BREAST CANCER DRUG DELIVERY SYSTEMS BY DIFFERENTIAL DELIVERY SYSTEM USING FINITE ELEMENT ANALYSIS

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BREAST CANCER DRUG DELIVERY SYSTEMS BY DIFFERENTIAL DELIVERY SYSTEM USING FINITE ELEMENT ANALYSIS

SRI POOVEYNINTHRAN NAIR

Thesis submitted in partial fulfilment of the requirements
for the award of the degree of
Bachelor of Chemical Engineering (Biotechnology)

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JULY 2013

SUPERVISOR'S DECLARATION

We hereby declare that we have checked this thesis and in our opinion, this thesis is adequate in terms of scope and quality for the award of the degree of Bachelor of Chemical Engineering (Biotechnology).

Signature	:
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Date	: 1 JULY 2013

STUDENT'S DECLARATION

I hereby declare that the work in this thesis 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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Date : 1 JULY 2013

Dedication

Specially dedicated to my beloved family and friends

ACKNOWLEDGEMENT

Thanking the lord his help and guidance which enable me to complete this design project successfully.

Firstly, I would like to extend my sincerest gratitude to Dr. Balu Ranganathan, my Undergraduate Research Project supervisor, for his willingness in supervising the progress of my research proposal from its initial phases till the completion of it. Without his guidance, I would not be able to complete this project successfully. Next, I would like to extend my appreciation to the encouraging lecturers, and also my research members, for the roles they had played in giving me guideline and valuable advices during the progress of my proposal.

The experiences and knowledge I have gained throughout the process of completing this proposal will be invaluable experience for me. My sincere thanks also dedicated to my colleagues and lecturers who were there whenever I need their help and assistance. Their views and tips were useful indeed.

Last but not least, lots of love to my family members and my closest acquaintance. Not forgetting my beloved brothers and sisters, for their support, and for the audaciousness, as well as supporting me throughout my studies in University Malaysia Pahang (UMP). Thank you all.

ABSTRACT

Breast cancer is the most common form of cancer affecting women in Malaysia. Conventional drug treatment for breast cancer, chemotherapy would destroy the cancer cells because of the medicine targets on rapidly dividing cells. However, healthy cells and tissues in blood, mouth, intestinal tract, nose, nails, vagina and hair also divide rapidly, they could be damaged. A more promising technology called transdermal patch has been introduced due to side effects are common expected results from conventional treatment. Therefore, the aim of this study was to treat breast cancer by delivering drug from transdermal patch precisely and safely to targeted cancer cell so that reducing the side effects and dosage of drug used. The objectives of this study were to determine the drug concentration at breast tumor, to investigate the relationship between drug diffusivity and drug delivery efficiency, and to evaluate the efficiency of drug delivery under other parameters (i.e. deepness of tumor, temporal and spatial placement of transdermal patch). Available software, COMSOL was used in this study. Drug concentrations that able to diffuse and reach tumor in breast were studied. The simulation results showed that there was optimal drug diffusivity for maximum concentration of drug reached tumor in breast. However, below and higher than this drug diffusivity optimal value, the delivery of drug concentration was poorer when the lesser. Production of microchannels in the skin by microneedle can increase the drug diffusivity and ensure delivery of pharmacologically effective concentration of drug to the targeted site, breast cancer cell. Deeper the tumor grown within breast, lesser drug's concentration could be diffused to it. However, this could be solved by changing the place of transdermal patch application. The nearer the spatial placement of transdermal patch to tumor growth in the breast on the breast skin increased the effectiveness of drug delivery to tumor. The longer the temporal placement resulted in higher drug concentration could be delivered to breast tumor. However, this constant concentration gradient only achieved for less than one month. After this, the concentration gradient would become zero. As a conclusion, the drug diffusivity, deepness of breast tumor, spatial and temporal placement of transdermal patch must be taken into account when engineering, constructing and applying the transdermal patch in order to achieve the maximum breast cancer treatment with reducing the undesired side effects.

ABSTRAK

Kanser payudara merupakan jenis kanser yang paling utama di kalangan wanita di Malysia. Ubat rawatan konvensional untuk kanser payudara, kemoterapi akan menghancurkan sel-sel kanser kerana ubat target pada sel-sel yang membahagi dengan cepat. Namun, sel-sel dan rangkaian yang sihat dalam darah, mulut, saluran, usus hidung, kuku, vagina dan rambut juga membelah dengan cepat, mereka boleh dirosakkan. Satu teknologi yang lebih menjanjikan disebut patch transdermal telah diperkenalkan kerana kesan sampingan merupakan umum hasil daripada rawatan konvensional. Oleh itu, tujuan dari penelitian ini adalah untuk mengubati kanser payudara dengan menghantarkan ubat dari patch transdermal dengan tepat dan selamat pada sel kanser yang disasarkan supaya mengurangkan kesan sampingan dan dosis ubat yang digunakan. Objektif-objektif dari penelitian ini adalah untuk menentukan konsentrasi ubat pada tumor di payudara, mengkaji perhubungan antara keresapan ubat dengan keberkesanan penghantaran ubat, dan menilai keberkesanan penghantaran ubat dalam parameter yang berbeza seperti kedalaman tumor dalam payudara, penempatan spasial dan temporal patch transdermal pada kulit. Tersedia software, COMSOL digunakan dalam kajian ini. Ubat konsentrasi yang dapat menyebar dan mencapai tumor dalam payudara dipelajari. Keputusan simulasi menunjukkan bahawa ada ubat keresapan optimum untuk konsentrasi ubat maksimum capai pada tumor dalam payudara. Namun, di bawah atau di atas nilai keresapan ubat yang optimum ini, penghantaran konsentrasi ubat menjadi lemah ketika semakin berkurangan keresapan ubat. Produksi microchannels di kulit dengan microneedle dapat meningkatkan keresapan ubat dan memastikan penghantaran konsentrasi farmakologi ubat yang berkesan ke tempat yang disasarkan, sel kanser payudara. Semakin dalam pertumbuhan tumor dalam payudara, semakin berkurangan ubat dapat meresap ke tumor. Namun begitu, scenario ini dapat diatasi dengan menukarkan tempat menempatkan patch. Semakin dekat penempatan spasial patch transdermal pada pertumbuhan tumor dalam payudara pada kulit payudara meningkatkan keberkesanan penghantaran ubat untuk tumor. Semakin lama penempatan temporal menghasilkan kepekatan ubat yang boleh disampaikan untuk tumor payudara lebih tinggi. Namun, kecerunan konsentrasi ini hanya dapat dicapai kurang daripada satu bulan. Selepas ini, kecerunan konsentrasi ubat akan menjadi kosong. Sebagai kesimpulan, keresapan ubat, kedalaman pertumbuhan tumor dalam payudara, penempatan spasial dan temporal transdermal patch harus diperhitungkan sewaktu kejuruteraan, membina dan melaksanakan patch transdermal untuk mencapai rawatan kanser payudara maksimum dengan mengurangkan kesan sampingan yang tidak diingini.

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C	Concentration
D	Diffusivity

LIST OF ABBREVIATIONS

COMSOL	Multi-Physics Software Package

1 INTRODUCTION

This chapter presents the overview of the background for disease of breast cancer and breast cancer drug therapies. The problem statement of current technology is also stated in this chapter. The objectives of the study also presented in this chapter. The scope and importance of work are defined. Lastly, this chapter also outlines the organization of the thesis.

1.1 Background of study

Breast cancer is the most common form of cancer among women other than other skin cancer, and the number of cases for breast cancer is increased annually. About one in nineteen women in Malaysia are at risk. Breast cancer is also the leading cause of cancer-related death for women. In Peninsula Malaysia, the mortality rate per 100,000 showed an increase from 3.7 per 100,000 in 1982 to 5.8 per 100,000 in 1990. However, since only one-third of deaths in Peninsula Malaysia were medically certified, the mortality rate from breast cancer was actually higher. (Yip, C. H. and Ng, E. H., 1996).

Generally, chemotherapy is the common drug therapy for breast cancer. Many anticancer drugs are designed to simply kill cancer cells. They are often in a semi-specific fashion because the anticancer drugs target on rapidly dividing cells. Similar to cancer cells, the normal cells in blood, mouth, intestinal tract, nose, nails, vagina and hair also divide rapidly. Consequently, the distribution of anticancer drugs in healthy organs or tissues is especially undesirable due to the potential for severe side effects. This phenomenon greatly limits the maximal allowable dose of the drugs. However, low local drugs' concentration will cause less effect on destroying the cancer cells. Therefore, there is still a need for high or frequent drugs dosing.

To overcome such limitations, a new and more promising technology, transdermal technology has been introduced for breast cancer drug therapy. This application provides an alternative route for delivering drugs to cancer cells, which is through the largest organ of humans' bodies, skin. In this method, a transdermal patch is purposely engineered and constructed to allow the delivering of drugs precisely to the targeted

cancer cells with fewer side effects. Site-specific drugs delivery is a concept that has the potential to increase local drugs' concentrations, and thereby produce more effective medicines with reducing the dosage of drugs used.

1.2 Problem statement

The new technology, transdermal patch allows the delivering of anticancer drugs to targeted cancer cell as effectively as possible without side effects and reducing the dosage of drugs used. However, transdermal application has limitation due to the remarkable barrier properties of the outermost layer of skin, stratum corneum. This layer is mainly consisted of lipids, has no blood flow, and thus plays a key role in limiting the diffusion of drugs to the bloodstream. For transdermal drugs delivery system to be effective, the drugs must obviously be able to penetrate this skin barrier and reach the targeted cancer cells. To achieve this, suitable modification has been made on the transdermal delivery system. It is hard to deny that drug diffusivity is a very important factor to be considered.

1.3 Objectives

The aim of this study was to treat breast cancer by delivering drug from transdermal patch precisely to targeted cancer cells so that reducing the side effects and dosage of drugs used. This can be achieved by the following specific objectives:

1. To convert Materilaise's Interactive Medical Image Control System (MIMICS) image files into comsol,
2. To determine the drug concentration at breast tumor
3. To investigate the relationship between drug diffusivity and drug delivery efficiency, and
4. To evaluate the efficiency of drug delivery under other parameters (i.e. deepness of tumor, temporal and spatial placement of transdermal patch).

