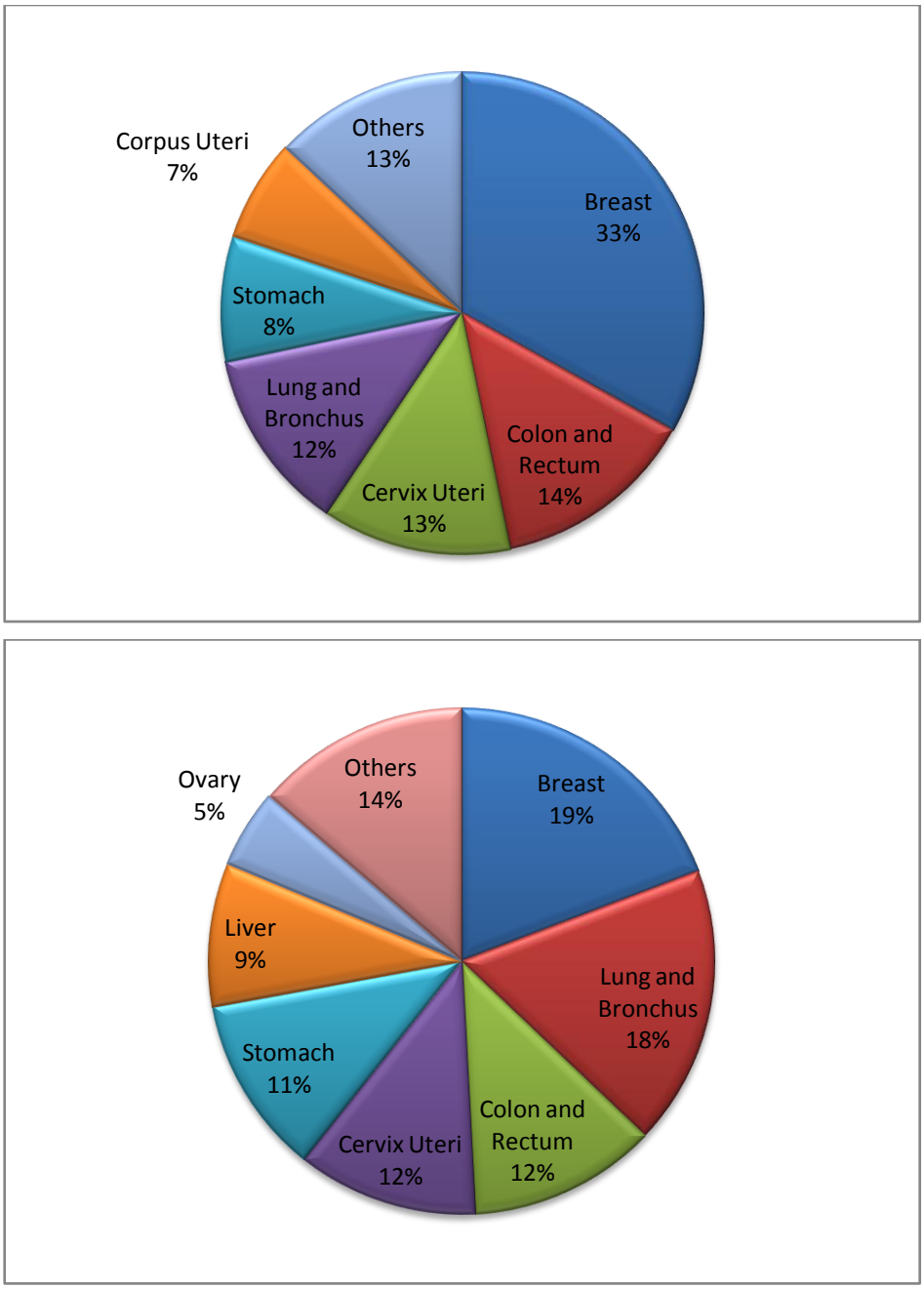


Figure 2.1: Distribution of cancer among women globally (top) and locally (bottom)

Source: National Cancer Registry (2008)

Nearly 70,000 new cancer cases were diagnosed among Malaysians in Peninsular Malaysia between 2003 and 2005, according to a report released in early

2008 on the incidence of the disease in West Malaysia. The Cancer Incidence in Peninsular Malaysia 2003-2005 report, published by the National Cancer Registry (NCR), states that the total 67,792 new cases were diagnosed among 29,596 males (43.7 per cent) and 38,196 females (56.3 per cent). The annual crude rate for males was 100.2 per cent per 100,000 population, and 132.1 per cent per 100,000 for females. The most frequent cancer Malaysians was breast cancer (18 per cent) followed by large bowel cancer (11.9 per cent) and lung cancer (7.4 per cent).

There were 3825 cases reported and 1707 death from breast cancer in Malaysia (Globocan, 2000). They estimated that among 100,000 populations, the crude rate of breast cancer in Malaysia is 34.9 with Age Standardised rate of 41.9 per 100,000. From 2003-2005, breast cancer formed 31.1% of newly diagnosed cancer cases in women, up 1.1% from 2002.

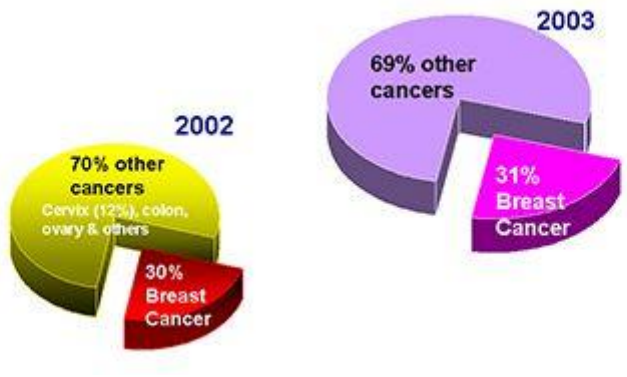


Figure 2.2: Percentage of breast cancer in Malaysia 2002-2003

Source: College of Radiology Breast Health Information Centre (2008)

Breast cancer is not a topical disease that can only affect certain population, the fact that it can kill anyone is very worrying. The National Cancer Institute of America estimated that by the age of 50, one out of 50 women is affected by breast cancer. This number will rise to ten when they reach 80 years old. Over the years from 1993 to 2003, there were a total of 1818 breast cancer patients in the University Hospital. The number of breast cancer patients increased annually, with the highest recorded in 2003. This was 6 times the number of breast cancer patients in 1993.

2.2 Conventional breast cancer treatment

The development in breast cancer treatment has brought about several ways in order to treat this disease. Some of the method that has been used to treat breast cancer is through breast surgery, chemotherapy of strong drugs, and also hormonal therapy.

2.2.1 Breast surgery

Surgery treatment for breast cancer can be divided into two - mastectomy and breast conserving surgery. Mastectomy is the method where the breast structure will be removed in order to remove the cancer cells. For breast conserving technology, it requires more advanced technology, where the cancer cell will be removed using sentinel node biopsy, complimented with radiation. This method allowed women with different form of breast cancer to conserve their breast (Apantaku, 2002).

Study shows that survival rate after breast conserving technology complimented with radiation are equal to the survival rate after mastectomy for stage 1 and 2 breast cancer (Winchester, 1998). Although both method of surgery has been proven to be reliable for cancer patients, mastectomy remains the most common treatment for women with invasive tumor or treatment for early stage of cancer (Morrow et. al., 2001).

The type of surgery that is suitable for the patient depends on the size of the cancer in the breast, whether it has spread to any other part of the body, the size of the breasts and personal wish (CancerHelp UK). According to Opatt et. al., due to lack of knowledge about the option, the patients are not aware with the choices that they have, and still choosing the widely known mastectomy technique, although there are better choices for them.

From the research done by International Breast Cancer Intervention Study (IBIS) in 2002, the women who are eligible for breast cancer surgery are those with high risk benign lesion, which are:

1. Lobular Neoplasia (lobular carcinoma in-situ)
2. Ductal hiperplasia/ atypical lobular hiperplasia
3. Multiple papillomatosis
4. Some type of proliferative fibrocystic mastophaty
5. Primary breast phylloide tumor and relapses.

Recommended surgical care for invasive breast cancer includes removal of the primary tumor and a level I and II axillary lymph node dissection (ALND). The status of the axillary nodes helps to determine the prognosis and guide treatment decisions. Unfortunately, side effects after ALND are relatively common. Some of the effects of ALND are:

- Upper-extremity
- Lymphedema (6%-49%),
- Arm numbness/tingling (7%-75%)
- Pain (16%-56%),
- Impaired shoulder mobility (4%-45%),
- Arm weakness (19%-35%),
- Infections in the breast, chest, or arm (8%).

(Kakuda *et al*,1999 and Petrek *et al*, 2001)

The side effects of axillary lymph node dissection can range from mild to severe and can be a chronic condition that affects patients' quality of life for years after cancer surgery (Maunsell *et al*, 1993).

Recently, a less invasive procedure, sentinel lymph node dissection (SLND), has been developed to stage the axilla for invasive breast cancer. This technique is performed by using a blue dye and a radioactive tracer injected into the breast tissue. SLNs are removed during the surgical procedure, and the pathology results from these nodes have been found to be highly predictive of metastatic involvement in the axilla (Albertini *et al*, 1996). As a result, SLND has become an acceptable alternative to ALND for patients with clinically negative lymph nodes.

Treatment of cancer using surgery can cause physical alteration and emotional trauma to the patients. Most of the patients that undergo mastectomy will need reconstruction for the breast structure. Because surgery is not a safe method, complex and often does not give satisfactory result, it is difficult to accept it as preventive method for breast cancer (Diaz-Faes, 2003).

2.2.2 Chemotherapy

The most common type of breast cancer therapy, chemotherapy, in its simplest sense, is a therapy by ingestion of strong drugs, either orally or through injection, where the drugs will attack the targeted cancer cells and kill it. The main principal of the growth of invasive tumor depends on angiogenesis, which is the formation of blood vessels that will provide the tumor with nourishment and nutrients (Folkman, 1990). Because of this feature, the chemotherapy was designed so that the drugs can pass through the blood vessels to reach the targeted cell and attacking the tumor.

Most popular chemotherapy agents like taxanes and anthracyclines has distinct anti-angiogenic activity (Miller et. al., 2001), while others such as doxorubicin can inhibit collagenase of the cancer cells, preventing it from dividing and stop the growth (Benbow et. al., 1999). Although this method is widely used and has been proven effective, it can cause severe side effects to the patients. The drugs, which were taken orally or through injection, will be distributed to the entire body affecting other rapidly dividing cells, such as hair follicles, nails, mouth and bone marrow as it do not have the ability to distinguish between normal and tumor cells.

Docetaxel and doxorubicin, two widely used drugs for cancer treatment, cause significant drop of blood cell in patients' bone marrow, increasing their risk of getting an infection (Cancer Health UK, 2009). The drop in red blood cell can cause fatigue and breathlessness, while drop in platelets contributes to bruising. Some drugs, like letrozole, caused the depletion of circulating estrogen, causing the patients to experience hot flashes and suffer from bone damage in a long time (Mom et. al., 2006). Letrozole

which were taken by oral capsule is difficult to be administered the right dosage that suitable for the body (Li et. al., 2010)

2.2.2.1 Docetaxel

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel (anhydrous) is (2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β-20epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate. Docetaxel (anhydrous) has the following structural formula:

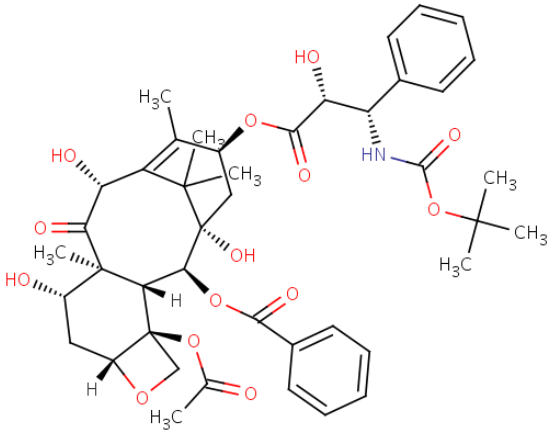


Figure 2.3: Structure of Docetaxel

Source: Drugbank (2005)

Docetaxel kills cells by disrupting the function of microtubules, which are essential for cell survival (Shelley *et al.*,2007). It also inhibits the anti-apoptotic gene Bcl2 and encourages expression of p27, a cell-cycle inhibitor (Van Poppel, 2005), preventing new cells from forming, and causes existing cells to undergo apoptosis and stops other cells from maturing and replicating. As with all cytotoxic agents, the effect of the drug is not specifically aimed at the tumour cells, so 'healthy', normal cells may be affected too, resulting in drug-related side effects.

Docetaxel-containing treatment regimens that is potentially associated with a 20% or greater risk of febrile neutropenia. The incidence of treatment-related mortality associated with docetaxel therapy is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive docetaxel as a single agent at a dose of 100 mg/m². Baker (1999), has also outline some non-haematological toxicity effect to the patients, such as hypersensitivity reaction, fluid retention, nail toxicity and neuropathy effect.

2.2.2.2 Doxorubicin

Doxorubicin is an anthracycline topoisomerase inhibitor isolated from *Streptomyces peucetius* var. *caesius*. Doxorubicin HCl, which is the established name for (8S,10S)– 10- [(3– amino - 2,3,6– trideoxyαL– lyxo- hexopyranosyl) oxy]– 8- glycolyl- 7,8,9,10- tetrahydro- 6,8,11 trihydroxy- 1- methoxy 5,12- naphthacenedione hydrochloride, has the following structure:

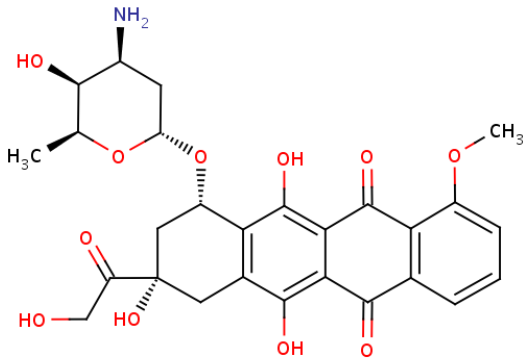


Figure 2.4: Structure of Doxorubicin

Source: Drugbank (2005)

It is a common drugs used in the breast cancer therapy, which work as an anthracycline antibiotic, closely related to the natural product daunomycin, and like all

anthracyclines, it works by intercalating DNA, which inhibits the progression of the enzyme topoisomerase II, that relaxes supercoils in DNA for transcription. Doxorubicin stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby stopping the process of replication. The formula is $C_{27}H_{29}NO_{11}$, and the molecular weight is 543.52 g/mol.

The use of doxorubicin may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m². Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with doxorubicin.

The acute effects are mainly myelo-suppression, nausea, vomiting, weight loss, arrhythmias and decreased survival, whereas the main chronic effect of doxorubicin is severe cardiomyopathy with precipitant congestive heart failure (Olson *et al*, 2007).

2.2.2.3 Herceptin

Herceptin is a humanized IgGl kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Herceptin is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The important chemical data for herceptin is the chemical formula, which is $C_{6470}H_{10012}N_{1726}O_{2013}S_{42,}$ and the molecular weight is 145531.5 g/mol.

Herceptin administration can result in sub clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving herceptin with anthracycline containing chemotherapy regimens. The treatment of breast cancer using

herceptin can also result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of the treatment with herceptin.

2.2.3 Hormonal therapy

Women hormones, oestrogen and progesterone, can trigger the growth of some cancer cells. Oestrogens exert a large variety of responses in target cells, including promotion of tissue differentiation, morphogenesis, mitogenic activity and development of the mammary gland, which us very beneficial to the general function of human body. However, aside from their essential function in female reproduction, it is also responsible in oncogenesis and maintenance of tumor growth (Ameller *et al*). In fact, oestrogens are regulators of a number of proto-oncogenes coding for nuclear proteins. Oestrogens act on cells via interaction with two types of intracellular receptors. Eventually, the recent discovery of ER has greatly enhanced our understanding of oestrogen action.

The used of hormonal therapy in breast cancer treatment are done in order to lower the level of these hormones and/or block their effect. The goal of the therapy is to develop anti-oestrogens, compounds capable of blocking the effects of estradiol (E2) without displaying any oestrogenic activity on their own.

Hormone therapy can be done either before or after the surgery, or to treat relapses, which is breast cancer that comes back after the surgery (CancerHelp UK). Hormonal therapy is considered as one of the better treatment of cancer as it does match chemotherapy in terms of survival and tumor response. In addition, hormonal therapies produce fewer and less severe adverse effects than chemotherapy (Jordan, 2002)

Patients' response to hormonal therapy depends on their hormone receptor status – estrogen receptor positive (ER+) or progesteron receptor positive (PgR+). Higher response to it brought a greater likelihood to response to the treatment (Osborne et. al., 1980). Approximately 50% to 70% of women benefit from hormonal therapy if their

tumors are positive for both ER and PgR, 33% benefit if their tumors are positive for either type of receptor, and only 11% benefit if their tumors are negative for both types.

There are several therapies that have been developed regarding hormonal therapy for breast cancer, which are including the selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), and estrogen receptor (ER) antagonists.

2.2.3.1 Selective Estrogen Receptor Modulators (SERMs)

The first type of hormonal therapy for breast cancer is Selective Estrogen Receptor Modulators (SERMs). The drugs used for this treatment can mimic the action of estrogen in the body, and modulating the estrogen receptor. The most popular drugs that is used in hormonal therapy for breast cancer treatment is Tamoxifen, which is considered the gold standard of the procedure since 1970's. Other drug that has similar function with Tamoxifen is Toremifene.

Some of the adverse effects between Tamoxifen and Toremifene is similar, which are hot flashes, nausea, vomiting and vaginal discharge. Tamoxifen, however, was associated with a higher incidence of thromboembolic events (1.3%- 8.0% vs 0.6%-5.1%), vaginal bleeding (0%-19.8% vs 0.9%-3.7%), and endometrial cancer (0%-1.8% vs 0%) compared with toremifene (Cummings, 2002)

This drug usually recommended to be taken for five years usage, as the used of it longer than five years did not further the benefits, instead it increase dangerous side effects such as blood clots within deep veins (pulmonary embolism), endometrial cancer and stroke.

2.2.3.2 Aromatase Inhibitors (AI)

Aromatase inhibitors stop the production of estrogen in post-menopausal women. Aromatase inhibitors work by blocking the enzyme aromatase, which turns the

hormone androgen into small amounts of estrogen in the body. In postmenopausal women, the primary estrogen source is derived from conversion of androstenedione (produced by the adrenals) to estrone and estradiol in the peripheral tissues. Aromatase inhibitors block the conversion of androstenedione to estrone and testosterone to estradiol, hence lowering the production of estrogen in the body. (Lake and Hudis, 2002)

Aromatase Inhibitor has been developed and widely used since 1995 (Cummings, 2002), but the application of AI in hormonal therapy is only recommended for the patient that has unsuccessful attempt at therapy of SERMs. Anstozole and Letrozole are some of the popular drugs that have been used in AI.

Study show that the treatment using AI has similar effect with the treatment using SERMs, accept for thromboembolic effect. The common side effects of AI are hot flashes, nausea, asthenia, and pain. Study shows that AI also lacks the stimulatory effect to the endometrial compared to SERMs drugs, which makes vaginal bleeding to be less common.

2.2.3.3 Estrogen Receptor Antagonist

The most recent development in hormonal therapy for breast cancer is by using estrogen receptor antagonist without the agonist effect, and the drug- Fulvestrant, is still in the assessment for the treatment of breast cancer (Cummings, 2002), and currently being tested for the patient that has failed the SERMs treatment.

Some of the common side effects of this treatment are gastrointestinal disturbances, hot flashes, nausea, asthenia, headache, and sweating (Curran and Wiseman, 2001). Because fulvestrant is a potent antiestrogen with no estrogenic activity, estrogenic effects on organs such as the endometrium are not expected.

2.3 Transdermal patch application

Transdermal drug delivery system is the system which the delivery of the active ingredients of the drugs occurs by the mean of the largest organ of human body, the skin. This type of drug delivery system has actually been used for a long time, by the application of certain plaster or ointment to the skin (Plotkin, 2005). The first official transdermal patch that is approved by the United States Food and Drugs Administration (USFDA) on December 1979, contain socopolamine, to remedy motion sickness.

In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. Moreover, it over comes various side effects like painful delivery of the drugs and the first pass metabolism of the drug occurred by other means of drug delivery systems.

2.3.1 Components of Transdermal Patch

The design of transdermal patch has been developed on order to increase the efficiency of the treatment for breast cancer therapy. The basic concept of transdermal patch structure is divided into five, which are the liner, drugs, adhesive, membrane and backing.

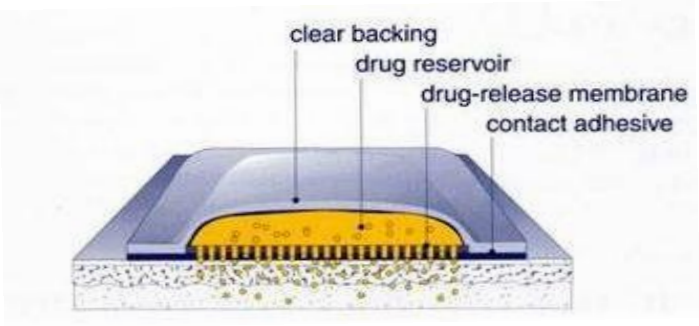


Figure 2.5: Structure of Transdermal Patch

Source: Shreeraj, S. (2008)

The liner is the protective part of the patch, and it is used to protect the drug from being exposed to outside environment. It is removed prior to the usage of the drugs. The drug is the medicine that wants to be used for treatment, and this drug is in direct contact with the liner. Adhesive is the component used to adhere the patch onto the skin, so that the patch will not move from the targeted spot. Membrane is the structure that controls the release of the drugs onto the tissue. Sometimes, for rapid release of drug, this membrane was equipped with micro needles that will puncture through the skin layer. Backing is the structure that enclosed the whole patch.

2.3.2 Type of Transdermal Patch

In the market nowadays, there is several type of transdermal patch that has been developed. The applications of different type of transdermal patch are depends on the type of the drugs and also type of disease or ailments that the drug is used for. Five type of transdermal patch are:

- Single Layer Drug-in-Adhesive
- Multi Layer Drug-in-Adhesive
- Reservoir
- Matrix
- Vapor patch

For Single-layer Drug-in-Adhesive, the adhesive layer of this system is containing the drugs. This is because the adhesive layer is not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

The multi-layer drug-in adhesive patch is similar to the single-layer system regarding the function of the adhesive layers are. The different of multi layer patch is that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not

in all cases). This patch also has a temporary liner-layer and a permanent backing for additional support.

The reservoir type transdermal patch is quite different, compared the Single-layer and Multi-layer Drug-in-adhesive. In this transdermal system, the drug layer was separated from the adhesive layer altogether. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer.

The adhesive layer for the transdermal patch with matrix system will surrounds the drug layer of the patch. Meanwhile, the drugs will be contained in a matrix like system, which composed of semisolid material where the drug will reside. It will be partially surrounded by the adhesive layer.

The vapour patch is similar to single layer and multiple layer drug-in-adhesive, where the drugs is contained in the adhesive layer, but instead of releasing the drugs, it will release it as vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. This type of patch was used mainly to for indigestion. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Nicotine patch, the patch that helps to reduce the quantity of cigarettes that one smokes in a month are also available on the market.

2.3.3 Mechanism of Transdermal Drug Delivery

The mechanism of drug delivery for transdermal patch is actually very simple, where the drugs will be targeted straight to the vascular system of the patient. When the patch is applied on the skin, the medication that is released from the reservoir will permeate through the skin barrier. The rate of diffusion of the drugs will be regulated by the membrane. After the drugs have penetrates though the epidermal and dermal, it will be taken by the blood vessels, where the drugs will be transported to the target area.

Through a diffusion process, the drug enters in the blood stream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time (Pankaj *et al*, 2011).

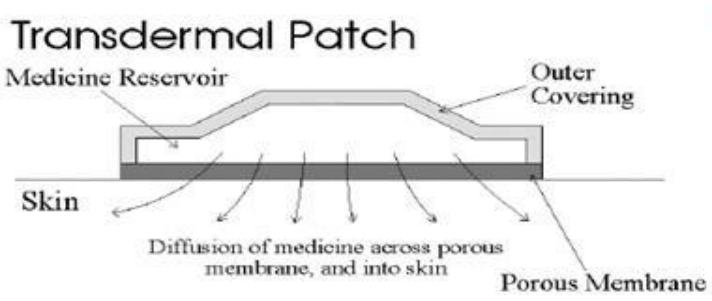


Figure 2.6: Basic principal of transdermal drug delivery system

Source: Shreeraj. S. (2008)

The main principal of transdermal drug delivery system is it will provide the mean of topical drug delivery system to human body through the largest organ of human body, which is the skin. Hence, there is a need to consider the structure of the skin before the mechanism of drug delivery can be applied.

2.3.4 Skin Barrier

Skin is the largest organ system in human body. The structure of the skin itself is composed of several components, which can be seen in this figure:

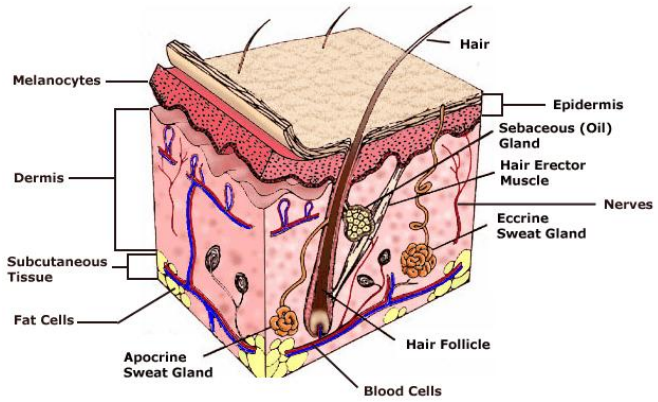


Figure 2.7: 3D structure of human skin

Source: Drug Development Services (2009)

Skin is made up of several 2 main layer, which are the outer, thin layer of epidermis and thick layer of dermis. In dermis, it contains several structures that are essential for the built of the skin, which includes glands, hair follicles, muscle and receptors. The blood vessels, which is the transport system of the drugs also resides here. For the drugs to arrive at the blood vessels, it needs to penetrate through the layer of epidermis.

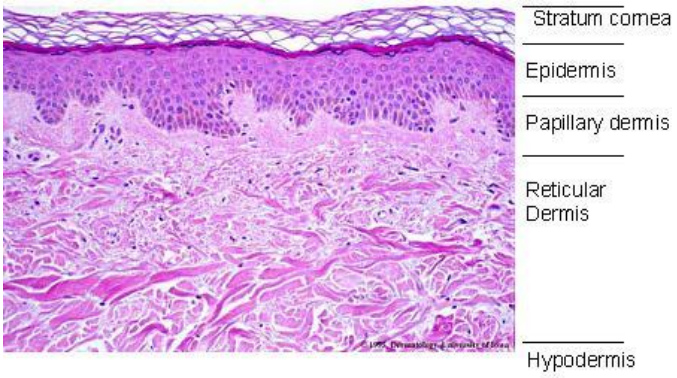


Figure 2.8: Cross section of human skin

Source: Drug Development Services (2009)

The epidermis layer of the skin is comprised of 100-150 µm layers, and it forms the protective boundary of skin. The stratum cornea is non-elastic, keratin cells that are surrounded by lipid rich-extracellular matrix (Mark *et al*, 2004) with thickness around 10-20µm. This layer is also known as horny layer, and it plays a major role in the mechanism of the transdermal drugs delivery system as it form the permeability layer on the outermost part of the skin.

Compared to outer layer of the skin, the inner part of the skin, known as dermis is consist of elastic layer that will provide structural support to the structure. This part also contains nerve endings, with a rich microcapillary system. The features of this enables the drug to diffuse rapidly through the skin before it could reach the vascular system. Because this structure provides minimal resistance towards the drug diffusion, it is generally accepted that the penetration of the drugs through the stratum cornea layer of the skin plays the major role of transdermal drugs diffusivity.

2.3.5 Dermal Transfer Enhancement Technique

The movement of the drugs through the stratum cornea layer of the epidermis provides the major resistance and limitation for the transdermal drug delivery system. Because of this limitation, there are several techniques that have been developed in order to overcome the resistance to the drugs and enhance the performance of the drug delivery system. Some of the enhancement techniques are:

- Microneedles
- Iontophoresis
- Sonophoresis
- Skin Ablation

2.3.5.1 Microneedles

Microneedles are the device that is developed in order to increase the rate of penetration of the drugs through the startum cornea layer of the skin. The device also enables the larger particles of drugs that usually cannot enter through the skin permeates through it. The microneedle is an array of micro scale needle that is coated on the surface of the patch. Microneedles can be classified into solid microneedles and hollow microneedles. This figure shows the mechanism and the structure of solid microneedle:

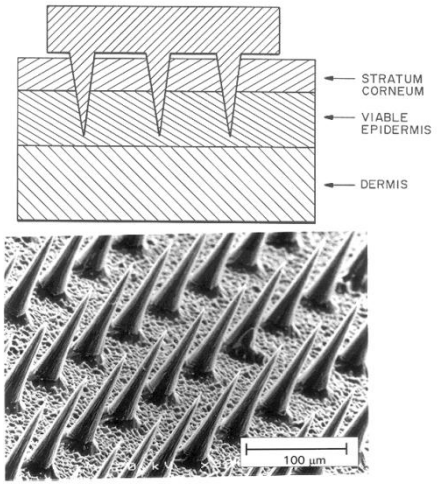


Figure 2.9: Structure of microneedle

Source: Ramasubramaniam, M.K. (2008)

The principal when solid microneedles are used follows one these administration methods

1) Puncturing skin at the site to be treated with a microneedle array to form pore canals, and then applying a drug-containing patch onto the site;

2) Coating the surface of a microneedle array with a drug, and then puncturing the skin with the microneedle array to perform sustained drug release.

When hollow microneedles are used, drug delivery is generally performed by microinjection, which is suitable for liquid drugs and drugs with a high therapeutic dosage. In addition, hollow microneedles can be used in transdermal suction and detection of a trace amount of body fluid. The figure below shows the mechanism when the hollow microneedles was applied on the skin. The formulation will be transferred through the stratum corneum layer to the dermis, enabling it to reach the blood vessel much more effectively.

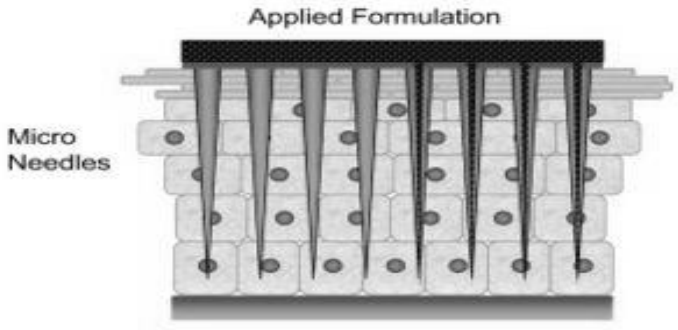


Figure 2.10: Basic principal of microneedle

Source: Kaushik S. *et al* (2001)

The small size of the needles enables the drug to reach the blood vessel much faster by creating a so-called pathway for the drugs by punching small holes on the stratum corneum layer of the epidermis, which can ultimately leads to uptake by capillary system for systemic delivery. The microneedle is also too short to reach the nerve-rich region of the lower part of the skin, hence the when the patch with microneedle are applied to skin, the sensation is very weak and can be perceived as painless (Kaushik *et al*, 2001).

2.3.5.2 Iontophoresis

Iontophoresis is the mean of enhancement of transdermal drug delivery by the application of electrical field onto the skin. This method was done by applying two

electrodes on the skin of the patient. Once the electrical voltage was supplied to the electrodes, the drug will start to migrate through the skin (Niclas, 2007).

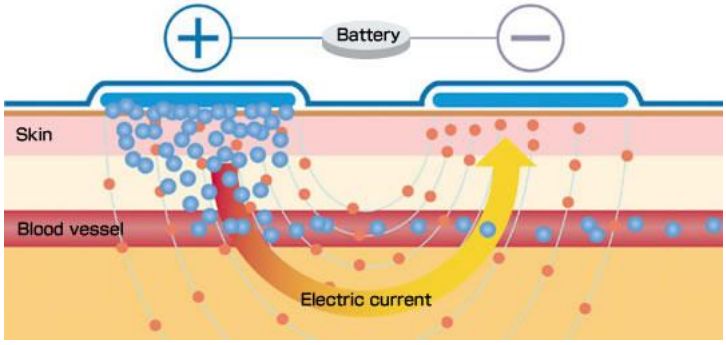


Figure 2.11: Basic Principal of Iontophoresis

Source: Niclas, R. (2007)

This method effectiveness relies upon the construction of the system itself, where the iontopohoresis electrode section (active) and the ground electrode section (inactive are in a stably energized over a long period of time. This factor is very important to ensure that the active ingredient on the patch (drugs) is sufficiently driven towards the skin (US7398121, 2008). The efficiency also is closely related to properties such as polarity, valency and mobility, whereby mobility is tightly linked to the size of the drug particles.

2.3.5.3 Sonophoresis

The mechanical of sonophoresis is quite similar to the iontophoresis, but instead of electrical charges, it relies upon sound waves to enhance the drug delivery. The skin is made permeable or more permeable under the influence of ultrasonic waves (Niclas, 2007). The lipid/water bi-layers on the stratum corneum act s a principal line of barrier defense o protect the lower layers of the dermis. At this point, many substances with high molecular weight is prevented from permeating, as the microscopic gap on the stratum corneum is too small for it to enter (Ralph, 2004). The sound waves will

increase the kinetic energy of the drug particles; hence increase its potential to permeate through.

2.3.5.4 Skin Ablation

Besides the enhancement method that used other devices or material, the most straightforward method of enhancement is simply removing the skin layer of the patient. The outermost layer of the skin is consist of dead particles, known as keratinized cells, and since the removal of the skin only involving these part, it is assumed to be painless (Niclas, 2006). Some of the method used in skin ablation is by using adhesive tape to remove or weaken the layer (Dickel *et al*, 2004), cut through the layer using microjets of particles (Herndon *et al*, 2004), and thermal ablation method- making microconduits by burning away small micrometer sized area on the skin (Niclas,2007)

2.3.6 Advantages of Transdermal Drugs Delivery System

Transdermal drug delivery system has numerous advantages compared to the conventional method of chemotherapy using oral drugs or injection. Because this method is site-specific, and the drugs will be delivered straight to the targeted cancer cell without going through the blood vessel, eliminating the harmful side effect of the drugs to other body cells. The other remarkable advantage of using transdermal drug delivery system is it can reduce the dosage of the drugs needed for the breast cancer treatment, because of the shortened pathway of the delivery.

On a study published by Girish (2006) showed that when the drugs was delivered topically, only 5% of the taken dosage are able to reach the targeted cancer cell. This is because large portion of the drugs was either neutralized or destroyed along the digestive tract and the liver before reaching the targeted cancer cell. On the other hand, when using transdermal patch, the shortened tract of delivery ensures as much as 95% of the total concentration of drug to reach the target cancer cells (Department of Pharmacology, University of Dublin).

CHAPTER 3

METHODOLOGY

This chapter of this study will focus mainly on the instrumentation of the study, and also the method used to in order conduct the study. This instrumentation and methodology will focusing on investigating the diffusivity of different type of drugs through breast tissue, and also the effect of density of breast tissue to the diffusivity.

3.1 Materials and Instrumentation

To conduct this study, we first have to gather information and data about the subject that we need to investigate. For the research, two type of drug are for the first simulation, which are Doxurubicin and Paclitaxel. In order to start the simulation, the physical data of the drugs are obtained so that we can construct the mathematical model. The simulation was done by applying the mathematical model into the multi-physics software, COMSOL.

3.2 Methodology Flow Chart

This methodology flow chart represents the steps of process that needed to be done in order to complete this study. From the figure, the study will be started by gathering information on the specific drugs that wants to be simulated. The data that need to be collected is the specific diffusivity and the molecular weight. The volume of the simulated breast are also calculated. All of the data, obtained and calculated, will be used to construct the mathematical model, which then will be implemented in the

COMSOL. In order to use the COMSOL, a model need to be build up, by drawing the breast shape, and also determining the position of the transdermal patch on the breast. After the simulation was done, the data and graphs obtained from it was analyzed and observed. This study was ended by doing the comparison between the different results obtained from the simulation.