1.4 Research scope

This study mainly focused on the efficiency of drug delivery from transdermal patch, which was evaluated by response parameter, drug concentration successfully reaching at the breast tumor. The study was carried out by using COMSOL software. Before implementing the COMSOL software, data collection for drug diffusivity and breast volume were needed. After data collection, Materilaise's Interactive Medical Image Control System (MIMICS) image files where converted by using COMSOL software. After converting the image files, simulation was run by using COMSOL software. The simulation was conducted with identified independent variables (i.e. drug diffusivity, deepness of tumor, temporal and spatial placement of transdermal patch). Simulation produced with different parameters was saved for further analyses. Graphs that relate the drug concentration at breast tumor were also developed. From the developed graphs, the association between the efficiency of drug delivery and drug concentration could be made.

1.5 Rationales and significances

This study had the significance to do a new strategy on developing a more promising technology to treat breast cancer. This study also important for eliminate the side effects or toxicities caused by conventional drug therapies. This was replaced by the application of new technology, transdermal patch. The other significance was including reducing the drug dosage used for breast cancer treatment. Reduce side effects and drug dosage used, thereby decreasing the cost of breast cancer treatment.

1.6 Organization of thesis

This thesis is mainly delegated into five different chapters. In first chapter, the background of study, problem statement, objectives, scope and significances of project are reviewed in order to list out the tasks and act as a guideline for this study. The statistic of breast cancer, skin structure, theoretical background, previous studies and

some basic information related to the project title are detailed in the second chapter. Chapter 3 presents the methodology used from the starting until the end of the study, which including the material or instrument used for completing the study, designing the simulation and how to run the simulation. An overview of overall methodology that designated in a flow chart as guideline for task sequences also included in this chapter.

Chapter 4 shows the results obtained from the simulation. Several graphs made to preview the relationship between the drug concentration and time, which were resulting from different parameters also presented. At the end of this chapter, results, some of findings and the sources of errors that affect the simulation outcomes are discussed in details. The last chapter, chapter 5 states the conclusions of the study. Recommendations for improvement of the study in the future also are outlined in this chapter.

2 LITERATURE REVIEW

This chapter includes the statistic of breast cancer, drug therapies of breast cancer, structure of skin, theories of transdermal application and some basic information related to the study. Studies on some recent patents related to the field of transdermal patch are also presented.

2.1 Overview of breast cancer statistic

The problem of cancer in Malaysia is in a growing trend, and breast cancer is the most common cancer among women. 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 (Figure 2.1).

Figure 2.1: Breast cancer in University Malaya Medical Centre, Kuala Lumpur 1993-2003, with total number of 1818 cases.

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

Breast cancer formed 30% and 31.1% of newly diagnosed cancer cases in women in 2002 and 2003. This was followed by cancer of the cervix, which only formed 12% and 12.9% of total female cancers in 2003 and 2003 respectively (Figure 2.2).

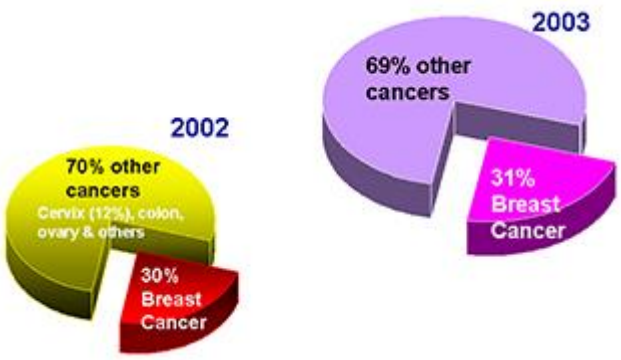


Figure 2.2: Percentage of different kinds of cancer in Malaysian women, in the year

of 2002 and 2003.

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

The number of deaths form breast cancer also showed an increasing trend, which were 260, 320 and 339 for the year of 1994, 1995 and 1998 respectively. And within these numbers, only 1/3 of all deaths in Malaysia were medically certified (Table 2.1). This indicated that the awareness of breast cancer among women still low and not effective enough. Within the detected women with breast cancer, only 55.6% of Malaysian women presented with early stage breast cancer (Stage 0 – 1) compared with 72% of Singaporean women in 1990. (Yip, C. H. and Ng, E. H., 1996) From the year of 1993 to 2004, there were 30-40% of the patients presented in the late stage and although women are now presenting with smaller tumours, the decrease in size is not significant. (College Of Radiology Breast Health Information Centre, 2008).

Table 2.1: Deaths from cancers in Malaysia women for the years of 1994, 1995 and 1998

	1994	1995	1998
Breast	260	320	339
Lung	244	254	272
Cervix	165	142	177
Colorectal	128	164	149
Leukemia	128	142	139
Stomach	99	105	103
Liver	98	102	106
Ovary	88	95	122

Source: Vital Statistic Malaysia

2.2 Conventional breast cancer drug therapy

The most common breast cancer drug therapy, also known as chemotherapy, in simplest sense, is a treatment with the aid of drugs that killing microorganisms or cancerous cells. The chemotherapy drugs can be swallowed by someone as tablets or capsules, or injected intravenously through the veins. When the drugs reach cancer cells, the drugs work by disrupting the growth of cancer cells.

However, when the drugs circulate in the blood, they not only reach cancer cells, but wherever they are in body. Many anticancer drugs are designed simply kill cancer cells. They have no the capability to distinguish between the cancer cells and normal cells. In contrast, they work by killing the cells that are actively growing and dividing into new cells. Cancer cells do grow and divide much more often than normal cells because most normal cells grow and divide in a precise, orderly way. Thus, cancer cells are more likely to be killed by the chemotherapy drugs. However, there are still some normal cells do divide and grow rapidly such as cells in hair follicles, nails, mouth, intestinal tract and bone marrow. Chemotherapy drugs can unintentionally harm these other types of rapidly dividing cells. As a result, the distribution of anticancer drugs in healthy and normal cells is especially undesirable due to the potential for severe side effects.

The side effects caused are significantly depending on the types of drugs, drugs dosage used, how long the drugs are taken and how though of the own body of the one who

consuming these chemotherapy drugs. The possibilities of common side effects caused by some different kinds of anticancer drugs are discussed with details in the next sub-topic.

2.2.1 Docetaxel

Docetaxel is one of the taxane drugs that were originally developed from the yew tree. Docetaxel is a man-made drug that was first made from the needles of the yew tree. It is known by its brand name, Taxotere. It works by stopping the cancer cells from separating into two new cells, so it blocks the growth of the cancer. Common side effects caused by this drug are as following (Cancer Health UK, 2009):-

- Have temporary drop in the number of blood cells made by the bone marrow. For example, a drop in white blood cells result a person with increased risk of getting an infection. When there is a dropping of red blood cells, a person will easy feel tired and breathless. Besides, bruising easily is another common side effect due to a drop in platelets.
- Fatigue is the most disruptive side effect where tiredness often carries on after treatment has just ended.
- Patients may experience fluid retention such as swelling of the hands and feet and resulting in weight gain and breathless.
- Some people develop soreness, redness and peeling on the palms of the hands and soles of the feet.
- Patients may have rash, hair loss, sore mouth, diarrhoe, numbness and tingling in hands and feets, allergic reaction during the infusion and fingernails become discoloured.
- Docetaxel may have a harmful effect on a baby developing in the womb.

2.2.2 Doxorubicin (adriamycin)

Doxorubicin works by binding to the cancer cells' DNA and blocking an important enzyme called topo-isomerase II. This makes the DNA get tangled up and the cancer

cells cannot divide and grow. The common side effects associated with doxorubicin are listed below (Cancer Health UK, 2009):-

- Have temporary drop in the number of blood cells made by the bone marrow. For example, a drop in white blood cells result a person with increased risk of getting an infection. When there is a dropping of red blood cells, a person will easy feel tired and breathless. Besides, bruising easily is another common side effect due to a drop in platelets.
- Fatigue during and after treatment.
- Feeling or being sick may be severe.
- Urine may become a pink or red colour for one or two days after treatment.
- Patients may have hair loss, sore mouth, sensitivity to sunlight, black or brown lines may appear in the creases of skin, watery eyes and conjunctivitis but very rare to happen.
- A woman may stop or temporarily stop having periods, and loss of fertility.
- Doxorubicin may have a harmful effect on a developing baby.

2.2.3 Herceptin (trastuzumab)

Herceptin is a monoclonal antibody. It targets a protein called HER2. This protein is found in roughly 25 to 30 percent of breast cancers. By interfering with this protein, this medicine can stop cancer cell growth. With this drug, the common side effects are:-

- Breathing difficulties.
- Chest pain or palpitations.
- Cough.
- Dizziness or fainting.
- Fever or chills, sore throat.
- Skin rash, itching or hives.
- Swelling of the legs or ankles.
- Usually weak or tired.
- Loss of appetite.
- Headache.
- Muscle aches.

2.2.4 Paclitaxel (taxol)

Paclitaxel is in a class of drugs known as taxanes. It slows or stops the growth of cancer cells in body. Side effects from paclitaxel are common, and include:-

- Nausea and vomiting.
- Loss of appetite.
- Change in taste.
- Thinned or brittle hair.
- Pain in the joints of the arms or legs lasting 2-3 days.
- Changes in the colour of the nails.
- Tingling in the hands or toes.

2.2.5 Methorexate (maxtrex)

Methotrexate is similar to a normal body molecule called folinic acid, but has a slightly different in structure. So it stops some cells working properly. Cancer cells need to make and repair DNA to grow and multiply. Anti-metabolites often stop cells making and repairing DNA. Methotrexate also stops some normal cells working properly, causing side effects as following (Cancer Health UK, 2009):-

- Have temporary drop in the number of blood cells made by the bone marrow. For example, a drop in white blood cells result a person with increased risk of getting an infection. When there is a dropping of red blood cells, a person will easy feel tired and breathless. Besides, bruising easily is another common side effect due to a drop in platelets.
- Fatigue during and after treatment.
- A patient may experience taste changes, mouth sores, diarrhoe, gritty eyes and hair loss or hair thinning.
- This drug may harm a baby developing in the womb.

Besides of individual chemotherapy drugs, there are some chemotherapy combinations of drugs used for killing cancer cells such as doxorubicin and cyclophosphamide (AC), methotrexate, mitozantrone and mitomycin (MMM), epirubicin, cyclophosphamide and

fluoruocil (FEC) and the list goes on. These combinations are kwon as combination regimens and different combinations of drugs have different side effects.

2.3 Materilaise's interactive medical image control system (MIMICS)

Materilaise's Interactive Medical Image Control System (MIMICS) is an interactive toolbox for the visualization and segmentation of stacked images (CT, microCT, MRI,…) and 3D rendering of objects. It provides the users the tools to convert the images to 3D objects and prepare these objects for different application domains.