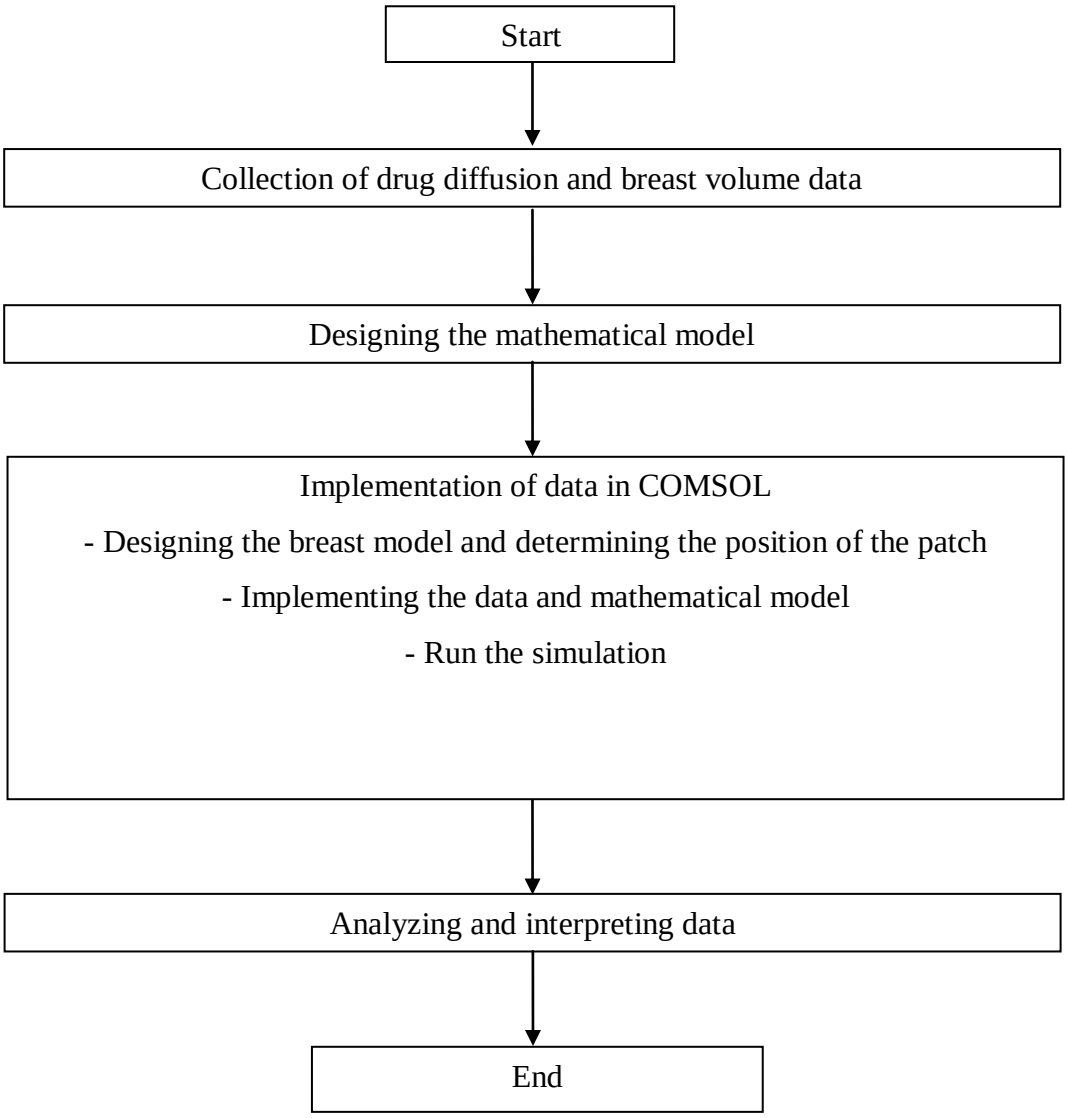
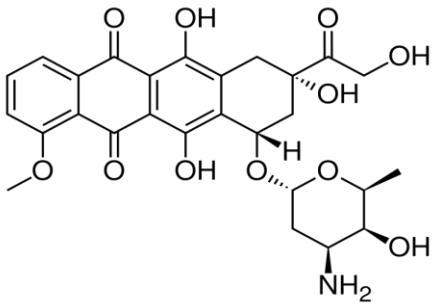
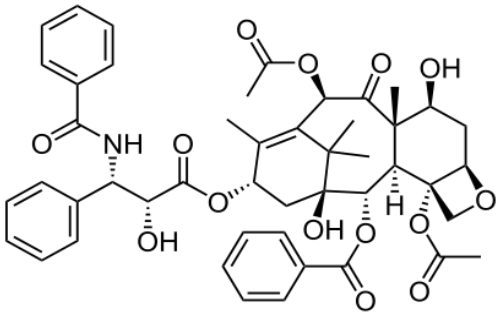


Figure 3.1: Methodology Flowchart

3.2.1 Collection of Drug Diffusivity Data

For this study, the drug chosen for the simulation is Doxurubicin and Paclitaxel, which were the type of drugs that is widely used on the transdermal patch for breast cancer treatment. The properties of these two drugs are varied; hence the data need to be collected to simulate the diffusivity of the drugs. The data collected for both drugs is represented in table below:

Table 3.1: Data of Doxorubicin and Paclitaxel

Doxorubicin	**Paclitaxel**
	
Molecular Formula: $C_{27}H_{29}NO_{11}$	Molecular Formula: $C_{47}H_{41}NO_{14}$
Molecular Mass: 543.52 g/mol	Molecular Mass: 853.906 g/mol
Diffusivity: 2.7 x 10^-10 cm2/s (Khan and Shafiq, 2009)	Diffusivity: 2.5 x 10^-12 cm2/s (Chi *et al*, 2005)

3.2.2 Collection of Breast Volume Data

The volume of the breast between women, or between the left and right breast are varied. For this study, we need to gather the different volume for different breast, in order to calculate the density of it. According to Senie R. *et. al.* (1980), the volume of the breast can be assumed by using the formula to calculate the volume of the cone, and this formula has been widely used in determining the volume of the breast for mammogram. The formula is:

$$1/3\ (\pi r^2 h)$$

Where r is half of the width of the breast or radius, and h is the breast height.

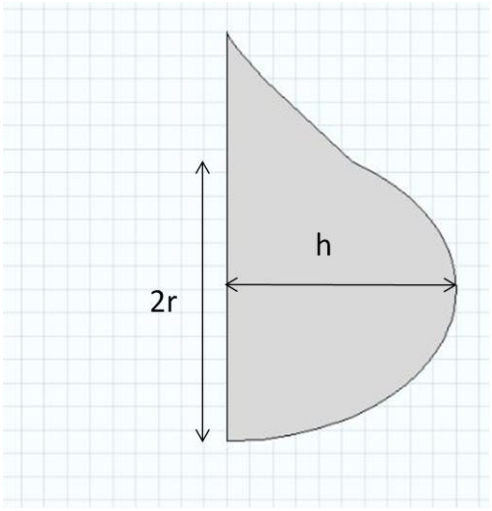


Figure 3.2: The radius and the height of the breast model

3.2.3 Designation of Mathematical Model

For design of mathematical model, the applied concentration of drugs on the surface of the skin will be governed by using Fick's law in one, two and three dimension. The boundary condition, such as the position of the patch and initial concentration of drugs in the tissue was also determined. Drug delivery in the breast tissue is assumed only to diffusion, hence the governing equation is:

$$\frac{dc}{dt} = D[\left(\frac{1}{r}\right)\left(\frac{d}{dr}\right)\left(r\frac{dc}{dr}\right) + \frac{d^{2c}}{dz^2}]$$

Where c is the concentration of the drugs, D is the specific diffusivity of the drug in the breast tissue and t is the time, one week.

3.2.4 Implementation in COMSOL

To solve the equation of Fick's Law of Diffusion into the COMSOL software, the domain is first created while the boundary condition stated. The details of the used of the software can be referred to handbook of An Introduction to Modeling of Transport Processes: Application to Biomedical System (Datta et. al., 1996). The version of the COMSOL used is 4.2, which is the newest version, hence the procedure are specified:

1. First, the problem was specified as Chemical species transport > transport of diluted species. Because the problem is simulated on certain time, time dependent option is selected.

2. The grid was set and the geometry was created; a semi-ellipsoid is drawn to represent the structure of the breast. We will manipulate the height of the semi-ellipsoid to get a different size structure.

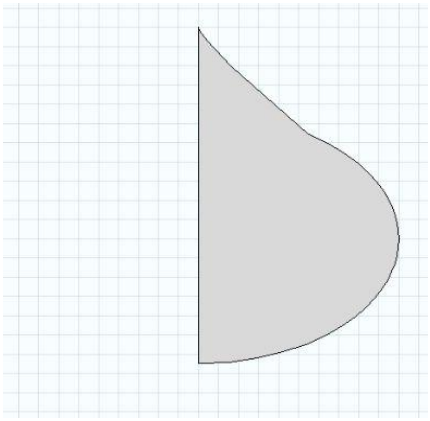


Figure 3.3: Basic structure of breast modelling

3. Meshing: structured mesh was created in the domain. This step is to build the structure inside of the breast model. Basic, meshing program is used to build the structure

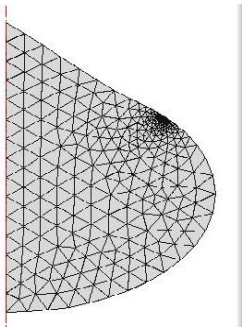


Figure 3.4: Basic mesh Structure

4. Boundary condition was defined, such as the flux of the drug and also the initial concentration of the drugs in the tissue. The initial concentration of drugs on the patch was specified as 2.592 x 10^5 mol/m^3, and the concentration of drugs in the tissue is 0. The constant drug flux is specified as 8.849 x 10^{-7} g/cm^2 s (Datta and Rakesh, 2008)

5. The start, end and the step for the time is specified. The process start at 0s, end at 6.048 x 10^5 s (a week), and the step is 1000s. The process was computed.

6. The concentration of drugs on specific depth of the breast is obtained by drawing a 2d cut line on the breast model.

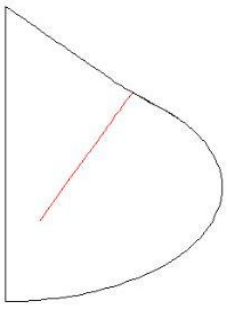


Figure 3.5: 2D cut line on the breast model

7. The graph of concentration vs time was plotted.

CHAPTER 4

RESULTS AND DISCUSSIONS

This chapter will provide the results from the simulation which has been completed. The findings will be focused on three parameters that has been chosen to be examined, which are the type of drugs used on the transdermal patch- doxorubicin and paclitaxel, the specific diffusivity of the drugs used and also the effect of breast volume to the concentration of the drugs that will be able to reach the targeted cancer cells.

4.1 Diffusivity of Different Type of Drugs through Breast Tissue to The Targeted Cancer Cell

The diffusivity of two types of drugs, doxorubicin and paclitaxel, were simulated using multi-physics software, COMSOL. From this simulation, we will have a graph of concentration of the drugs on the targeted breast cancer cell for a week time. The data that has been put into the software will provide us with graphical representation of the transdermal drug delivery process, after the study was computed. The concentration gradient for diffusion of doxorubicin is represented by figure 4.1 and 4.3, while the concentration gradient for paclitaxel is represented by figure 4.2 and 4.4

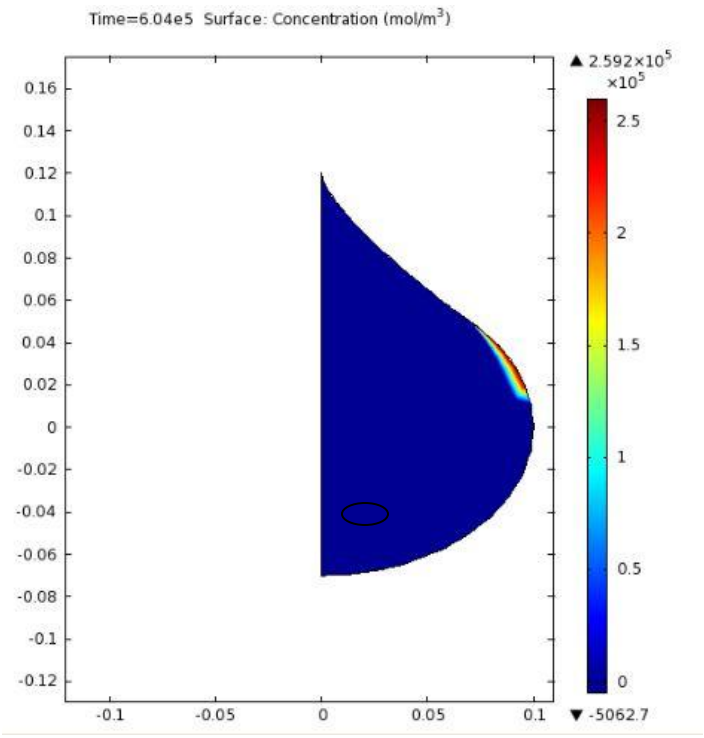


Figure 4.1: Diffusion of Doxorubicin after a week with breast volume $1.83x10^{-4}$ m^3

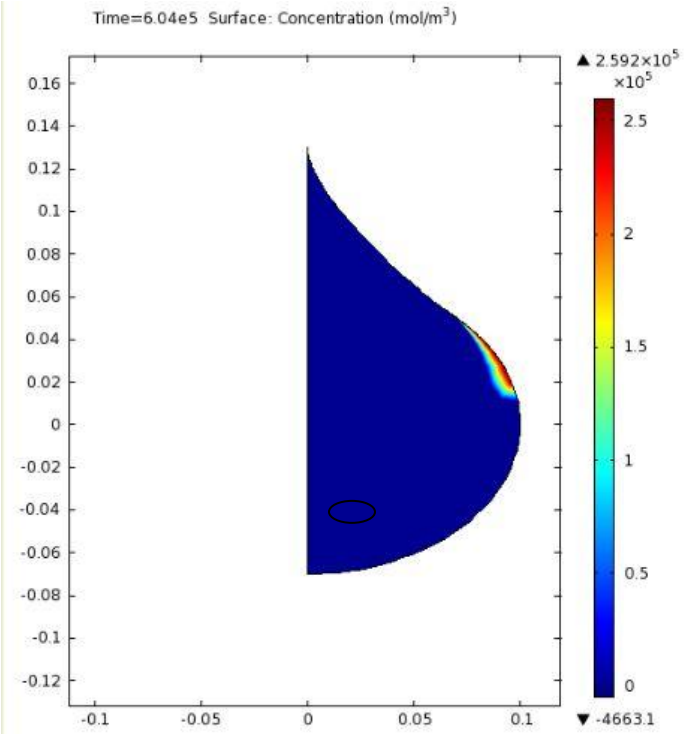


Figure 4.2: Diffusion of Paclitaxel after a week with breast volume $1.83x10^{-4}$ m^3

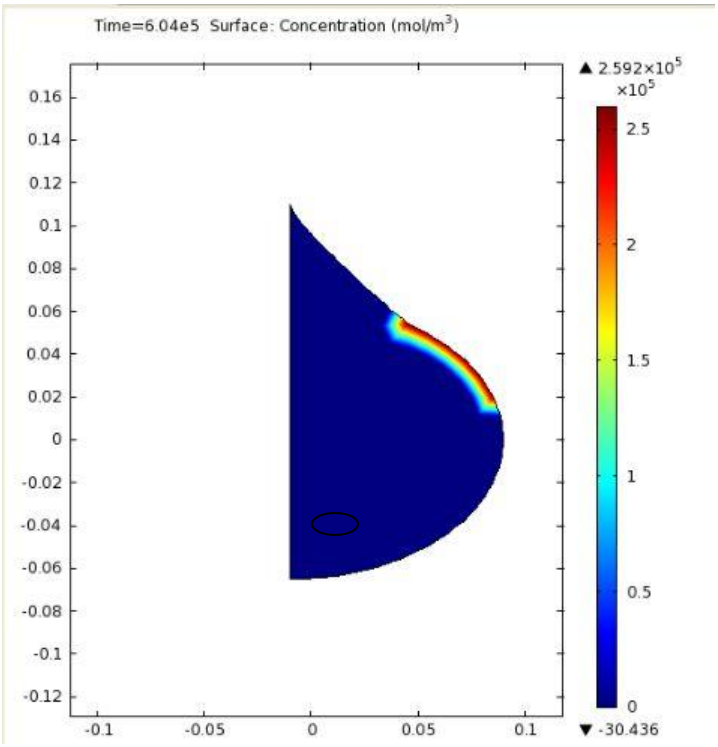


Figure 4.3: Diffusion of Doxorubicin after a week with breast volume $1.70x10^{-4}$ m^3

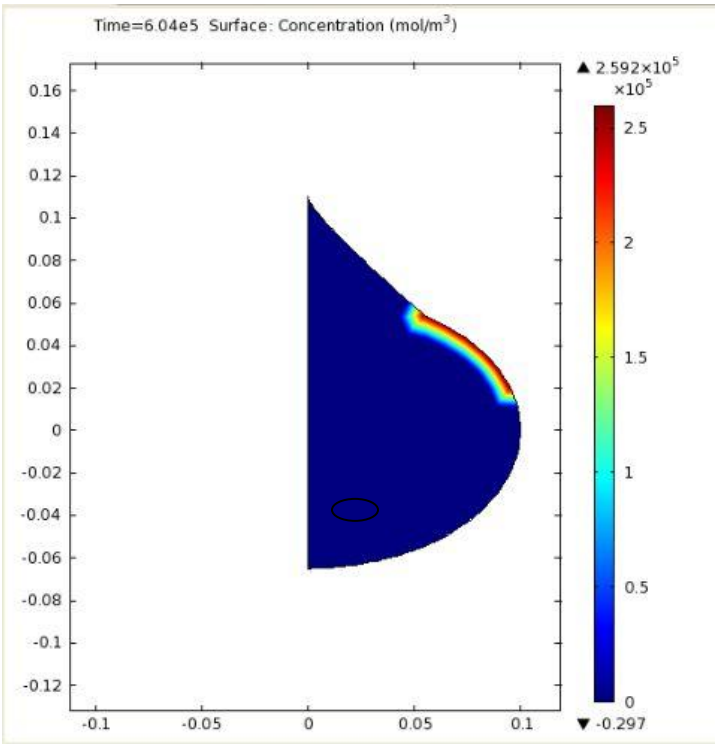


Figure 4.4: Diffusion of Paclitaxel after a week with breast volume $1.70x10^{-4}$ m^3

From the graphical representation of the simulation obtained from COMSOL, the gradient of the colour spectrum shows the concentration of the drugs in the breast tissue. It can be seen clearly that both drugs shows similar pattern of drugs distribution, for the breast with volume of $1.83x10^{-4}$ m^3. The drugs also show the similar pattern for both Doxorubicin and Paclitaxel on breast with volume of $1.70x10^{-4}$ m^3. When the concentration of drugs was tested for the marked region, the concentration of both drugs on each region is 0.00 mol/m^3, where the drugs cannot reach the specific region in one week time.

4.1.1 Discussion on the Efficiency of Treatment Based On the Type of Drugs

The drugs chosen for this simulation are doxorubicin and paclitaxel, two of the most widely used breast cancer drugs globally. Doxorubicin is a chemotherapy drug, and it can be categorized as anthracycline antibiotics, and it works by intercalating DNA. The drugs have molecular mass of 543.52 g/mol, and the specific diffusivity of doxorubicin in the breast tissue is 2.7×10^{-10} cm^2/s (Khan and Shafiq, 2009). The second type of drugs chosen for the study is paclitaxel, which is a mitotic inhibitor, and can be categorized as taxanes. It has the molecular mass of 853.906 g/mol and the specific diffusivity of paclitaxel on breast tissue is 2.5×10^{-12} cm^2/s. The concentration profile will be represented by the colour spectrum, where the red indicates the highest concentration and the blue indicates the lowest concentration.

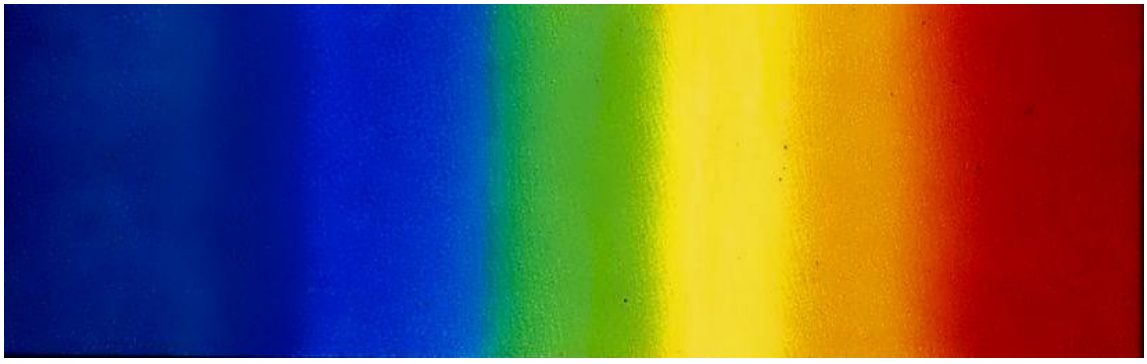


Figure 4.5: Color Spectrum

From the concentration profile of doxorubicin and paclitaxel with breast volume of $1.83x10^{-4}$ m^3, there are no distinguishable features that can be seen on it to differentiate between the two drugs. The location where the drugs are distributed on the breast tissue for both drugs is almost the same. It also can be seen that the drugs is not widely distributed, and only diffuses into the outermost layer of the breast tissue. Both drugs is unable to reached the designated area for of the breast cancer cells.

Doxorubicin and paclitaxel has the diffusivity of 2.7×10^{-10} cm^2/s and 2.7×10^{-12} cm^2/s. The dffusivity of doxorubicin is the floor value of the drugs diffusivity for transdermal patch, as it can only gives the minimum amount of drugs to the cancer region. Drugs with smaller diffusivity value will also give the similar profile, and that is the reason why the profile between these two drugs is similar to each other.

When the smaller the breast volume was changed to a smaller one, $1.70x10^{-4}$ m^3, the concentration profile between the two drugs also seem almost identical, although the drugs spread more widely than in the larger breast volume. This further proves that the diffusivity of the both drugs is the minimum value for this type of treatment, and it cannot give an effective treatment for the patient.

4.2 Efficiency of Treatment Based On the Specific Diffusivity of Drugs

The specific diffusivity of drugs is examined, in order to understand how significant the impact of it to the efficiency of this treatment is. The diffusivity factors will be adjusted from the value of diffusivity of doxorubicin- 2.7×10^{-10} cm^2/s, and this value will be increased tenfold 10 times. The size of the drugs will be kept constant at $1.96x10^{-4}$ m^3. The concentration profile for drugs with different diffusivity can be interpreted as such:

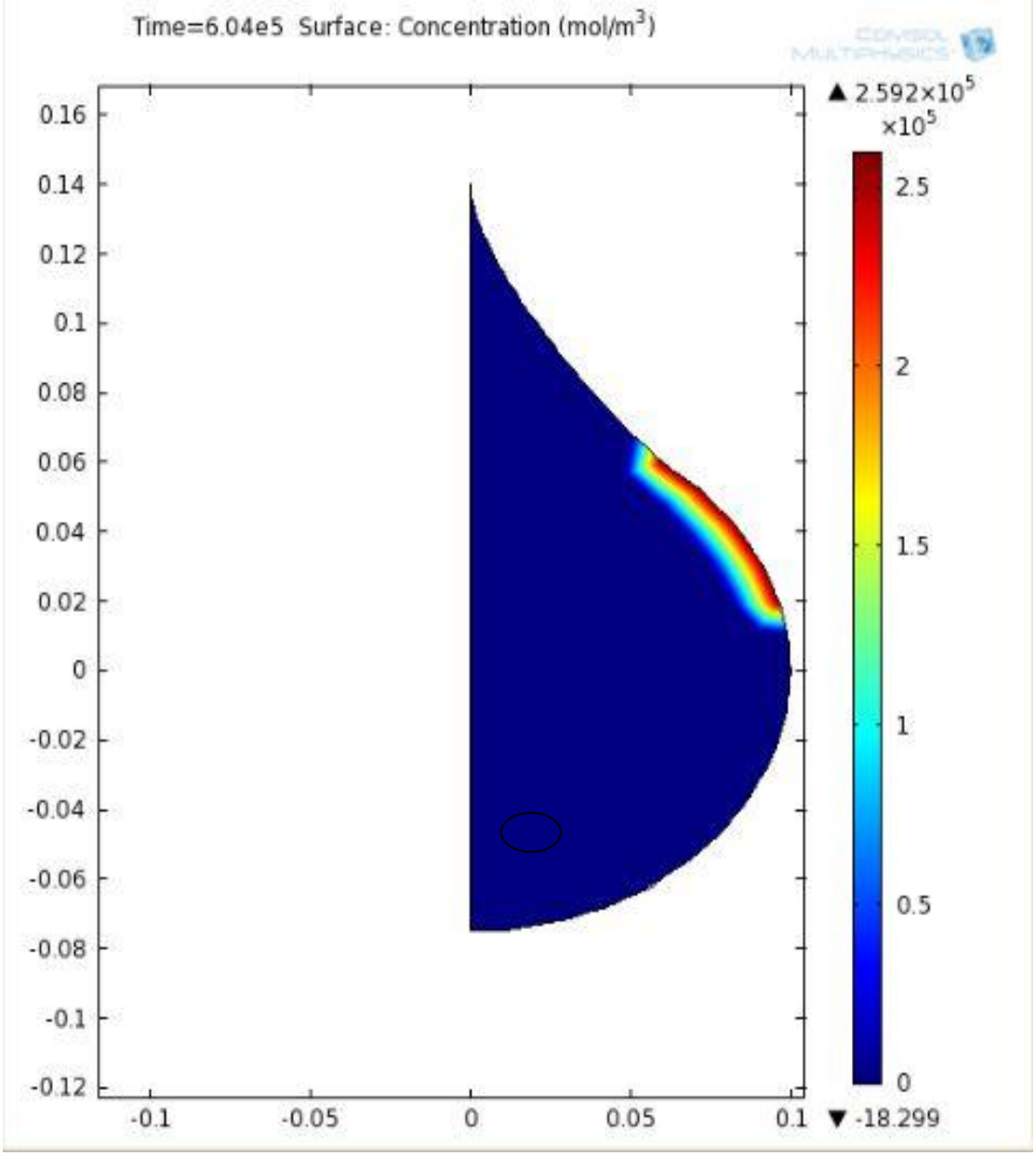


Figure 4.6: Diffusion of drugs with diffusivity of 2.7×10^{-10} cm^2/s after a week with breast volume 1.96×10^{-4} m^3

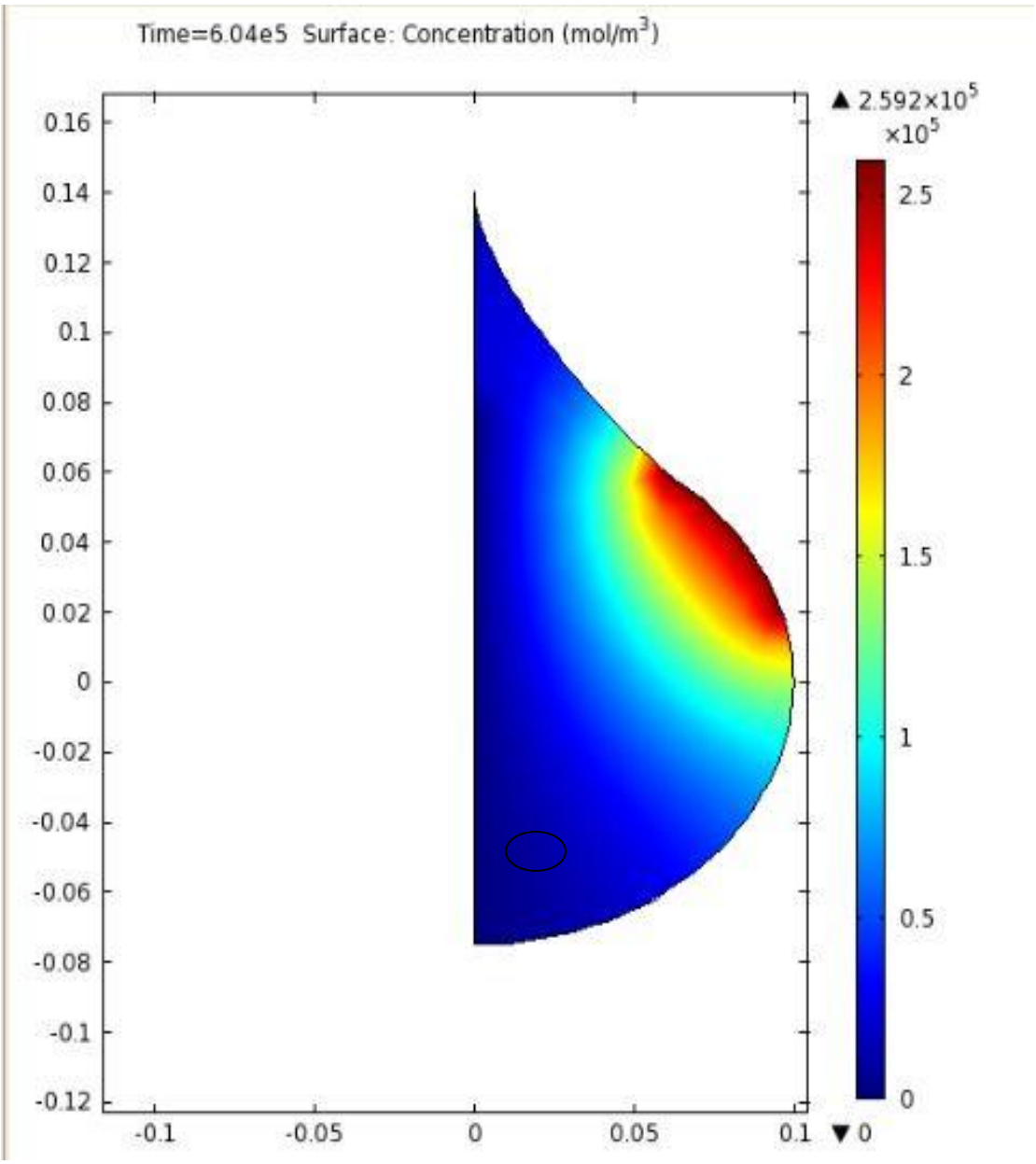


Figure 4.7: Diffusion of drugs with diffusivity of 2.7×10^{-5} cm^2/s after a week with breast volume 1.96×10^{-4} m^3

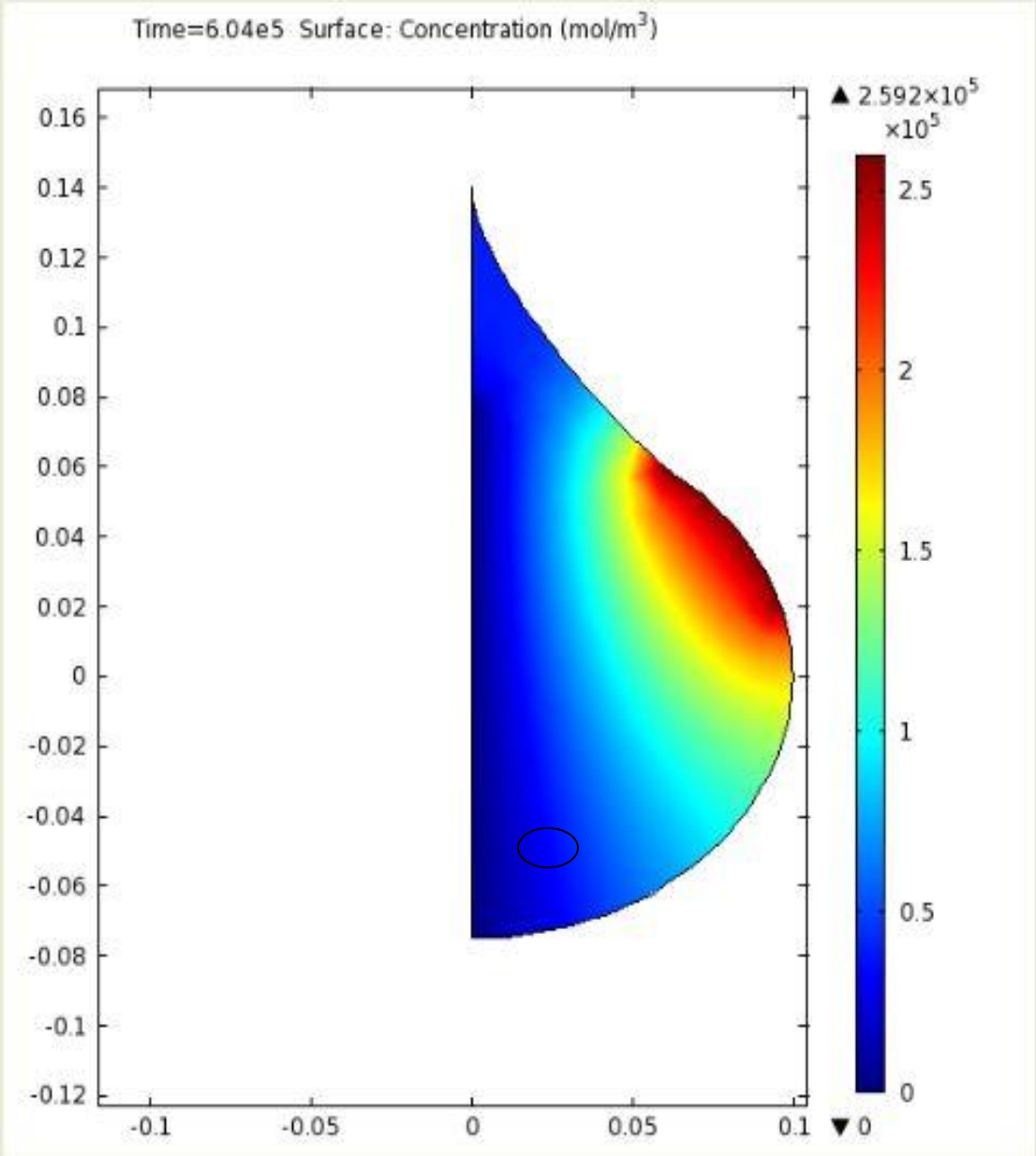


Figure 4.8: Diffusion of drugs with diffusivity of 2.7×10^{-1} cm^2/s after a week with breast volume 1.96×10^{-4} m^3

The graphics shows the concentration profile of drugs at the lowest, midpoint and highest diffusivity of drugs that is tested on the simulation. The concentration of drugs at the specific point which indicates the position of the breast tumor is defined in the table below:

Table 4.1: Concentration of drugs at the breast cancer cells at different diffusivity

Drug diffusivity (cm^2/s)	**Concentration of drugs (mol/m^3)**
$2.7x10^{-10}$ cm^2/s	0.00
$2.7x10^{-9}$ cm^2/s	0.02×10^{-4}
$2.7x10^{-8}$ cm^2/s	0.018×10^{-2}
$2.7x10^{-7}$ cm^2/s	0.052×10^{5}
$2.7x10^{-6}$ cm^2/s	0.136×10^{5}
$2.7x10^{-5}$ cm^2/s	0.214×10^{5}
$2.7x10^{-4}$ cm^2/s	0.366×10^{5}
$2.7x10^{-3}$ cm^2/s	0.470×10^{5}
$2.7x10^{-2}$ cm^2/s	0.482×10^{5}
$2.7x10^{-1}$ cm^2/s	0.482×10^{5}

From the tabulated values, it quantitatively indicates that the highest value of the drug concentration that is able to reach the breast cancer cells occur when the highest drug diffusivity value was chosen for the simulation. The maximum concentration of drugs that is able to reach the breast cancer cells is 0.482×10^5 mol/m^3, which is 18.6% of the initial value if the drugs on the transdermal patch. When the diffusivity of drugs is $2.7x10^{-5}$ cm^2/s, the concentration of drugs at the cancer cells is 0.214×10^5 mol/m^3, or 8.25 % of the initial drug concentration. Diffusivity of $2.7x10^{-10}$ cm^2/s is very low, and the concentration of drugs at the cancer cells is neglectable.

4.2.1 Discussion on the Effect of the Diffusivity of Drugs

For this part of simulation, the aim is to find the relationship between the specific diffusivity of drugs on the breast tissue with the concentration of drugs that reaches the cancer cells. Overall, the highest concentration of drugs that is able to reach the cancer

cells is 0.482 x 10^5 mol/m^3, and this is the ceiling value of drug concentration. When the diffusivity of drugs is further increased, this value will not change. The concentration of drugs at the cancer cells can be explained by the balance between diffusion and drug release rate from the reservoir system.

The release rate of the drugs from the reservoir after the patch was applied on the skin is maximal. Over some time, the drug released will underwent a slight decline, as the concentration of the drugs on the reservoir is slowly depleted. The appropriate design of the transdermal patch can provides a pseudo zero-order or apparently a constant drug release rate during the designated period of patch used (Ratna, 2004), causing the decline to be insignificant.