Mimics Software is developed by Materialise NV a Belgian company that is specialized in additive manufacturing software and technology. Nowadays, engineers are playing a crucial role by supporting doctors and improving the quality of life of patients through optimized implants and devices, scientifically validated surgical procedures, studying surgical simulation, and more. Together, these Engineering professionals are working towards a better and healthier world.

Mimics offers the following services as shown in Figure :

1. DICOM to 3D
2. 3D to CAD
3. 3D analysis
4. Medical models
5. FEA/CFD modeling

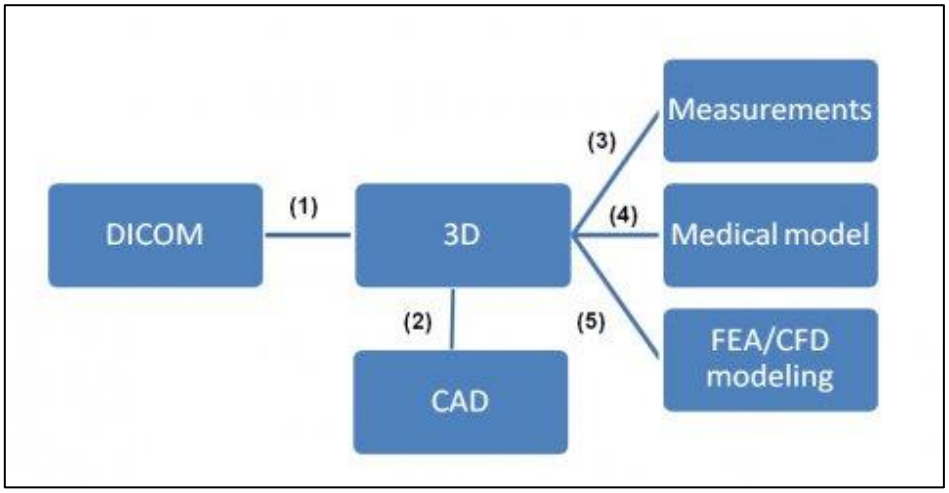


Figure 2.3: Process of converting in Mimics.

Source: application of ddm in medical implant

Mimics most involvement is in the biomedical engineering area and it's a purpose for research and development in various medical specializations such as:

- Orthopedic.
- Cranio-maxillofacial.
- Cardiovascular.
- Pulmonology.
- Dentistry.
- Orthoses & Prostheses.

As such Mimics provides a link between stacked images and the following:

- Rapid prototyping.
- Visualization.
- Finite element analysis.
- Computational fluid dynamics.
- Computer aided design.
- Surgical simulation.
- Porous structures analysis.

Mimics modules:

Mimics consist of six modules, the links between the base program, the modules and the main application areas as shown in figure 2.4

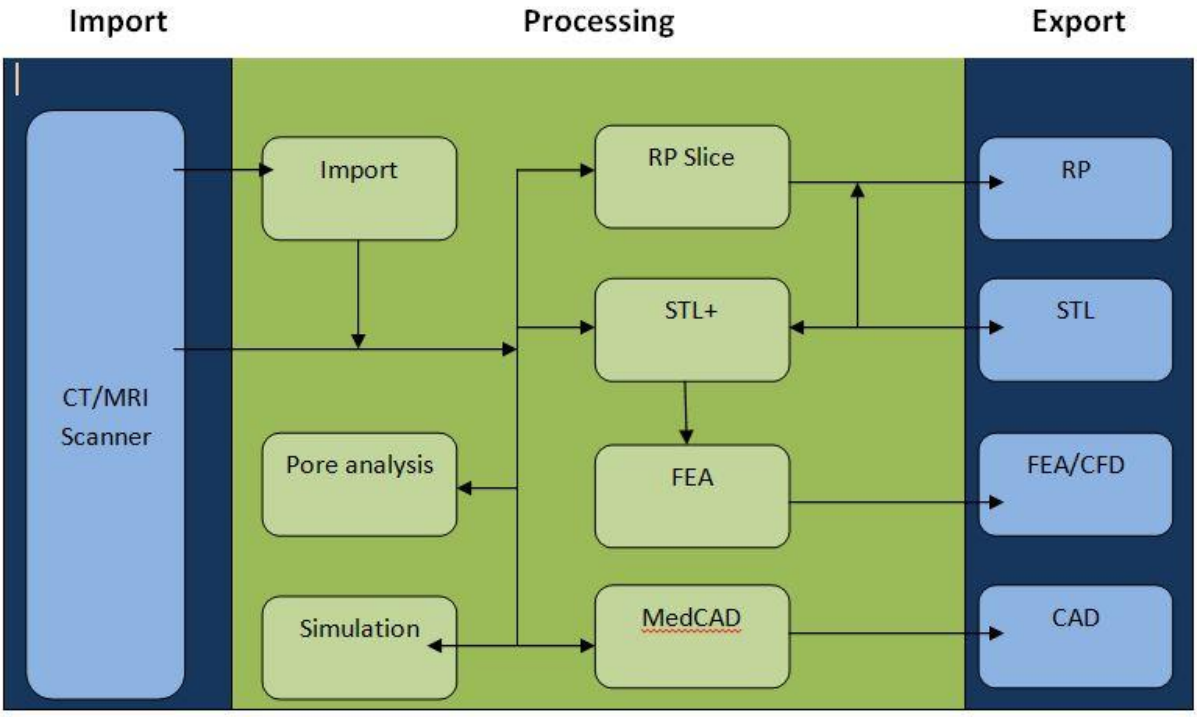


Figure 2.4 : Mimics six modules

Source: application of ddm in medical implant

2.4 Comsol

2.4.1 Introduction

COMSOL is all about flexible platform that allows even novice users to model all relevant physical aspects of their designs. Advanced users can go deeper and use their knowledge to develop customized solutions, applicable to their unique circumstances. With this kind of all-inclusive modeling environment, COMSOL gives us the confidence to build the model we want with real-world precision.

Certain characteristics of COMSOL become apparent with use. Compatibility stands out among these. COMSOL requires that every type of simulation included in the package has the ability to be combined with any other. This strict requirement actually mirrors what happens in the real world. For instance in nature, electricity is always accompanied by some thermal effect; the two are fully compatible. Enforcing compatibility guarantees consistent multiphysics models, and the knowledge that, even as the COMSOL family of products expands, we never have to worry about creating a disconnected model again.

COMSOL Multiphysics also has several problem-solving benefits. When starting a new project, using COMSOL helps us to understand our problem. You are able to test out various geometrical and physical characteristics of your model, so we can really hone in on the important design challenges. The flexible nature of the COMSOL environment facilitates further analysis by making "what-if " cases easy to set up and run. We can take our simulation to the production level by optimizing any aspect of our model. Parameter sweeps and target functions can be executed right in the user interface. From star t to finish, COMSOL is a complete problem-solving tool.

As we become a more experienced user of COMSOL, our confidence in computer simulation will grow. We will become a more efficient modeler, and the results will show it.

2.4.2 Concept

COMSOL Multiphysics brings an unprecedented level of clarity to our simulation work by giving you both an organized model overview and a streamlined model-building process. The COMSOL user interface reduces clutter and redundant tasks, so our attention can be focused on the substance of our design studies resulting in increased productivity.

2.4.2.1 Organize

The COMSOL Desktop helps us organize our simulation by presenting a clear overview of our model at any point. It uses functional form, structure, and aesthetics as the means to achieve simplicity for modelling complex realities. For instance, task-specific tools

appear on the Desktop right when we need them; showing only what is currently possible, which removes uncertainty from model building and brings order to our simulations. The Desktop is made up of several windows, which may or may not be displayed depending on the need. These windows include the Model Builder, Settings, Graphics, Messages, Progress, Help, and others as showed in figure 2.5 and figure 2.6.

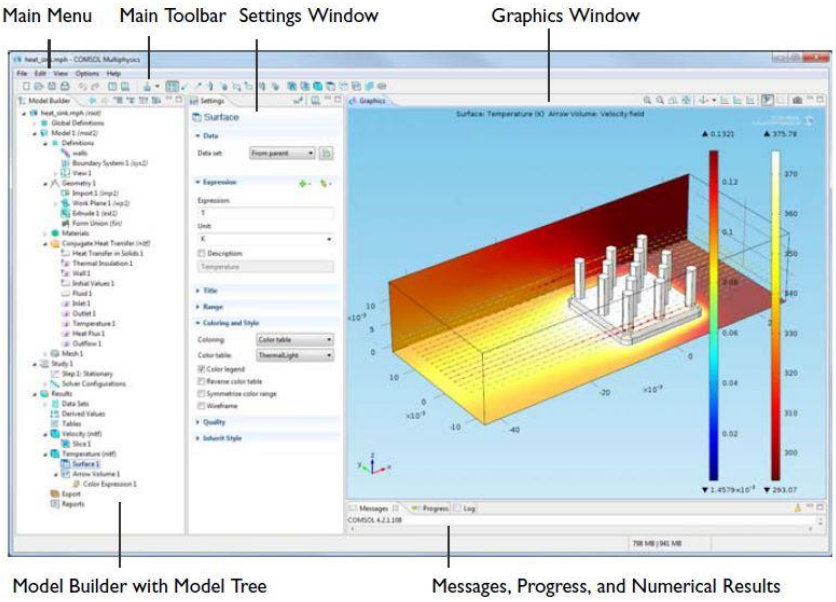


Figure 2.5 : COMSOL Desktop

Source: Introduction to Comsol Multiphysics® version 4.2a

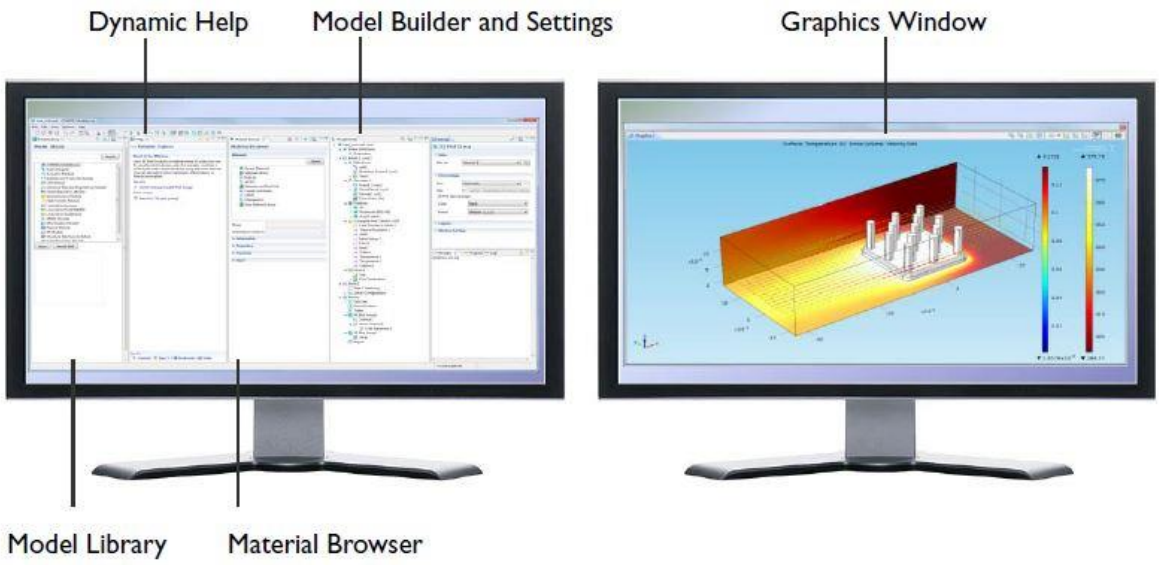


Figure 2.6 : COMSOL Model Builder, Settings, Graphics window

Source: Introduction to Comsol Multiphysics® version 4.2a

2.5 Transdermal application

Transdermal patch is providing an effective alternative route for delivering drugs to cancer cells, which is through the largest organ of human bodies, skin. Transdermal delivery of medications was foreshadowed in earlier eras by the use of certain plasters and ointments. (Stanley, S., 2004)

Since the drugs are delivered directly from human's skin to bloodstream, it has provided a wide variety of advantages compared to chemotherapy. First of all, side effects associated with traditional delivery method could be eliminated due to site-specific delivery of drugs to the targeted site, cancer cells without circulating through the whole body like chemotherapy. The second benefit resulted from this shortened metabolic pathway of transdermal route is allowing for reduced pharmacological dosing. (Girish, C., 2006) Studies have shown that when formulations are delivered topically, as little as 5% of the drug can be make it to the cells where we need it when we taking a drug orally. This is because a large proportion of drug is destroyed and neutralized in stomach, intestine and liver before reaching bloodstream. On the other hands, transdermal technology ensures as much as 95% of a supplement reaches the cells it is needed. (Department of Pharmacology, University of Dublin)

Some other benefits of using transdermal application are including the transdermal patch provides the controlled release of drugs directly into the bloodstream through intact skin. By delivering a steady flow of drugs into the bloodstream for an extended period of time, transdermal system can avoid peak- and – effect of oral or injectable therapy and can enable more controlled effective treatment. Furthermore, transdermal patch application is convenient to use because it offers multi-day dosing and is flexible to terminate the drug administration by simply removing the patch from skin when there is toxicity observed. Last but not least, patients who have difficulty with swallowing pills or receiving injections, patch offers an effective alternative for them. The pros of transdermal appliction over chemotherapy are summarized in the table below (Table 2.2).

Table 2.2: Differences between transdermal application and chemotherapy.

Chemotherapy	**Transdermal Application**
Form of delivery of drugs is oral route.	Provides an alternative route for delivering drugs, which is through skin.
Poor bioavaibility.	Site-specific drug delivery to obtain high local drug concentration.
Peaks and valleys in medication level.	Permits constant dosing.
A large proportion of drug are destroyed and neutralized in stomach, intestine and liver before reaching bloodstream.	Low circulating drug concentration avoiding the risk of side effects.
Gastrointestinal pathway, leading to a need for high and/or frequent dosing.	Allows for reduced pharmacological dosing due to the shortened metabolic pathway of the transdermal route.
Cost prohibitive and inconvenient.	Convenient, particularly when patches are applied once every several days.
As little as 5% of the drug can make it to the cells where we need it.	As much as 95% of a supplement reaches the cells where it is needed.

2.6 Patch design

Generally, patches are composted of four main components such as (1) Liner that protects the patch during storage and will be removed when prior to use. (2) A compartment in which the drug itself is held, which is in direct contact with release liner. (3) Adhesive that serves to adhere the components of the patch together along with adhering the patch to the skin. (4) A permeable membrane that controls the release of the drug into the skin. (5) Backing that acts as a protective seal that forms the external surface and protects the medication from the outer environment (Figure 2.7).

Figure 2.7: Components of transdermal patch, which consisted of five main key elements such as liner, drug, adhesive, membrane and baking

Source: Shreeraj, S. (2008)

There are four main types of transdermal patches in market, which are single-layer Drug-in-Adhesive, Multi-layer-Drug-in-Adhesive, Reservoir and Matrix. In the Single-layer-Drug-in-Adhesive, the drug is included directly within the skin-contacting adhesive. The adhesive layer is responsible for the releasing of the drug, and serves to adhere the various layers together, along with the entire system to the skin. The adhesive layer is surrounded by a temporary layer and a backing. The Multi-layer Drug-in-Adhesive is almost similar where the drug is incorporated directly into the adhesive. But, this multi-layer system adds another layer of drug-in-adhesive, usually separated by a membrane. In contrast, the Reservoir transdermal system design includes a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive. The adhesive component of the product can either be as a continuous layer between the membrane and the release liner or as a concentric configuration around the membrane. In Matrix type, the Matrix has a drug

layer of a semisolid matrix containing a drug solution or suspension, which is in direct contact with the release liner. The adhesive layer in this patch surrounds the drug layer partially overlaying it. (Yury, B., 2006).

2.7 Theory of transdermal drug delivery system

A transdermal drug delivery device, transdermal patch works in a very simply way. When the patient applies the patch to the skin, the medication is releasing form the vehicles and begins permeating through the skin into bloodstream at a rate regulated by the membrane. Once succeed to penetrate through the skin barrier, the drug will be uptake by the capillary network and finally reaches the targeted cancer cells. Lastly, activation of the pharmacological response to the cancer cells is happening. The whole process can be listed as below (Girish, C., 2006):-

1. Release of the medicament from the vehicle.

2. Penetration through the skin barrier.

3. Uptake of the drug by the capillary network in the dermal papillary layer.

4. Activation of the pharmacological response. (Banker, G.S. and Rhodes, C.T., 1990)

In this study, the second step, penetration through the skin barrier was the main key element to be emphasized. In theory, this step is carried out through a passive diffusion process and it will be discussed in the coming sub-topic later.

2.7.1 Penetration of drug from patch through passive diffusion process

As introduced in the sub-topic above, the transportation of drug from patch to bloodstream is done through a passive diffusion process (Figure 2.8). In other words, a drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. Then, the drug is diffused into the body directly from transdermal patch across the skin barrier due to there is high concentration of drug

on the patch and low concentration of drug in the bloodstream. The drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.

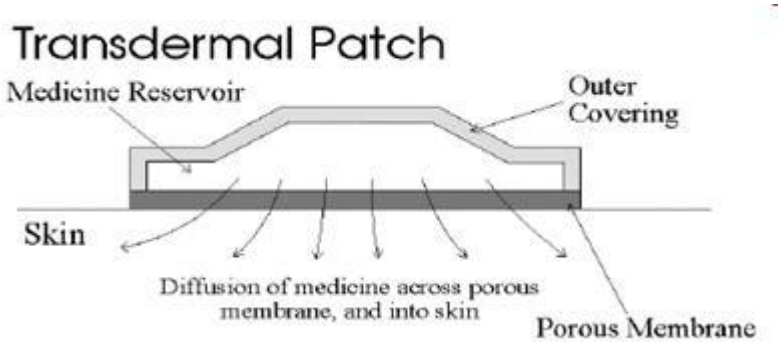


Figure 2.8: Mechanism of action of transdermal patch, diffusion.

Source: Shreeraj, S. (2008)

2.7.2 Fick's law

As described earlier, the transportation of drug across the skin barrier into bloodstream occurs primarily by passive diffusion. This is driven by the applied concentration of drug on the surface of the skin, and is best be governed by using Fick's Law of Diffusion, which states that the steady state of drug flux across a membrane can be expressed as:

$$\partial c/\partial t = D [(1/r) (\partial/\partial r) (r \partial c/\partial r) + \partial^2 c/\partial z^2]$$

Where c is the concentration of the drug and D is its diffusivity. (Datta, A. and Rakesh, V., 1996).

2.8 Skin barrier

Skin is the largest human organ and consists of three functional layers: epidermis, dermis and subcutis (hypodermis). Skin has a wide variety of functions. One major function of the skin is to protect the organism from water loss and mechanical, chemical, microbial, and physical influences. These protective properties are provided by the outermost layer of the skin, the epidermis. Out of the five layers of the epidermis, it is mainly the uppermost layer, stratum corneum which forms the permeability barrier (Figure 2.9). The dermis, located below the epidermis is an elastic layer that provides structural support, contains nerve endings, and a rich microcapillary network at the epidermal-dermal junction. The anatomical features of the skin provide an opportunity for minimally invasive transdermal delivery and rapid absorption of drug for systemic distribution.

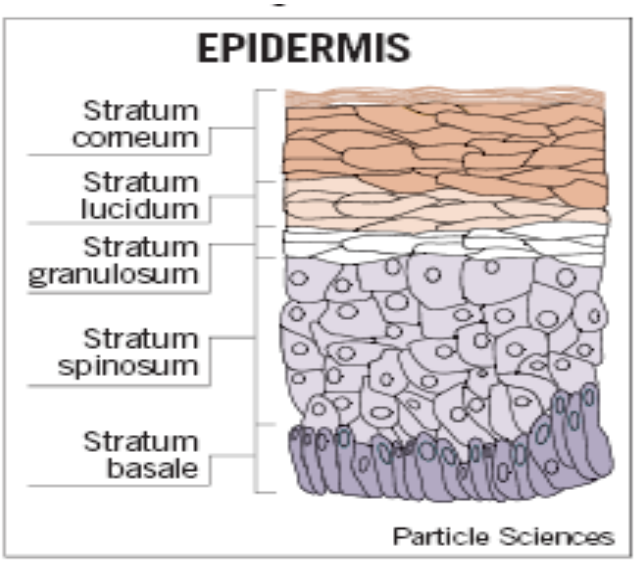


Figure 2.9: Schematic structure of the epidermis, which consisted by five layers.