One of the most important parts of the transdermal patch design is the initial concentration of drug on the reservoir, and the concentration is assumed to be 2.592 x 10^5 mol/m^3. This optimum value of drug concentration is the key factor to maintain the concentration gradient on breast tissue. The high initial drug release will not affect the efficiency of the patch, as the high drug concentration on the reservoir enable the zero-order drug concentration gradient to be maintained, even after longer period of time. High release of drug can be kept at constant even when the highest value of diffusivity is applied; proving that the initial drug concentration on the patch is optimum.

The highest possible diffusivity value is the aim in designing the transdermal patch while minimizing the drug concentration at the reservoir of the patch, as high concentration of drug used on the reservoir can become toxic to the patient, and will make this method of treatment more expensive.

4.3 The Effect of Breast volume on the Efficiency of Drug Diffusivity

The volume of the breast of the patient is one of the factors that will contribute to the effectiveness of the transdermal patch drug therapy. The volume of the breast will be manipulated by changing the width of the breast while keeping the radius at certain length. The volume of the breast will then be computed using the equation used to calculate the volume of the cone:

$$1/3\ (\pi r^2 h)$$

Where r is the half of breast height and h is the width of the breast. The height is specified to be 0.01 m, and the width of the breast that is used is 0.0065 m, 0.0070 m and 0.0085m. The volume for respective breast size is represented in the table below:

Table 4.2: Volume of breast for specific breast size

Size of breast, W x H (m)	**Volume of breast (m^3)**
0.01 x 0.0065	$1.70x10^{-4}$
0.01 x 0.0070	$1.83x10^{-4}$
0.01 x 0.0085	$2.09x10^{-4}$

For this simulation, the drug diffusivity that will be used is $2.7x10^{-5}$ cm^2/s , and the process was simulated for 1 week, hence the stop time for this process is 6.048×10^5 s. The concentration gradient of drug for each breast volume is represented by figure 4.7, 4.8 and 4.9.

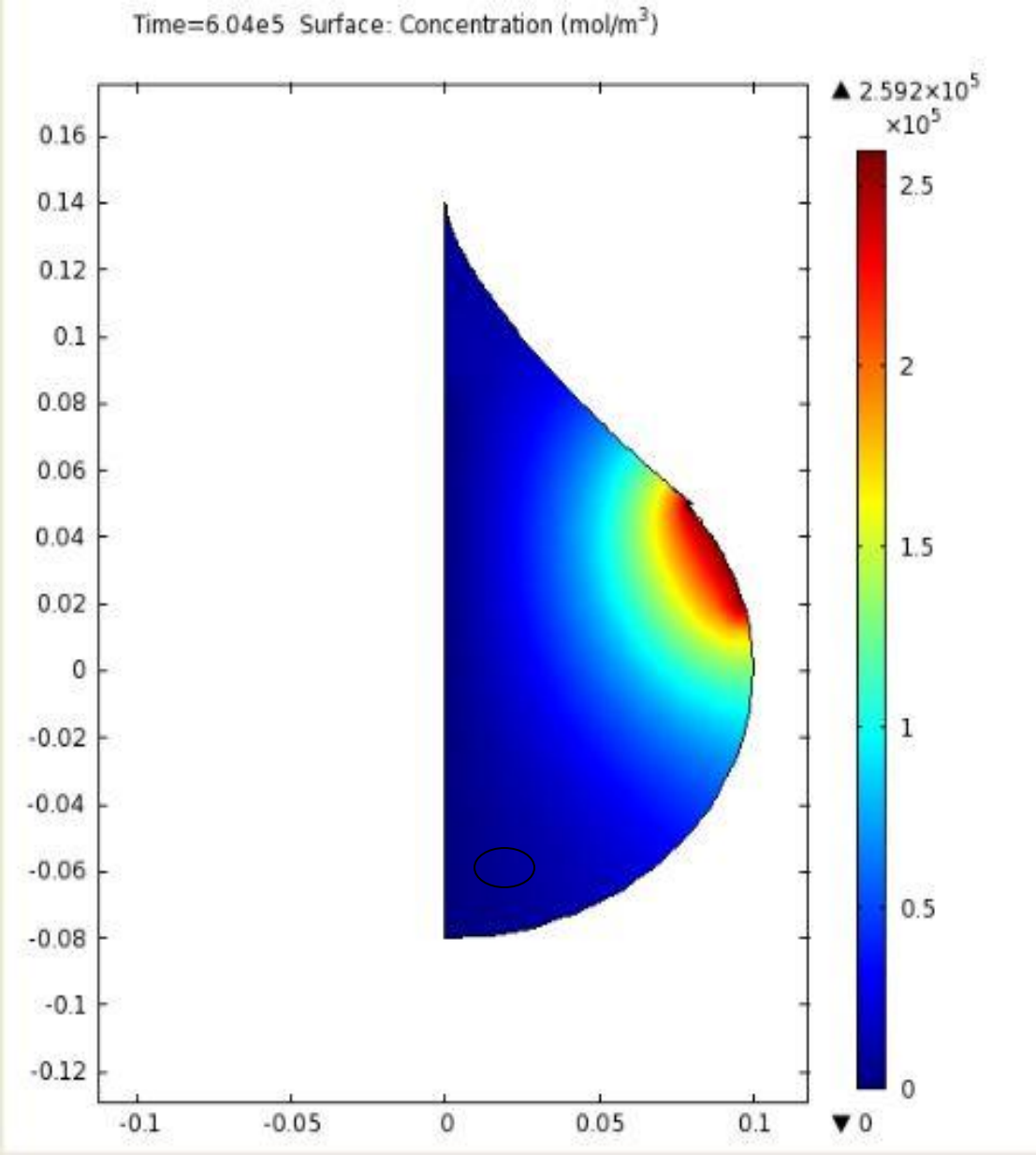


Figure 4.9: Drug concentration on breast tissue after a week for drug with diffusivity of 2.7×10^{-5} cm^2/s with breast volume 2.09×10^{-4} m^3

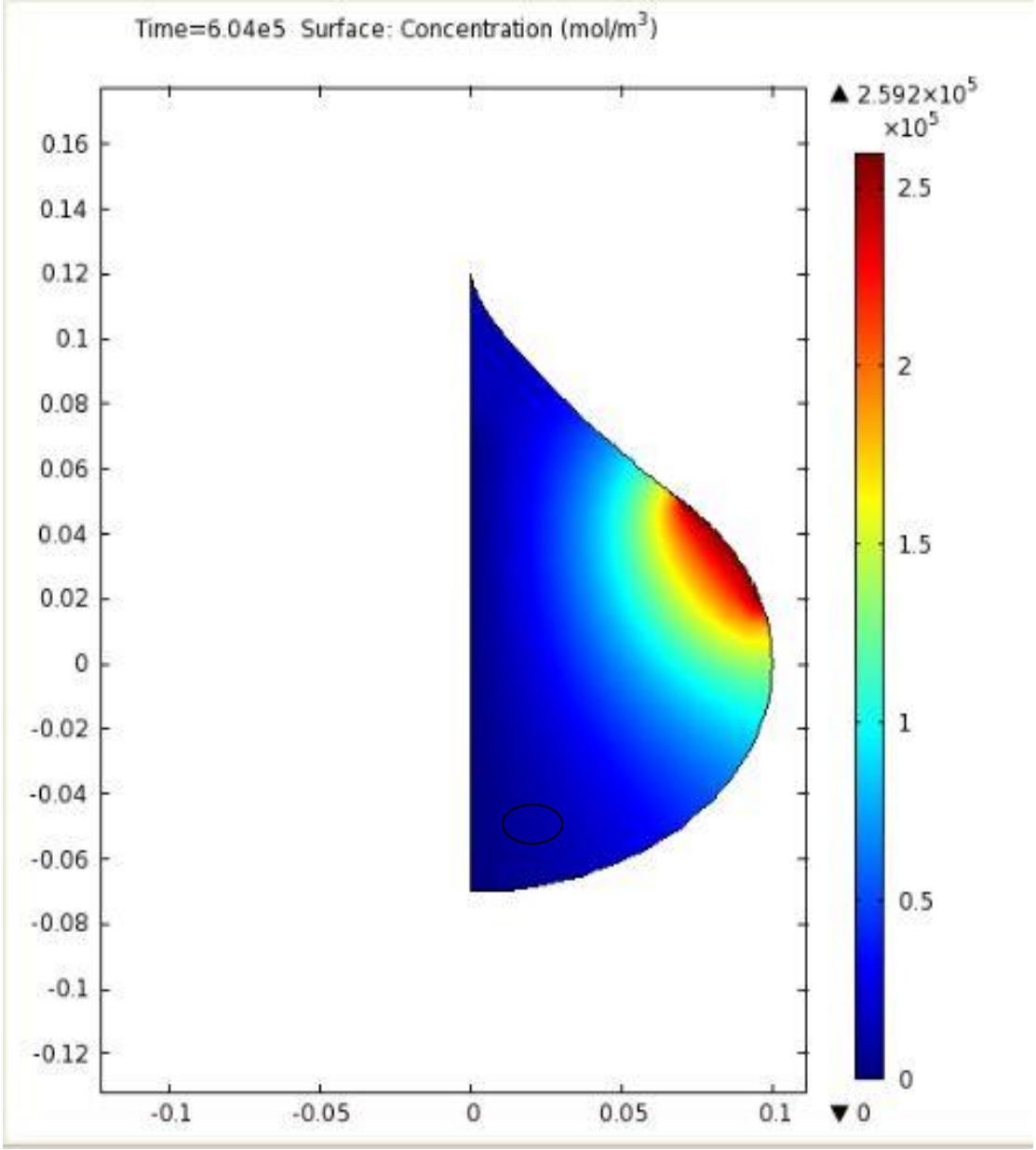


Figure 4.10: Drug concentration on breast tissue after a week for drug with diffusivity of 2.7×10^{-5} cm^2/s with breast volume $1.83 \times 10^{-4} m^3$

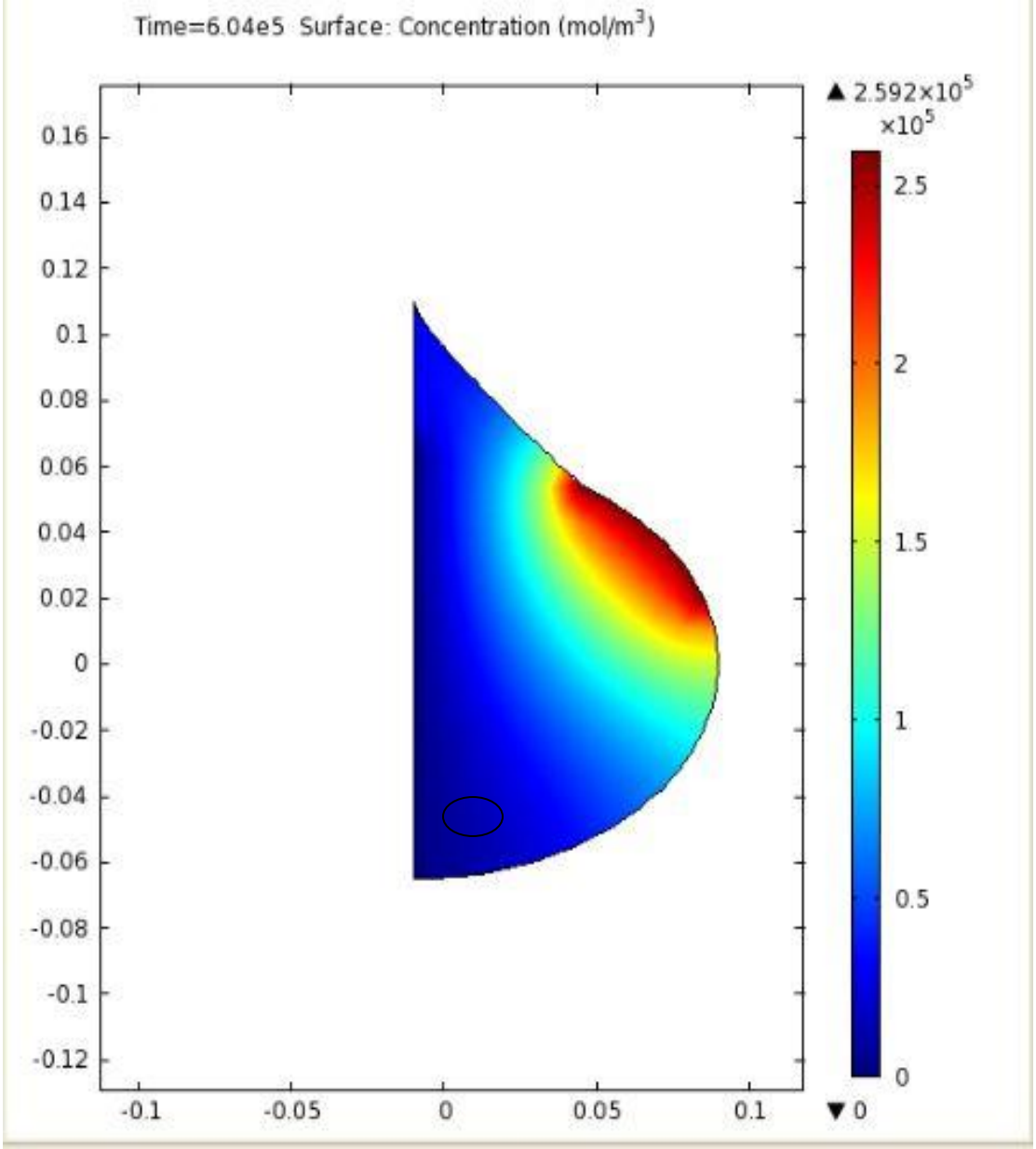


Figure 4.11: Drug concentration on breast tissue after a week for drug with diffusivity of 2.7×10^{-5} cm^2/s with breast volume $1.70 \times 10^{-4} m^3$

The graphical representation shows that the concentration gradient on the breast tissue. From the representation, it can be observed that the distribution of drugs is more widely for smaller breast volume, as the lightly coloured area for breast with volume of $1.70x10^{-4}m^3$, compared with breast with volume of $1.83x10^{-4}m^3$ and $2.09x10^{-4}m^3$. The specific point on the breast is also examined to compare the concentration of drug at similar depth for different breast volume. The result is tabulated below:

Table 4.3: The concentration of drug on specific depth for different breast volume

Volume of Breast (m^3)	**Drug Concentration (mol/m^3)**
$1.70x10^{-4}$	0.398×10^5
$1.83x10^{-4}$	0.337×10^5
$2.09x10^{-4}$	0.286×10^5

The highest concentration of drugs is 0.398×10^5, when the simulation was done on the smallest breast volume, which is 1.70×10^4. The drug concentration for breast with volume of 1.83×10^{-4} and 2.09×10^{-4} is 0.337×10^5 and 0.286×10^5 respectively.

4.3.1 Discussion on the Effect of Breast Volume

The transfer of drugs in the breast with smaller volume is much more rapid than the transfer of drugs in the breast with larger volume. This is shown by comparing the concentration of drugs on specific depth on the breast. This is because the drug can diffuse much easier when the volume of the breast is small. The larger breast volume will provides more hindrance to the diffusion of the drug, caused by numerous factors such as the higher density of breast tissue and the density of fats surrounding the cancerous cells.

Because of the effect brought about by the breast volume, the transdermal drug delivery system is much more suitable, and much more advantageous to the patient that has lower breast volume than those who has larger breast volume.

CHAPTER 5

CONCLUSIONS AND RECCOMENDATIONS

This chapter will provide the brief summary of the findings for the study that has been completed for the dissertation. It will conclude all the important observation and the results that have been obtained from the simulation. This chapter will also provide some recommendation that can be done in order to improve the quality of the study in the future research.

5.1 Conclusions

The study simulation of the transdermal drug delivery using COMSOL has been successfully done, and it can be conclude that the parameters chosen for this study has some effects on the efficiency of the transdermal drug delivery for breast cancer treatment. The first parameter which is the different type of drugs- doxorubicin and paclitaxel, did not gives an identifiable difference that can be used to compare the effect of it to the effectiveness of the method of therapy. Both drugs gives minimum concentration on the targeted breast cancer cells, hence, if the diffusivity value of the drugs that are used for this treatment is smaller than 2.7×10^{-10} cm^2/s, the drugs will shows the same effect as doxorubicin and paclitaxel. Both of these drugs is not suitable to be used for this type of treatment as the small diffusivity will only provides the cancer cell with minimum amount of drugs. The second parameter, which is the diffusivity of the drugs shows some significant impact, when the value of the parameter is manipulated. The highest concentration of drugs able to be achieved at the cancer cells is 0.482×10^5 mol/m^3, when the diffusivity of 2.7×10^{-2} cm^2/s is used. When the

diffusivity is further increased, the concentration of the drugs did not increase. The concentration of drugs also correlates with the initial concentration of drugs in the reservoir of the patch. Hence, the concentration of the drugs will increase with the diffusivity until a certain point, and it depends on the design of the patch to provide optimum drug dosage. The third parameter is the volume of the breast. Smaller volume of breast proves to be advantageous for this kind of treatment, as the drugs can be distributed more widely in shorter amount of time. The patient breast volume needs to be taken into account, in order to customize this method so that it is suitable for all patients.

5.2 Recommendations

There are some improvements that can be recommended in order to improve the study in the future. The drugs chosen for the simulation, doxorubicin and paclitaxel, has quite similar properties, and the diffusivity factors of both drugs is really low. The suitability of the drugs to be used for this method of treatment is no recommended, hence wider range of drugs with different properties might be chosen for future research.

The efficiency of the treatment is much related to the initial concentration of the drugs as much as the diffusivity of the drugs itself. For this study, the initial concentration of the drugs used is quite high, and this has some disadvantages, including the treatment can be more expensive, and the high dosage of drugs can be dangerous to the patient. For future research, the relationship between the concentration of the drugs and the diffusivity factors can be outlined, in order to obtain the lowest concentration with the highest diffusivity for existing drugs.

More research should also been done in order to find the diffusivity of chemotherapy drugs in breast tissue. As of right now, the information and the option are limited, and the study could not become broader and much more universal because of this limitation. The collection of drugs data need to be expanded so that the research can be done more widely.