Source: Drug Development Services (2009)

The stratum corneum, also called the horny layer, consists of cells called corneocytes that are embedded in a multilamellar, lipid-enriched extracellular matrix. The molar ratio of these barrier lipids were found to be cholesterol ester (15%), saturated long chain free fatty acids (16%), cholesterol (32%) and ceramides (37%). Higher molecular weight candidates (> 500Da) or large molecules fail to penetrate the uppermost of skin

barrier, stratum corneum. There have been challenges in expanding use of the transdermal technology to the delivery of peptides, proteins, and other macromolecules. These biopharmaceuticals cannot permeate the skin's outer stratum corneum layer at levels or rates that achieve significant therapeutic effect. Therefore, it is generally accepted that the extracellular stratum corneum lipids play a key role in limiting the diffusion of drugs through stratum corneum. (Drug Development Services, 2009).

2.9 Enhancement techniques

Microneedles are devices which are utilized in order to increase the permeability of the skin barrier and allow drug delivery. Their small size offers the potential advantages of delivering large molecules across the stratum corneum without extreme pain to the patients. (Jones, S. A.). The microneedle concept employs an array of micro-scale needles that can deliver drug into the epidermis and dermis, which ultimately leads to uptake by the capillaries for systemic delivery but too short for the microneedles to cause any pain to the receptors in the dermis (Figure 2.9). This is the reason for the device being less painful to the patients. (Kumar, R. & Philip, A., 2007).

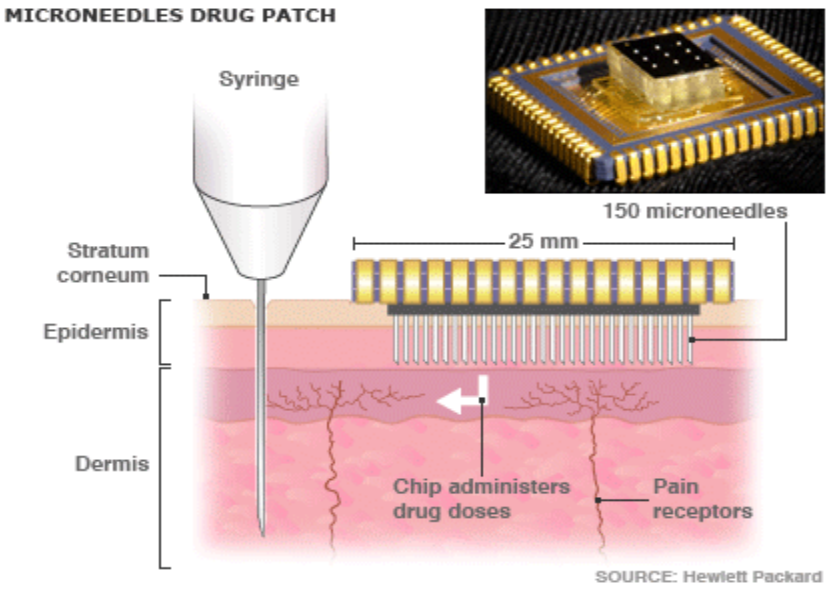


Figure 2.10: Microneedles drug patch

Source: Packard, H. (2007)

3 METHODOLOGY

Current chapter discusses methodology of the project with the focus on investigating the effect of drug diffusivity, deepness of breast tumor, temporal and spatial placement of transdermal patch on drug delivery efficiency. Relevant data was collected for further research analysis in Chapter 4.

3.1 Material and instrumentation

To design a transdermal patch, which allowing the drugs delivery from the skin barrier into the application position that is targeted cancer cells, additional data needed were including drug diffusion data and breast volume data. For measuring the permeability of drugs through the skin, the drug concentrations at the application position is calculated by using the multi-physics software package, COMSOL, which was installed in computer.

3.2 Methodology flow chart

The methodology flow chart is a visual representation of the sequence of a project. A completed flowchart organizes the topic and strategies done to ensure smooth working flow of project. Figure 3.1 illustrates a simple flow chart that shows the flow processes of this project. As shown below, the first was step collecting the data on drug diffusivity and breast volume. These were needed for proceeding with the next step, designing the mathematical model. It was followed by deciding the independent and dependent factors. Next, simulation work was performed using COMSOL software. To implement the COMSOL software, MIMICS image file was converted into COMSOL software and then key in the independent values, initial conditions and boundary conditions as decided early, and finally running the simulation by solver. After running the simulation, the drug concentration at the targeted site, tumor was found and observed for each simulation. Several graphs also be developed and from the developed graphs, the data were be interpreted accordingly. The methodology was ended by comparing and analysing the results obtained from simulation.

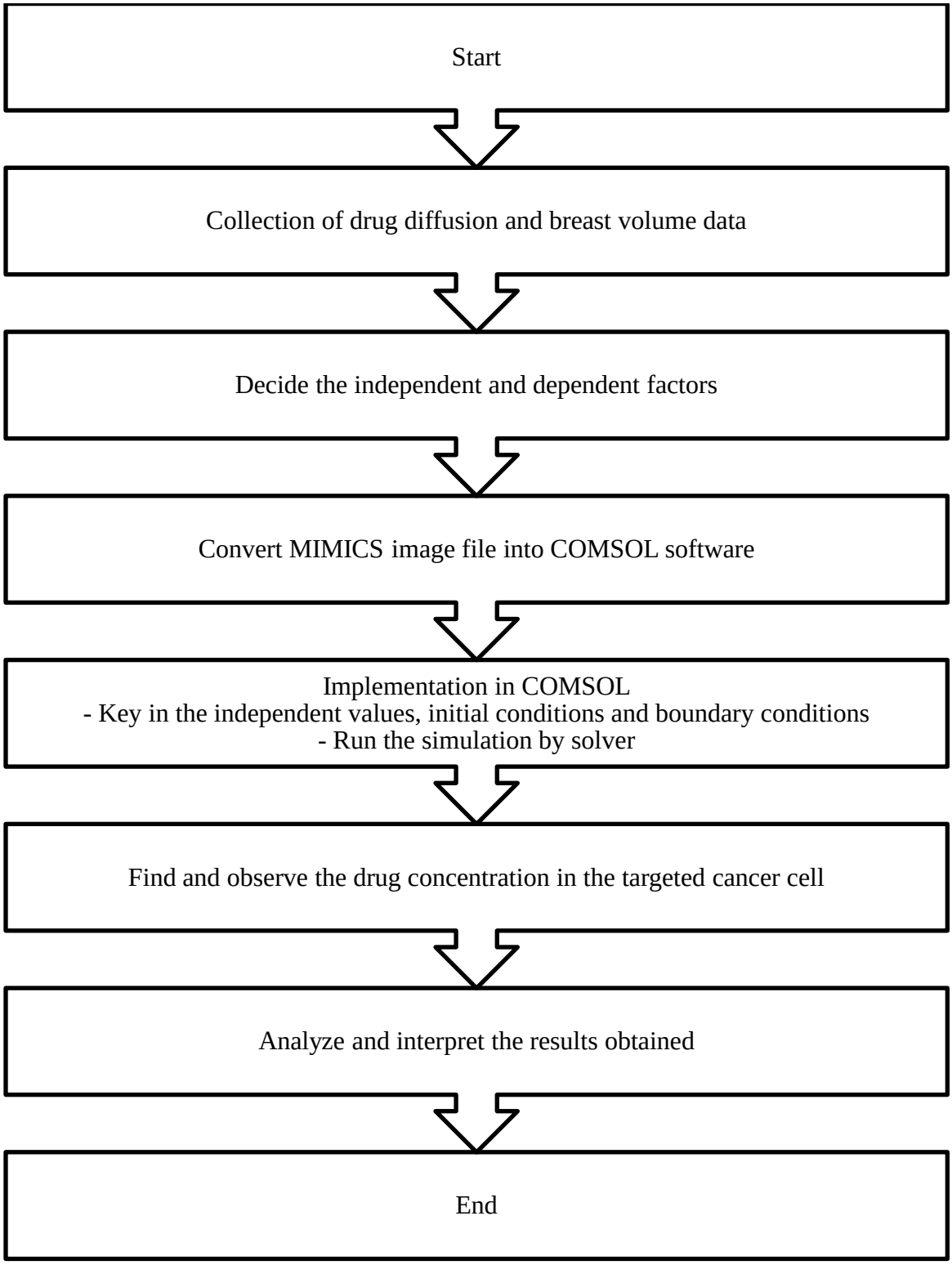
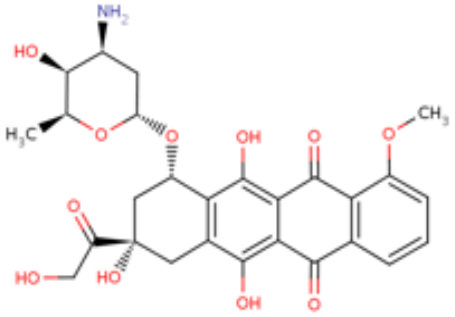


Figure 3.1: Flow chart of methodology

3.3 Collection of drug diffusivity data

Property	Value
Standard diffusivity	2.7×10^{-10} cm^2/s (Kaowumpai, W. et. al., 2008)
Average Molecular Weight	543.5193
Chemical Formula	$C_{27}H_{29}NO_{11}$
Chemical Structure	

3.4 Collection of breast volume data

The method employed for breast volume calculation from the mammograms was that used by Katariya and colleagues and Hoe and colleagues, which is highly reproducible. The formula used for calculating the volume was that for the calculation of the volume of a cone (Senie, R. et. al., 1980):

$$\frac{1}{3}\pi r^2 h$$

where r was half the breast width and h the breast height.

3.5 Implementation in comsol

There were two important steps to be stated as below for implementing the COMSOL software.

3.5.1 Steps for solving specified problem in comsol

1. Convert the MIMICS image file to COMSOL raw file (.mph)
2. Meshing: Create a structured mesh in the domain.
3. Defining material properties and initial conditions: Specify the diffusivity of the drug in the tissue. We will also enter the initial concentration of drug in the tissues as zero.
4. Defining boundary conditions: Supply the flux boundary condition for the patch and zero concentration boundary condition for the bottom edge of the tissue.
5. Specify solver parameters: Solve the problem for one week.
6. Postprocessing: Plot the drug concentration history as a function of time at point. Plot also the distribution of the drug in the domain after 3 days.
7. Save and exit: Finally, save the file and then exit.

3.5.2 Steps for monte carlo simulation

1. Open file: Open the file created in the last step.
2. Save as .m file: Save the COMSOL file, which is in .mph format originally, as a .m file.
3. Start editor and open .m file: Open a text editor to edit the .m file.
4. Modify the .m file in COMSOL script editor: Add commands in the .m file.
5. Run the .m file to perform Monte Carlo Simulations: Finally, run the file.

4 RESULT AND DISCUSSION

This chapter is mainly presents the results obtained throughout the study on the different parameters affect the drug delivery efficiency by observing and analysing the simulation results and developing several graphs for them. of chip formation and tool wear in machining titanium determined using optical microscope and software after a period of machining process.

4.1 Efficiency of drug dilivery under drug diffusivity parameter

Under this parameter, there were total of nine different diffusivity values, in the range of 10^{-9} to 10^{-1} were used to run out the simulation. From the simulation, the drug's concentration reached the targeted site, breast tumor was found out for each and then tabulated into a table according to the diffusivity values.These data were then used to perform the analysis in order to know the relationship between drug diffusivity and drug delivery efficiency. The results are shown in Table 4.1.

Table 4.1: Concentration of drug at breast tumor with different drug diffusivity, from 10^{-9} to 10^{-1}.

Drug Diffusivity, D (cm^2/s)	**Drug Concentration, c (mol/cm^2)**
2.7×10^{-9}	$-1.004595 \times 10^{-13}$
2.7×10^{-8}	3.178387×10^{-14}
2.7×10^{-7}	4.417303×10^{-8}
2.7×10^{-6}	0.006829
2.7×10^{-5}	0.00932
2.7×10^{-4}	0.001227
2.7×10^{-3}	1.227515×10^{-4}
2.7×10^{-2}	1.227515×10^{-5}
2.7×10^{-1}	1.227515×10^{-5}

From the data shown in the table above, it quantitatively showed that there was an optimum for the doxorubicin concentration at diffusivity of 2.7×10^{-5} cm^2/s. Lower or higher than this optimal diffusivity, the drug concentrations found at breast tumor were

lesser compared to the drug concentration at diffusivity of 2.7 X 10^{-5} cm^2/s. However, between both set of values, the drug diffusivities bigger than optimal diffusivity had higher drug concentrations than the drug diffusivities smaller than optimal diffusivity.

To have clearer analysis on those data, simulation results on three main diffusivities were shown in the following figures (Figure 4.1, 4.2 and 4.3). Form the images, a better comparison could be made.

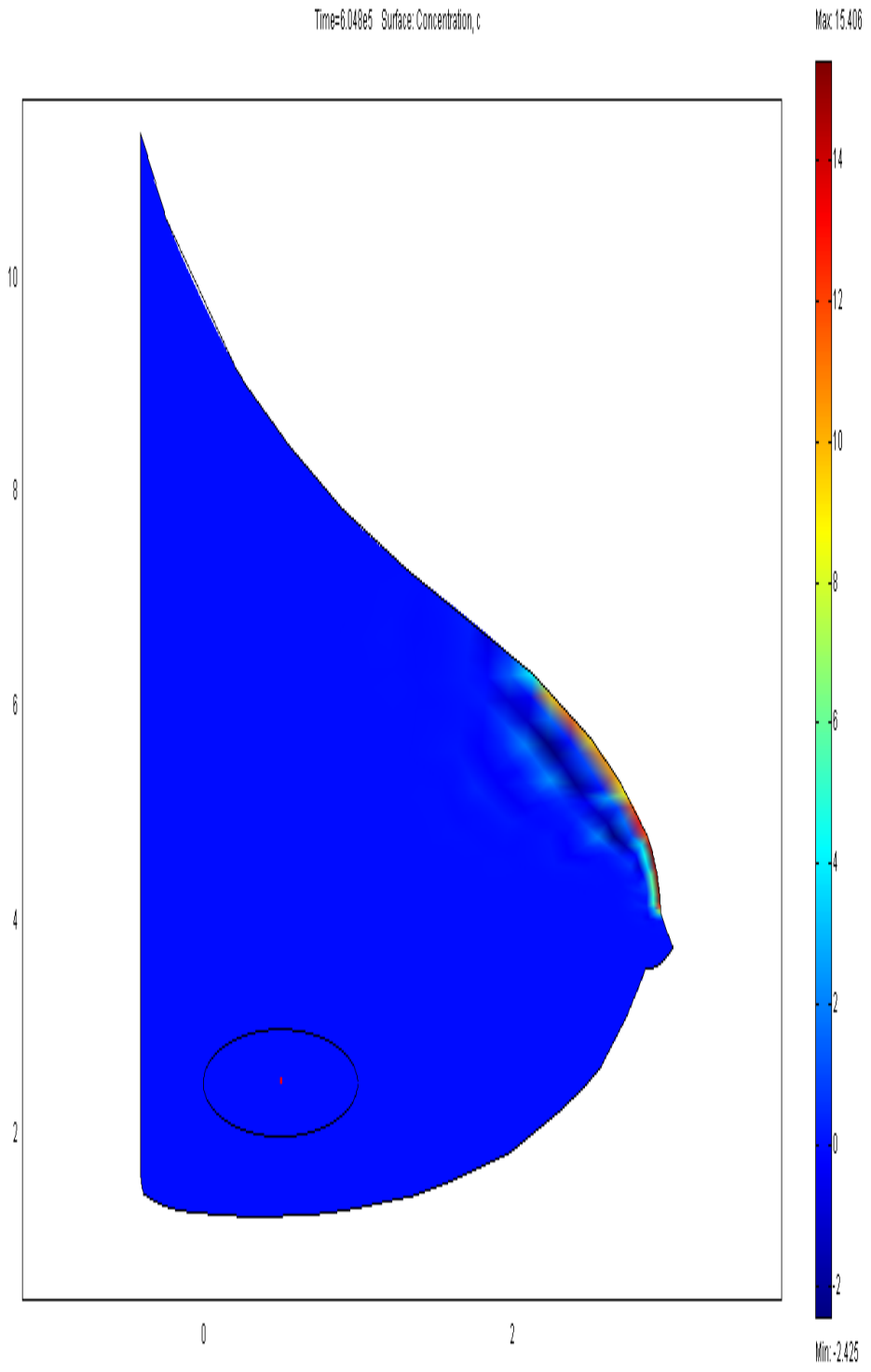


Figure 4.1: Drug's concentration after one week using drug diffusivity of 2.7 x $10^{-9}cm^2/s$.

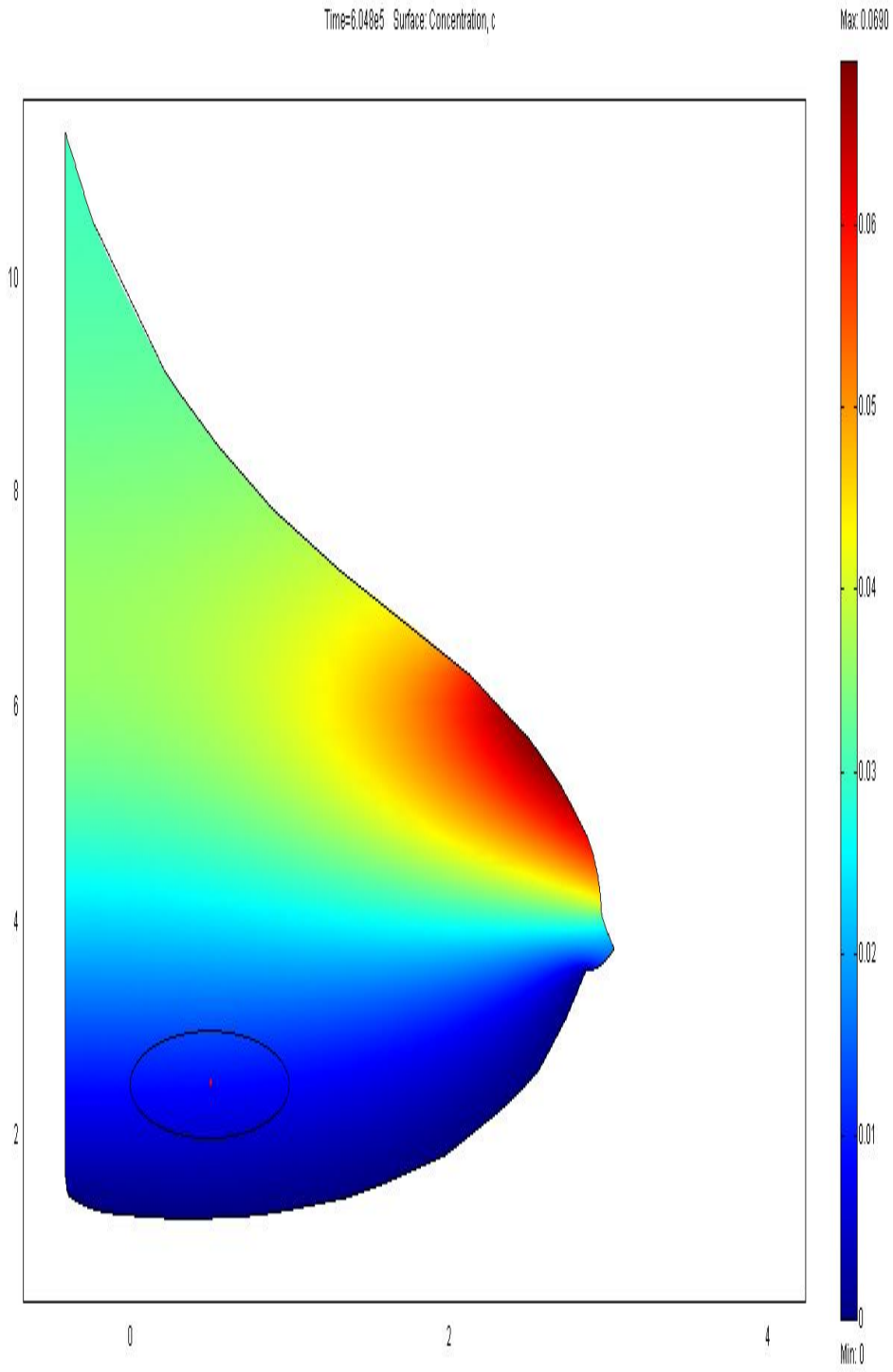


Figure 4.2: Drug's concentration after one week using drug diffusivity of 2.7 x 10^{-5} cm^2/s.