REFERENCES

Ameller, T. Legrand, P. Marsaud, V. Renoir, J.M. 2004. Drug delivery systems for oestrogenic hormones and antagonists: the need for selective targeting in estradiol-dependent cancers. *Journal of Steroid Biochemistry & Molecular Biology*. 92: 1–18

Benbow, U. Maitra, R. Hamilton, J. Brinckerhoff, C. 1999. Selective modulation of collagenase 1 gene expression by the chemotherapeutic agent doxorubicin. *Clinical Cancer Research.* 5: 203–208

Chi, A. Kim, J. Lambert, W. Lee, K. Wang, K. 2005. Effect of drug eluting stent in coronary arteries. *Cornell University*

Cummings, F.J. 2002. Evolving Uses of Hormonal Agents for Breast Cancer Therapy. *Clinical Therapeutics.* 24:C3-C25

Curran, M. Wiseman, L. 2001. Fulvestran. *Drugs.* 61:807-813

Datta A, Rakesh V. 2010. An Introduction to Modeling of Transport Processes Applications to Biomedical Systems. *Cambridge University Press.*

Diaz-Faes J. 2003. The role of surgery in hereditary breast cancer prevention**.** *Rev Oncol* 5(6): 313-3144

Docetaxel. Retrieved April 24 2012 from http://www.drugbank.ca/drugs/DB01248

Doxorubicin. Retrieved April 24 2012 from http://www.drugbank.ca/drugs/DB00997

Dickel, H. Bruckner, T.M. Erdmann, S.M. Fluhr J.W. Frosch, P.J. Grabbe, J. Lffler, H. Merk, H.F. Pirker, C. Schwanitz, H.J. Weisshar, E. Brasch, J. 2004. The strip patch test: results of a multicenter study towards a standardization. *Arch. Dermatol. Res.* 296: 212-219

Folkman J.1999. What is the evidence that tumors are angiogenesis dependent. *National Cancer Institute.* 82: 4–6

Girish G.V.; Sinha N.; Chakraborty K.; Bhattacharya G.; Kahn N.N.; Sinha A.K. 2006. Restoration of impaired plasma maspin level in human breast cancer. *Acta Oncol.* 45: 526–529.

Herndon, T. Gonzalez, S. Gowrishankar, T.R. Anderson, R. Weaver, J. 2004. Transdermal microconduits by microcissm for drug delivery and sample acquisition. *BMC Medicine*. 4:3

Hutton, L. (2009, 26 August), COMSOL Multiphysics Modelling Applications. *Warwick.* Retrieved March 5, 2011 from http://www2.warwick.ac.uk/fac/sci/chemistry/research/unwin/electrochemistry/research/modeling

IBIS investigators. 2002. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomized prevention trial. *Lancet.* 360: 817-24.

Jordan C. Historical Perspective on Hormonal Therapy of Advanced Breast Cancer. 2002. *Clinical Therapeutic.* 24: A3-A16

Kaushik, S. Hord, A.H. Denson, D.D. McAllister, D.V., Smitra, S. Allen, M.G. and Prausnitz, M.R. 2001. Lack of pain associated with microfabricated microneedles. *Anesth. Analg.* 92:502-504

Lake, D.E., Hudis, C. 2002. Aromatase Inhibitors in Breast Cancer: An Update. *Cancer Control.* 9:490-499

Li Li, Xinlan Xu, Liang Fang, Yu Liu, et al. 2010. The Transdermal Patches for Site-Specific Delivery of Letrozole: A new option for breast cancer therapy. *American Association of Pharmaceutical Scientists.* 2: 1054-1057.

Mark, R.P. Samir, M. and Robert, L. 2004. Current status and future potential of transdermal drug delivery. *Nature Reviews Drug Discovery*. 3:115-124

Miller K, Sweeney C, Sledge G:2001. Redefining the target: chemotherapeutics as antiangiogenics. *Clinical Oncology.* 19: 1195–1206

Mom C.H., Buijs C., Willemse P.H., Mourits M.J., De Vries E.G. 2006. Hot flashes in breast cancer patients. *Crit Rev Oncol Hematol.* 57: 63–77.

Niclas, R. 2007. A fully integrated microneedle –based transdermal drug delivery system.

Opatt D., Morrow M., Hawley S., Schwartz K., et. al. 2007 Conflicts in Decision-Making for Breast Cancer Surgery. *Ann. Surg. Oncol.* 14(9): 2463-2469

Osborne C.K., Yochmowitz M.G., Knight W.A. 3rd, McGuire W.L. 1980. The value of estrogen and progesterone receptors in the treatment of breast cancer. *Cancer:* 46:2884-2888.

Osborne C.K, Coronado-Heinsohn E.B.,Hilsenbeck S.G., et al. 1995. Comparison of the effects of a pure steroidal antiestrogen with those of tamoxifen in a model of human breast cancer. *National Cancer Institute.* 7:746-75

Plotkin, S.A. 2005. Vaccine: past, present and future. *Nature medicine*.11(4)

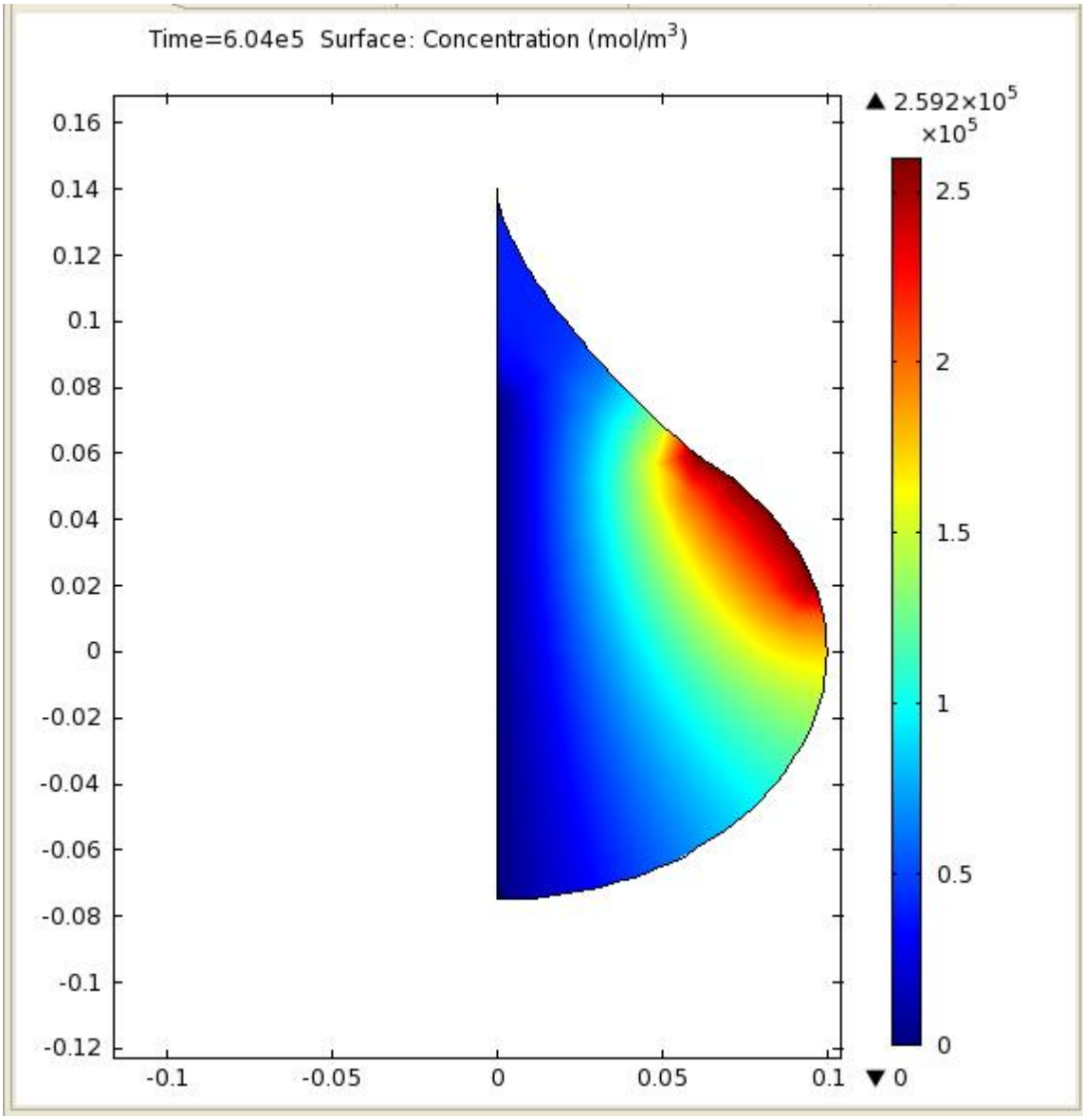
Ralph, H. 2004. Sonophoresis: increase the penetration of your actives

Scheindlin S. 2004 Transdermal drug delivery: past, present, future. *Molecular Intervention*. 4:308-312.

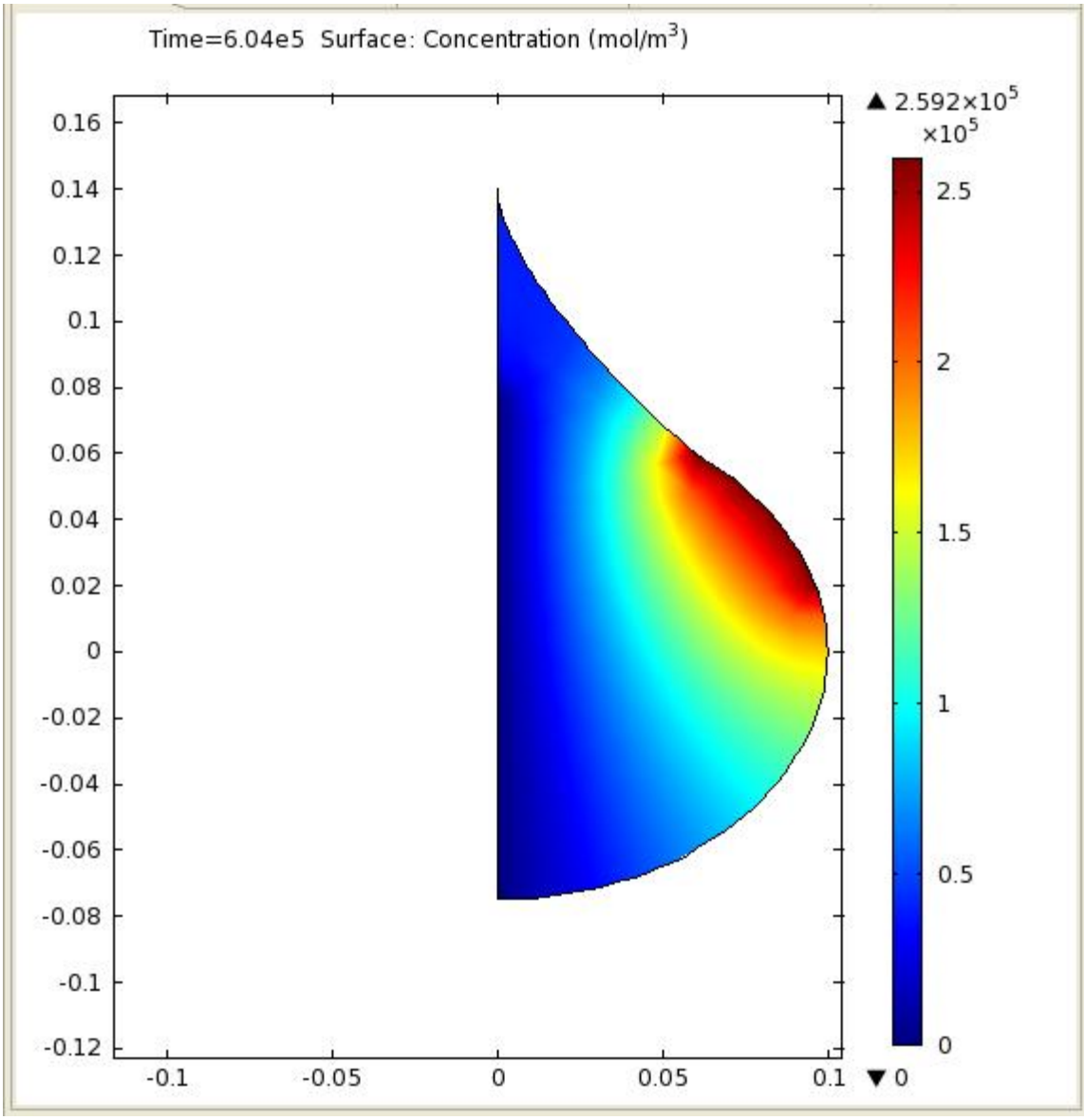
Senie R, Rosen P, Lesser M, Synder R, Scottenfield D, Duthie K. 1980. Epidemiology of breast carcinoma. Factors related to the predominance of left-sided disease. *Cancer,* 46:1705-1713.

APPENDIX A

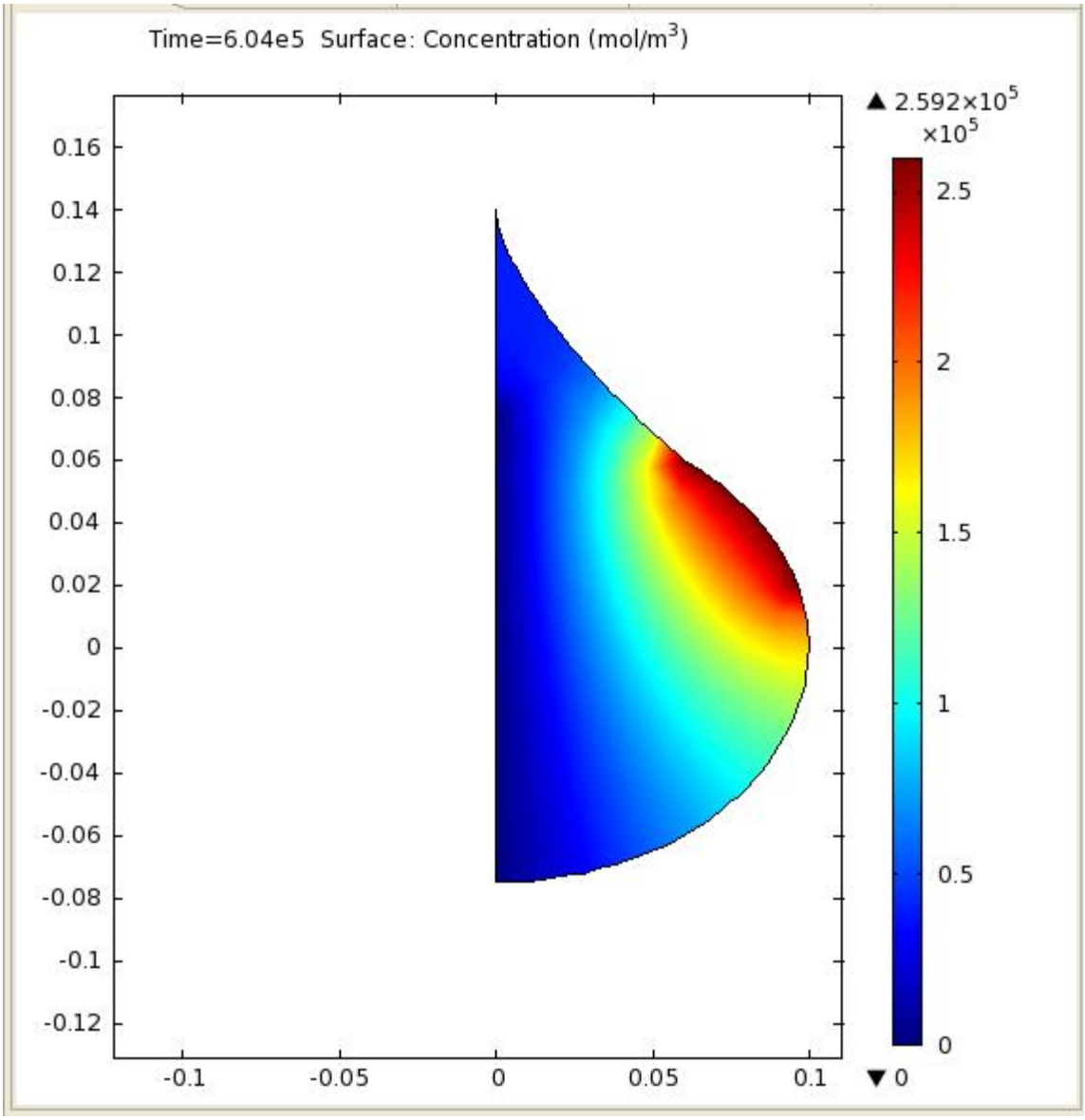
GRAPH IMAGES FOR SIMULATION RUN



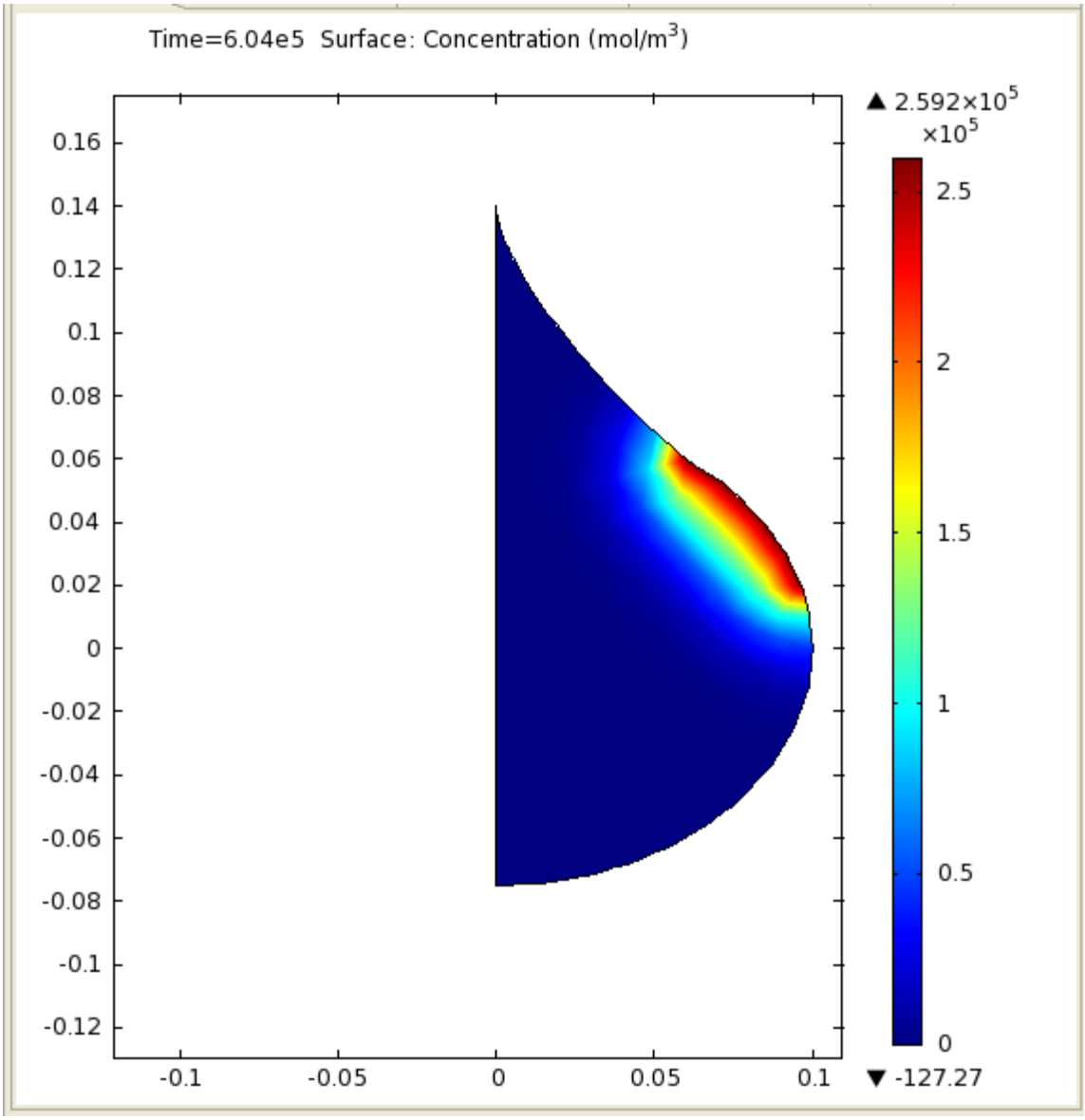
Diffusion of drugs with diffusivity of 2.7×10^{-2} cm^2/s after a week with breast volume 1.96×10^{-4} m^3