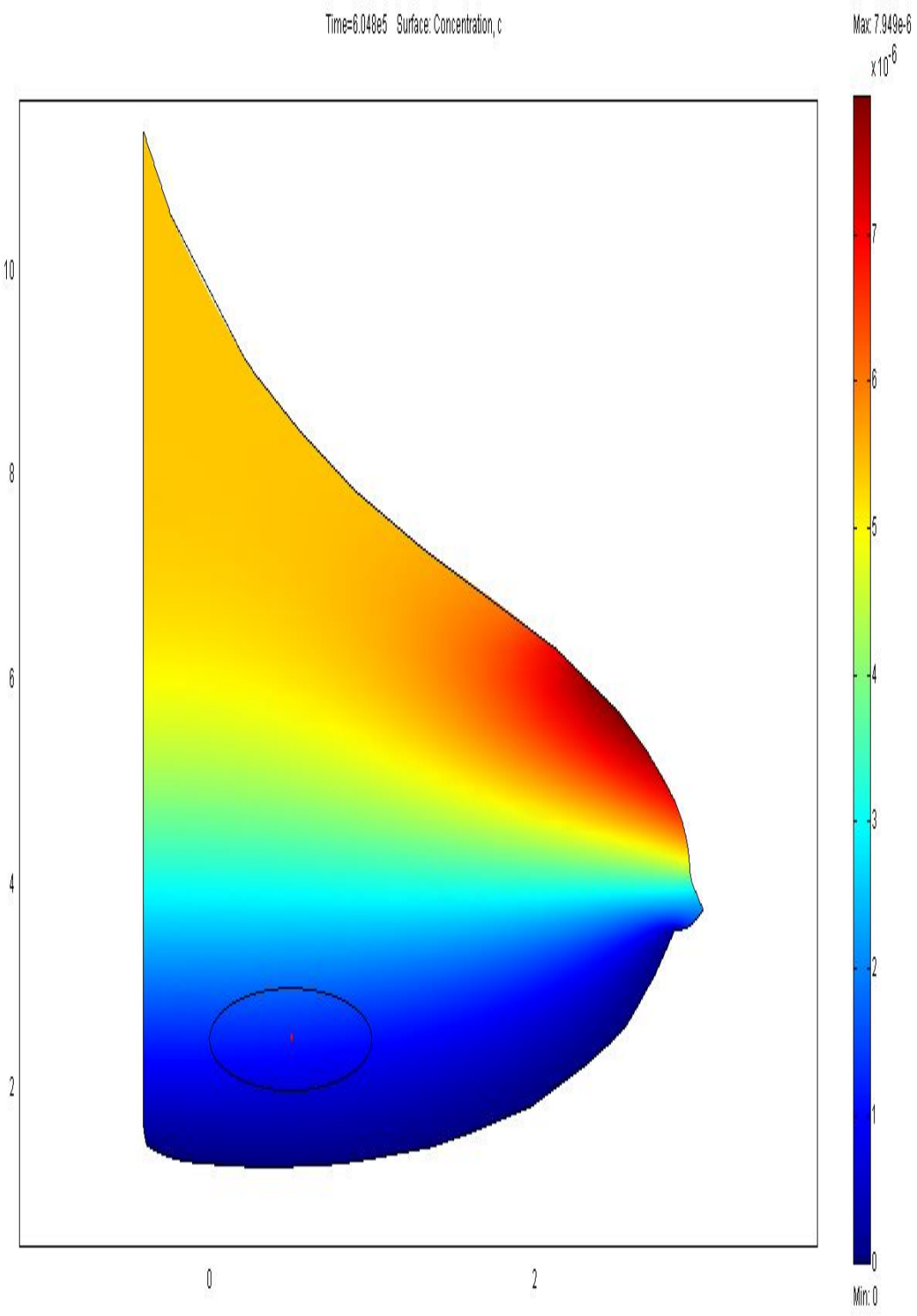


Figure 4.3: Drug's concentration after one week using drug diffusivity of 2.7 x 10^{-1} cm^2/s.

For information, red colour represented the highest of drug concentration, followed by orange, yellow and green colour. The lowest of drug concentration was represented by blue colour (Figure 4.4).

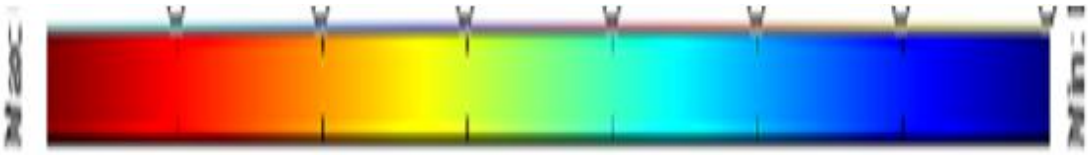


Figure 4.4: Indication of colours, from maximum to minimum.

According to the three figures, the diffusion rate to the breast tumor was poorest at diffusivity of 2.7 x 10^{-9} cm^2/s and was highest at the diffusivity of 2.7 x 10^{-5} cm^2/s. For diffusivity at 2.7 x 10^{-1} cm^2/s, the drug concentration was much more higher at the site of breast near to the surface of skin where transdermal patch was applied, in orange colour compared to the same site of breast at diffusivity of 2.7 x 10^{-5} cm^2/s, in green colour.

4.1.1 Discussion on efficiency of drug dilivery under drug diffusivity parameter

Overall, the highest drug concentration was found at diffusivity of 2.7 x 10^{-5} cm^2/s. This was not in expectation because it against the original believing that higher the drug diffusivity is, the higher the drug concentration will be obtained at breast tumor. The highest of drug concentration here could be explained by the balance between diffusion and drug release rate from the reservoir system

Once the transdermal patch was applied, the drug release rate from the reservoir would be maximal. But, over some time, the drug release rate from matrix system underwent a slight decline because of progressive increase in length of the diffusional pathway as the drug is being depleted. With most well-designed matrix systems, this decline is insignificant and provides a pseudo zero-order or apparently constant drug release rate during the designated period of patch use. (Ratna, M., 2004) These best to describe why there was an optimal drug diffusivity, but the higher the drug diffusivity is, the

higher the drug concentration will diffuse to breast tumor. As shown in Figure 4.3, there was higher concentration of drug existed at the site of breast tissue that near to the surface where transdermal patch was applied, compared to Figure 4.2. The initial release of large amount of drug from the matrix system caused the declination of drug release rate from reservoir for the progressive length in the diffusional pathway. As a result, the drug concentration reached on the breast tumor would be significantly reduced.

A best result could be accepted here was at the diffusivity if 2.7 x 10^{-5} cm^2/s, known as optimal drug diffusivity. Well, to achieve this diffusivity, this drug, doxorubicin may can replaced by another drug with diffusivty of 10^{-5} cm^2/s. Other device also can be used to enhance drug diffusitivity and there still a need for furthering the research.

4.1.2 Discussion on efficiency of drug delivery under temporal placement of transdermal patch parameter

With the reservoir system, there is a tendency for the drug molecules to diffuse into the control membrane over time and saturate it. As explained earlier, constant concentration gradient is important for most well designed patch. There needs to be a significantly large amount of drug in the device in order to maintain a uniform concentration gradient over the duration of patch use. When drug concentrations in the patch are depleted significantly, the drug release rate begins to drop, and the zero-order rate is no longer maintained. Most patches should be removed before reaching this stage. This means there is still a significant amount of drug remaining in the patch after it is 'used up'. (Ratna, M., 2004)

After one month, the concentration gradient turned to zero. Therefore, there was a need to remove and change the patch with another patch. Besides, longer placement and larger surface area of skin being contacted with the transdermal patch, these will cause skin irritation of patients. Thus, it is not encouraged for a patch to be put on the skin for too long. Moreover, there is a risk that the patch will become detached and subsequently supply inadequate medicinal product to the body. Hence, changing with another is needed for solving these stated problems. According to EVRA^{TM} Product monograph,

1.8% of patches needed to be replaced due to detachment and 2.8% due to partial detachment in a large clinical study using EVRA®.

4.2 Efficiency of drug delivery under deepness of breast tumor parameter

To investigate the relationship between drug delivery efficiency and deepness of tumor within breast, drug concentration for two different location of tumor in the same breast volume were analyzed, and the results obtained are shown in the Table 4.2, Figure 4.9 and Figure 4.10.

Table 4.2: Concentration of drug at tumor that grown at the top and bottom of breast.

Deepness of Breast Tumor	**Drug Concentration, c (mol/cm^3)**
Top of the breast	0.012219
Bottom of the breast	0.056516

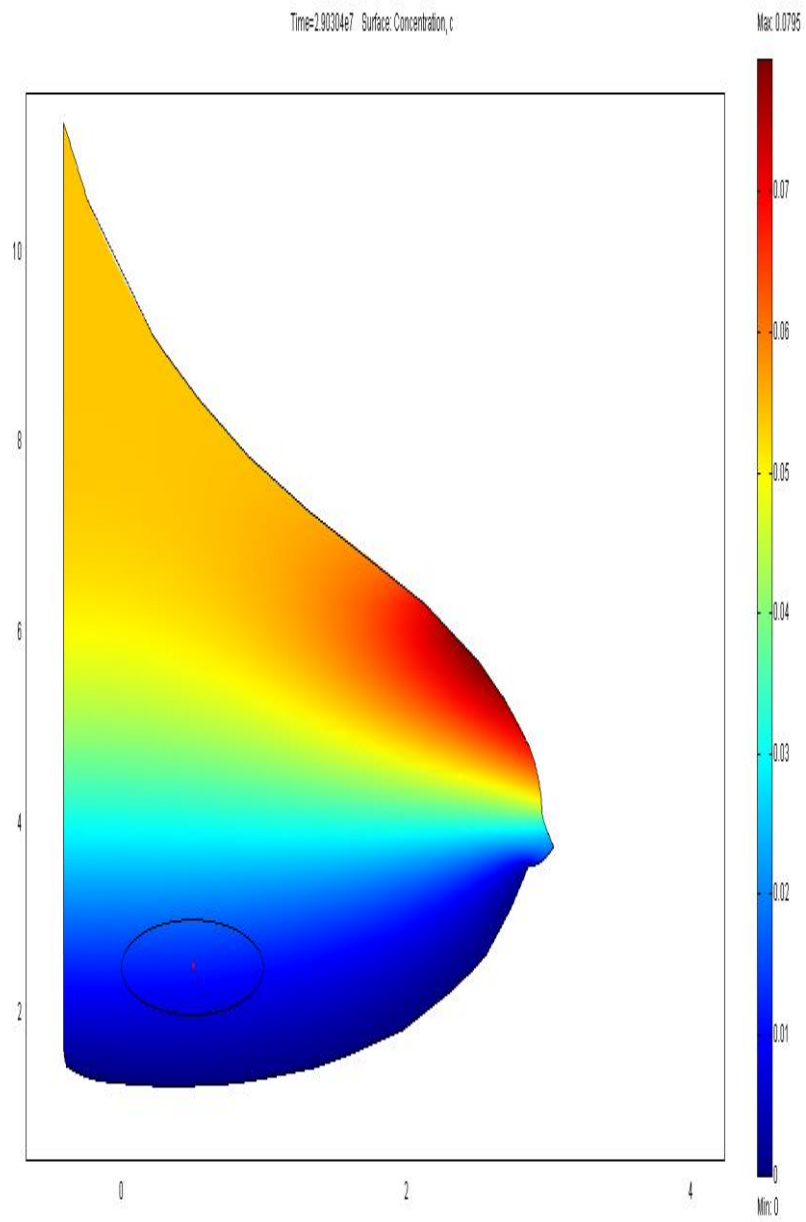


Figure 4.5: Diffusion of drug into skin to reach target site, tumor at the bottom of breast after one month