Diffusion of drugs with diffusivity of 2.7×10^{-3} cm^2/s after a week with breast volume 1.96×10^{-4} m^3



Diffusion of drugs with diffusivity of 2.7×10^{-4} cm^2/s after a week with breast volume 1.96×10^{-4} m^3



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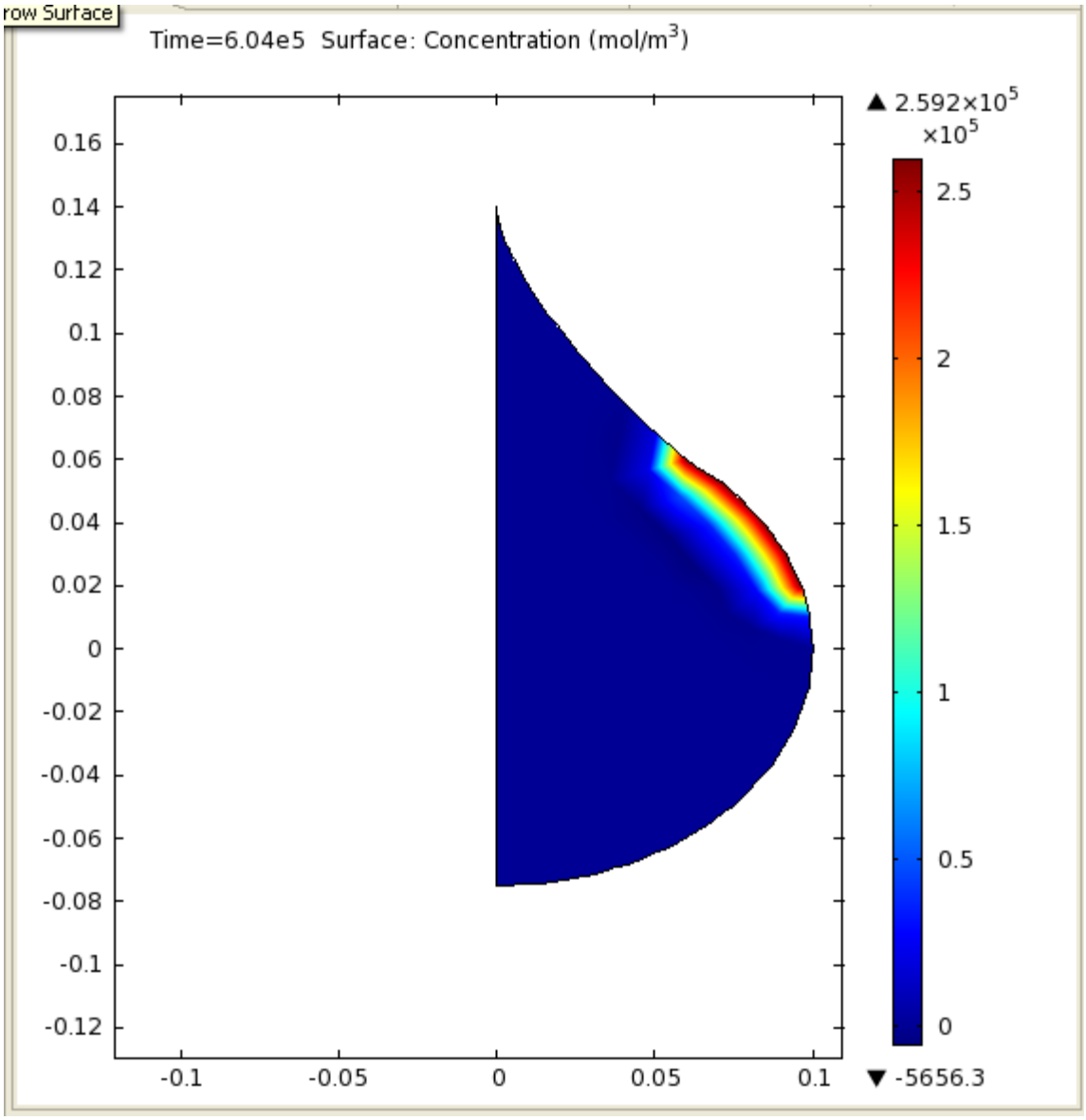

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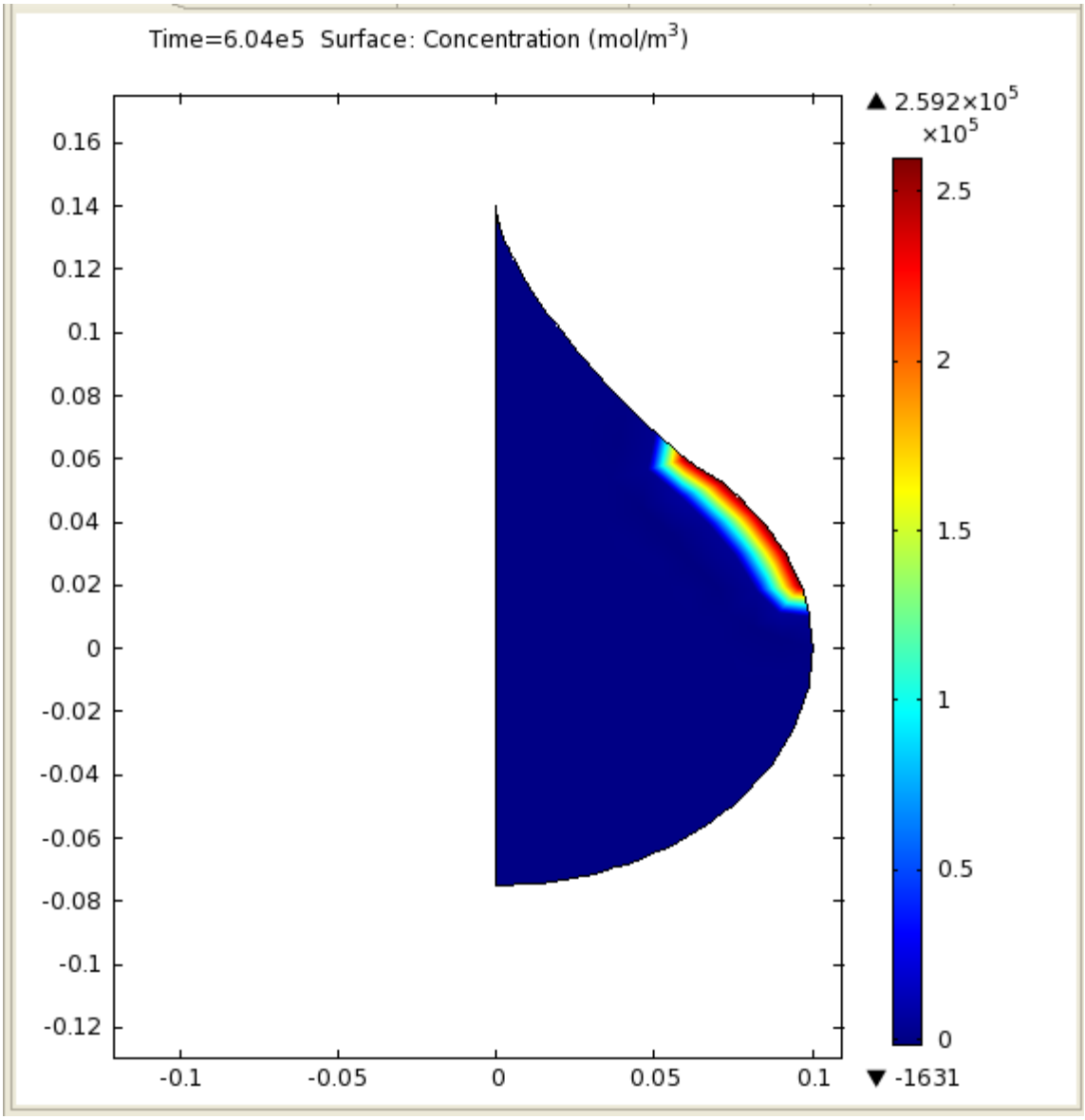

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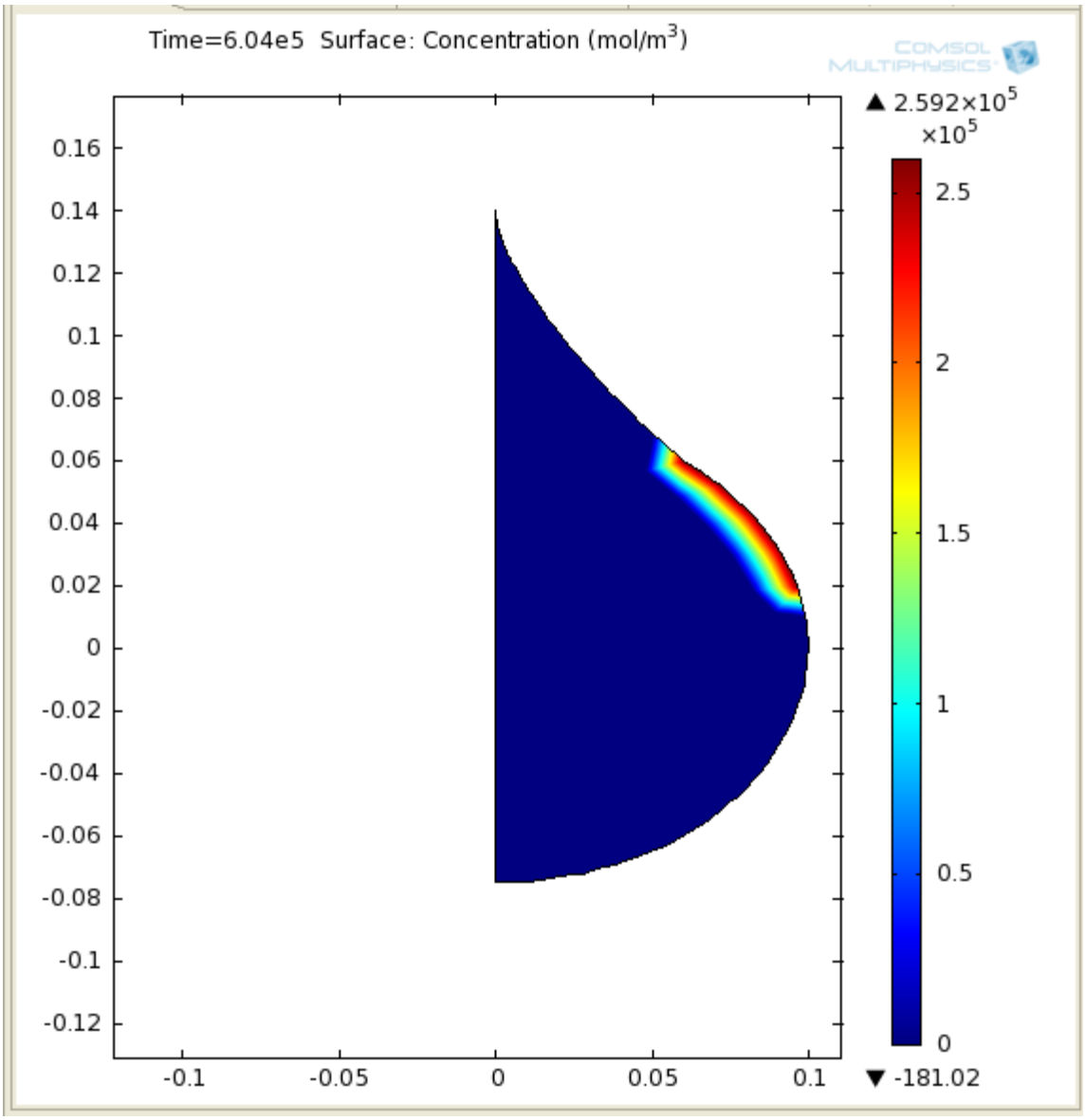

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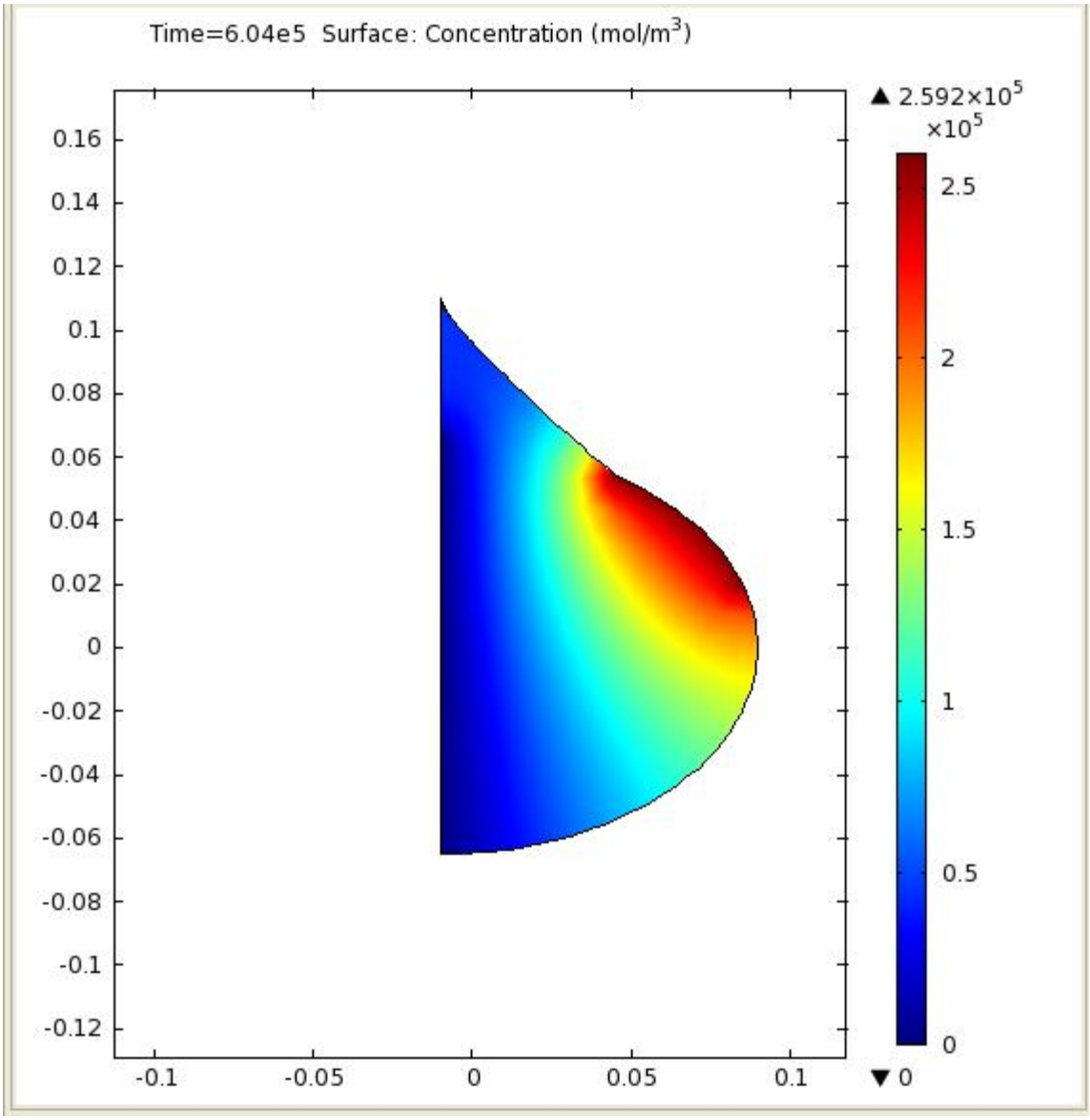
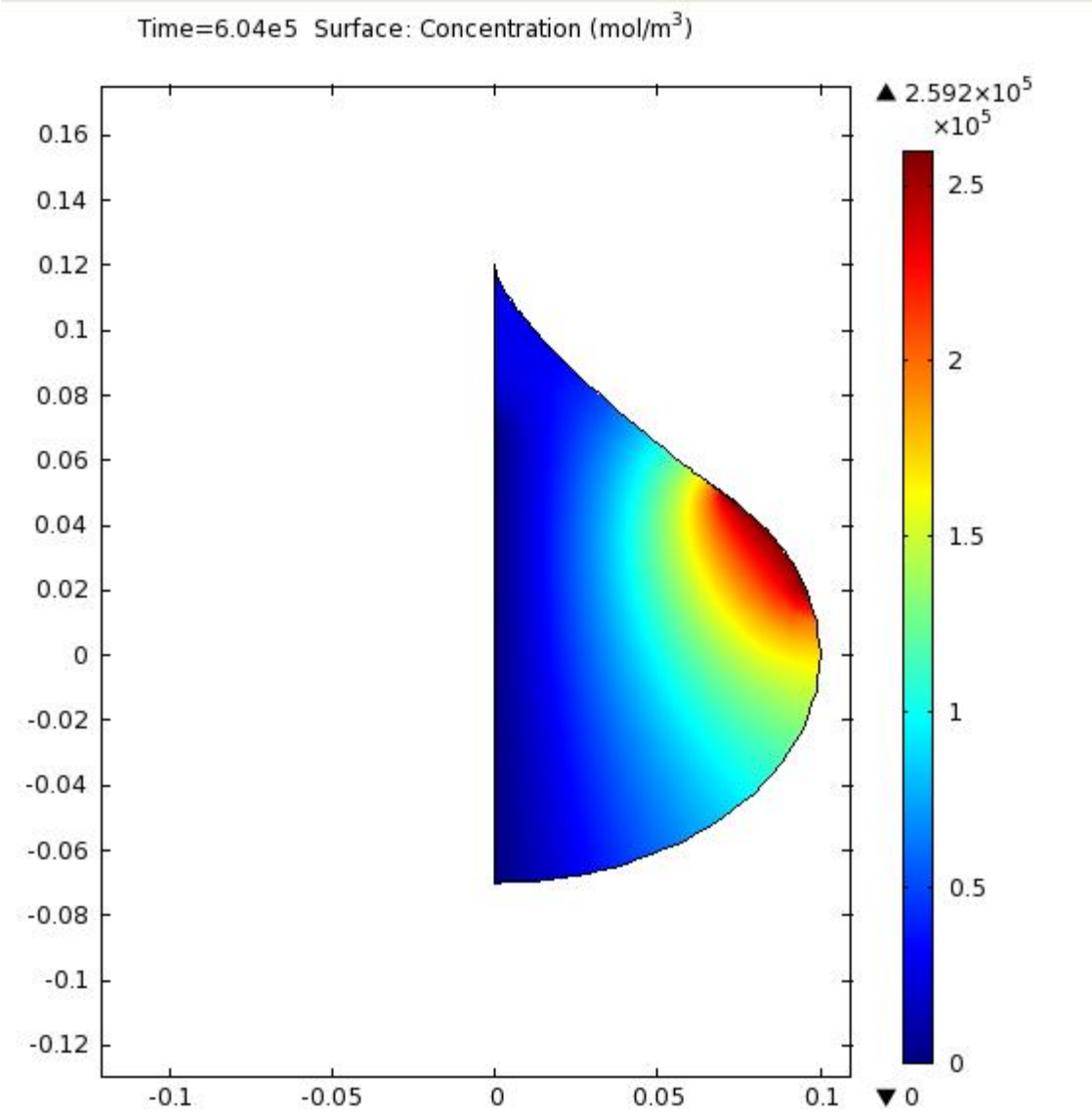


Diffusion of drugs with diffusivity of 2.7×10^{-1} cm^2/s after a week with breast volume 1.70×10^{-4} m^3



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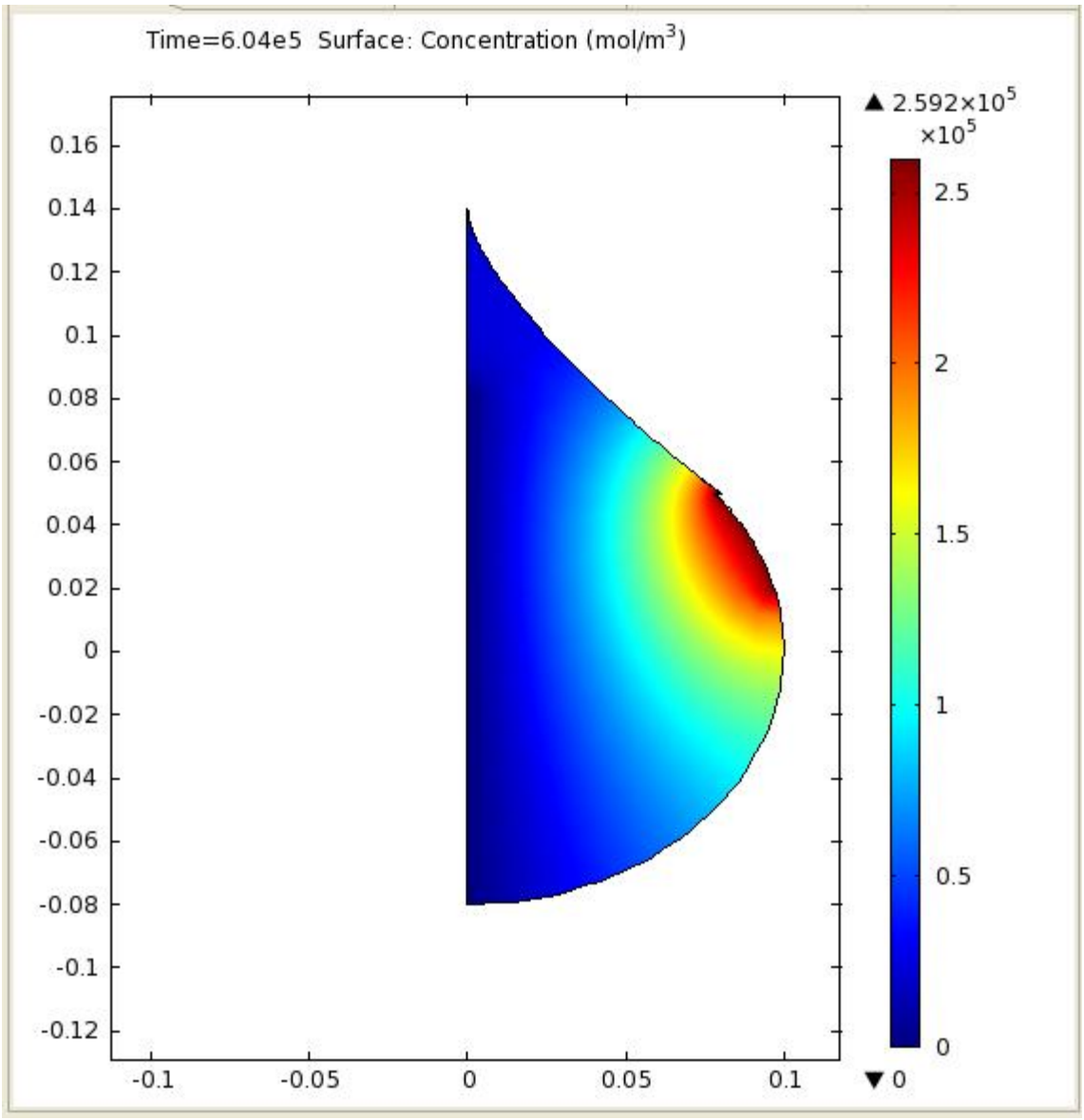
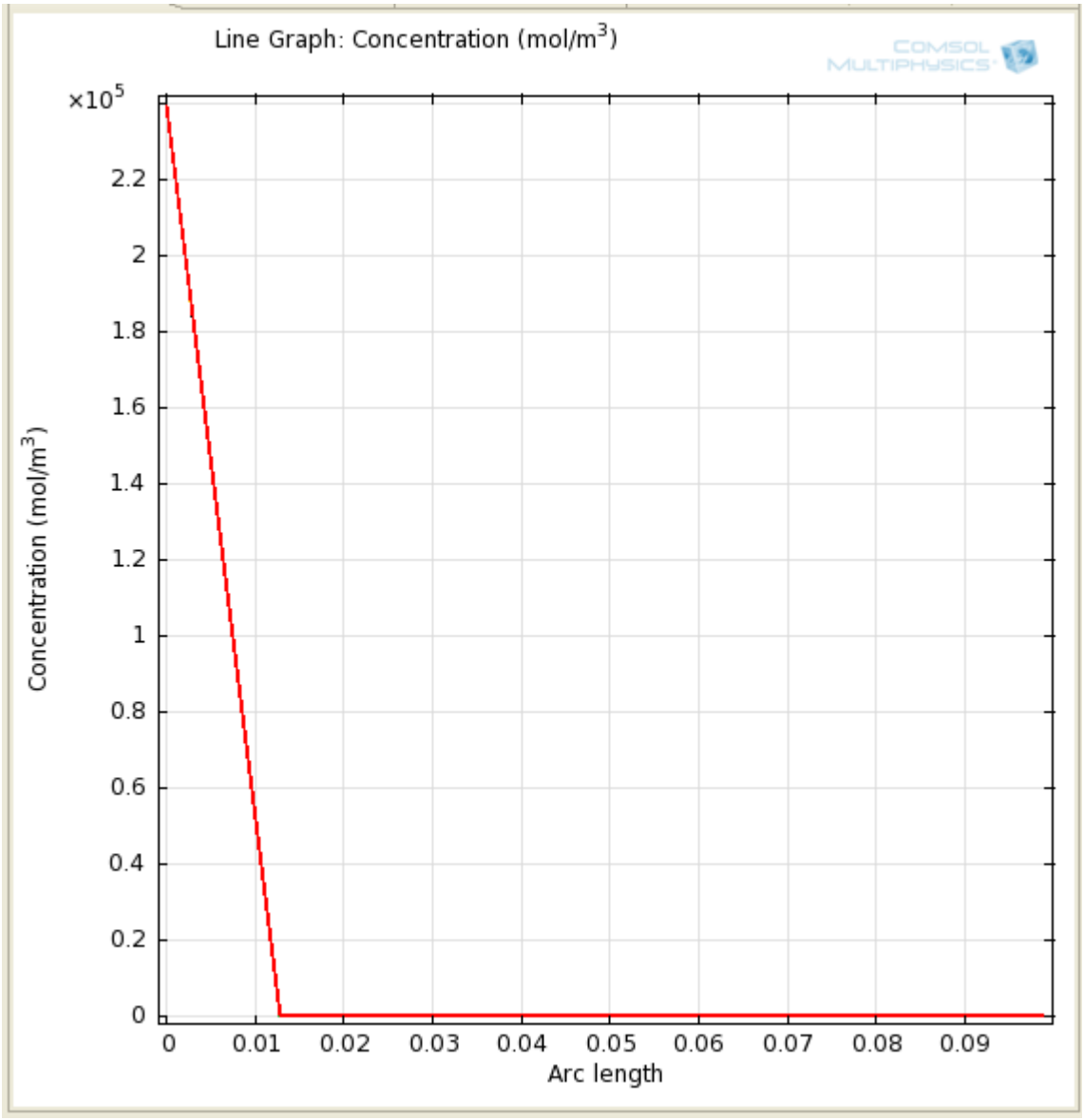


Diffusion of drugs with diffusivity of 2.7×10^{-1} cm^2/s after a week with breast volume 2.09×10^{-4} m^3

APPENDIX B

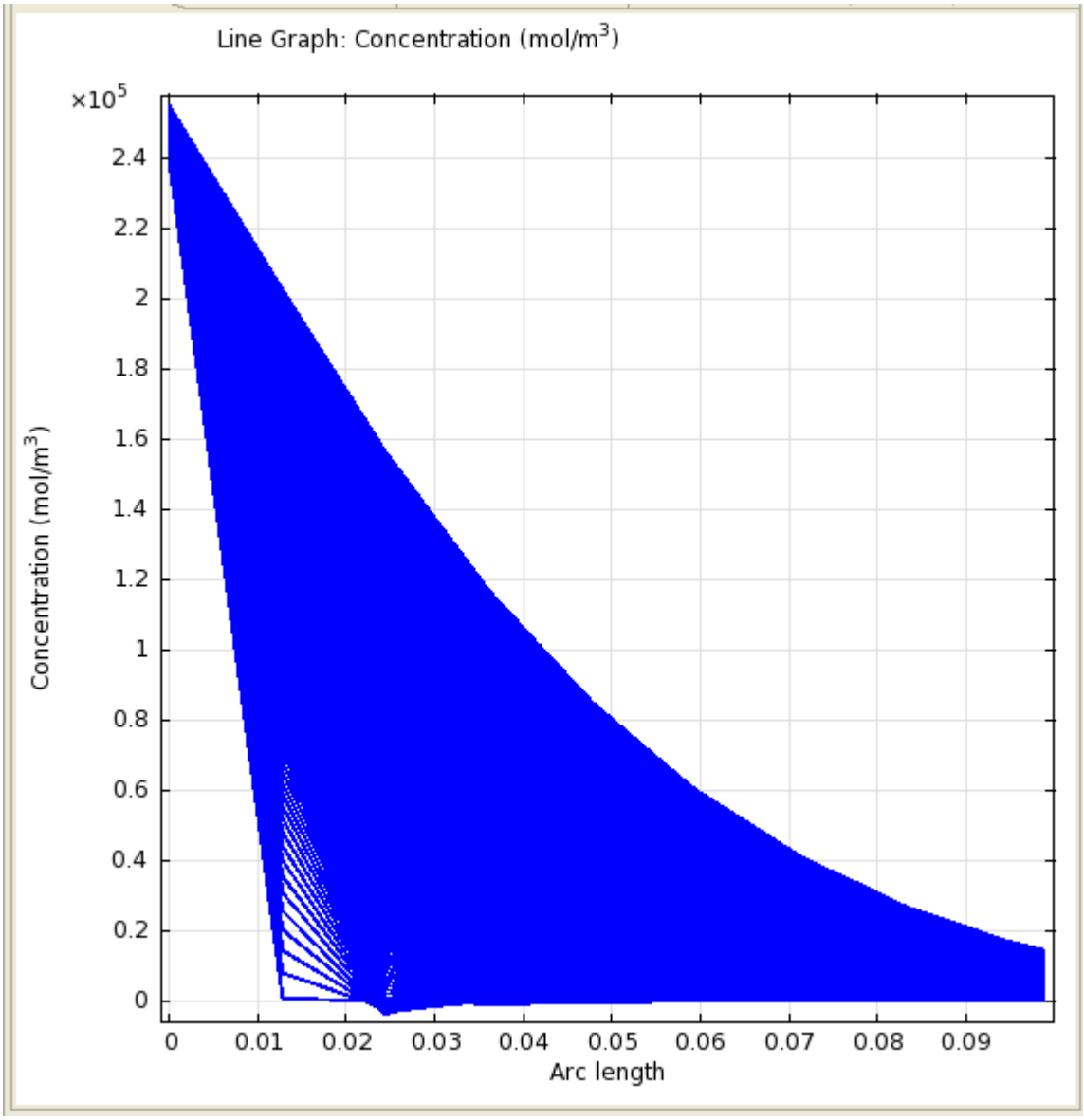
GRAPH FOR SIMULATION RUN

Graph of Concentration (mol/m^3) vs arc length



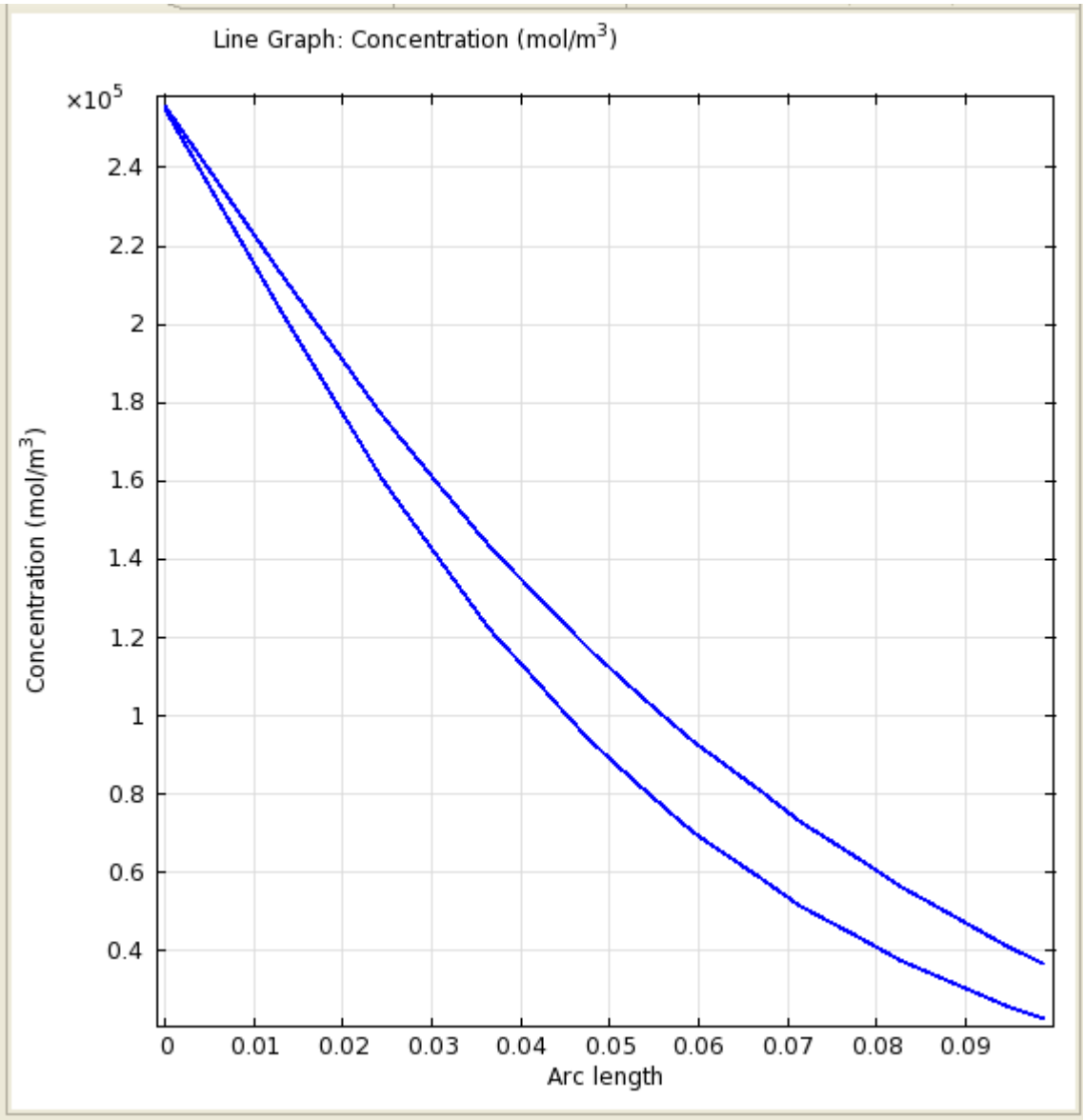
Graph for simulation run of drugs with diffusivity of 2.7×10^{-10} cm^2/s after a week with breast volume of 1.96×10^{-4} m^3

Graph of Concentration (mol/m^3) vs arc length



Graph for simulation run of drugs with diffusivity of 2.7x10^{-5} cm^2/s after a week with breast volume of 1.96x10^{-4} m^3

Graph of Concentration (mol/m^3) vs arc length



Graph for simulation run of drugs with diffusivity of 2.7x10^{-1} cm^2/s after a week with breast volume of 1.96x10^{-4} m^3