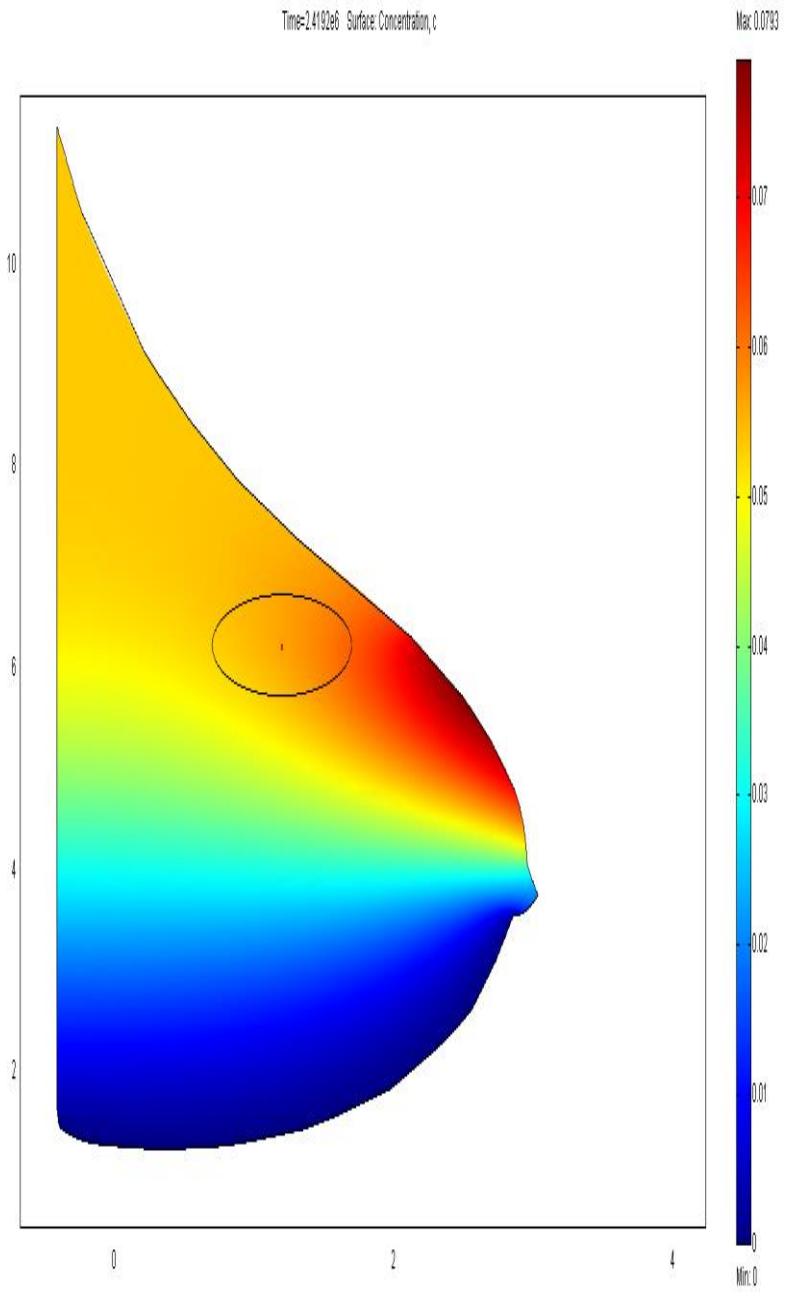


Figure 4.6: Diffusion of drug into skin to reach target site, tumor at the top of breast after one month.

From the results, when the tumor was grown at the bottom of breast, the drug concentration able to reach on was 0.012273 mol/cm^3. In contrast, when the tumor was grown at the top of breast, the drug concentration reach was 0.056516 mol/cm^3. Thus, deeper the tumor was in the breast, lesser the drug able to reach on the breast tumor.

4.2.1 Discussion on efficiency of drug delivery under deepness of breast tumor parameter

The concentration gradually declined from the maximum to the minimum with an apparent iso-contour distribution of concentration in Figure 4.9 and 4.10. The drug distribution had high concentration around the corner of patch and stratum corneum. These results confirmed that the interphase drug concentrations have a direct connection with the diffusion path. The concentration of drug had a uniform front, where the diffusions around the corner between the patch and stratum corneum showed greater local drug concentration, which was presented by red colour. In contrast, local drug concentration at the end from patch and stratum corneum was shown by blue colour, which was the minimal.

By commanding this concept, drug concentrations have direct connection with the diffusion patch, there is a potential for the controlling the highest of drug diffusion to the targeted site, breast tumor as presented on the following sub-topic.

4.3 Efficiency of drug delivery under spatial placement of transdermal patch

To relate drug delivery efficiency to spatial placement of transdermal patch on skin, drug concentration at tumor was analyzed when placing the trransdermal patch at different site of breast, one at the top of breast and one at the bottom of breast and the results were tabulated in the Table 4.4. Images of simulation also presented for a clearer view (Figure 4.10 and 4.11).

Table 4.3: Concentration of drug at tumor when patch aplied at different locations.

Spatial Placement	**Drug Concentration, c (mol/cm^3)**
Top of the breast	0.012219
Bottom of the breast	0.061773

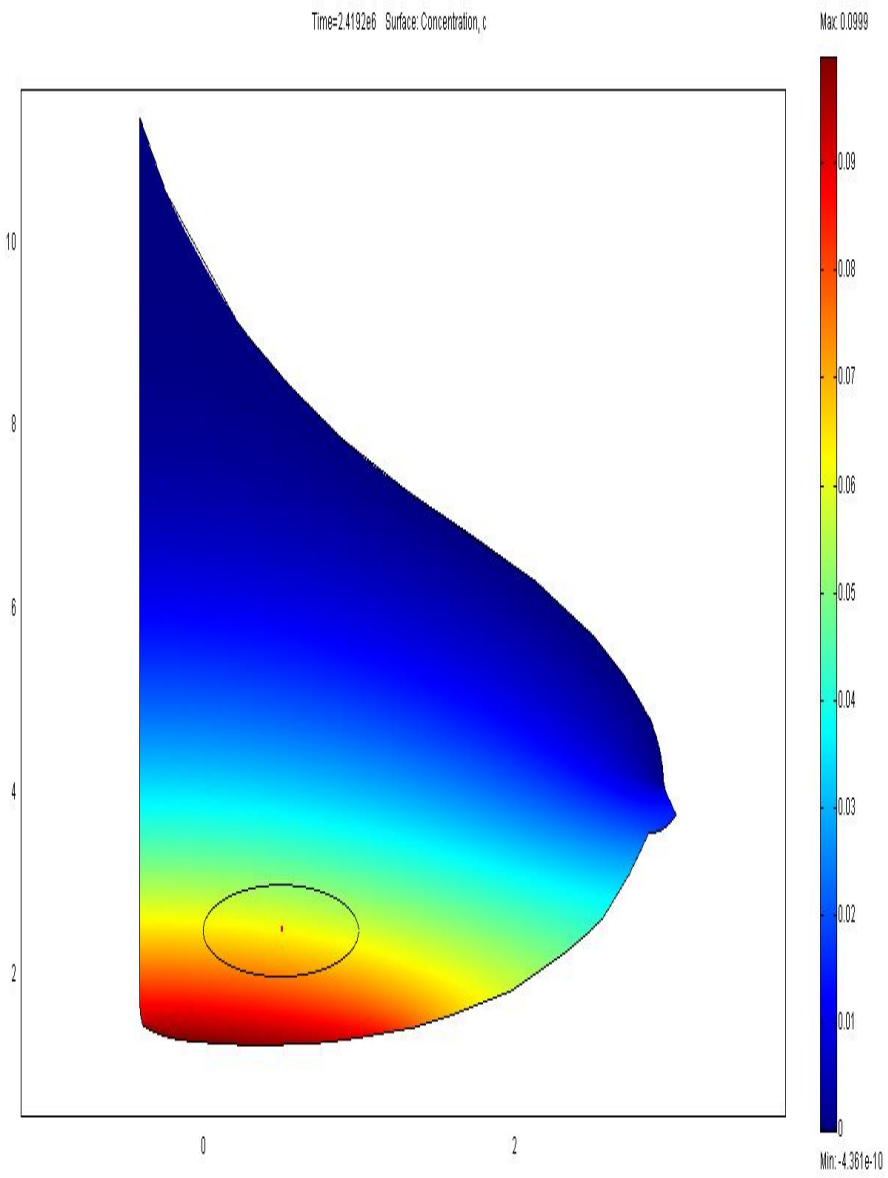


Figure 4.7: Diffusion of drug into skin to reach tumor after one month when patch was applied at the bottom of breast.

Based on the results obtained, when the transdermal patch applied at the bottom of breast, the drug concentration was 0.061773 mol/cm^3, which was higher than the drug concentration when the transdermal patch was applied at the top of breast, which only was 0.012219 mol/cm^3.

4.3.1 Discussion on efficiency of drug delivery under spatial placement of transdermal patch

In studying the effect of deepness of breast tumor on drug delivery efficiency, deeper the breast tumor was grown would cause lesser drug concentration being diffused and reached on tumor was discovered. Therefore, applying patch on different position of breast had been examined on the drug delivery efficiency.

From the results, poorer of drug concentration could be diffused when the deeper of the breast tumor was. However, this could be solved by applying the transdermal patch on different location due to the nearer of patch to the tumor, the drug concentration able to diffuse to the tumor will be higher. So, when the tumor was grown at the bottom of breast, the patch could be placed at the bottom of breast for better drug delivery and in otherwise.

4.4 Summary

From a practical point of view, the result obtained above can be interpreted as follows. Drug diffusivity had significant effect on drug delivery efficiency. There was optimal drug diffusivity was at 10^{-5} for maximal drug delivery. Below or above this optimal value, drug delivery efficiency would be reduced.

In addition, there was also a relationship between drug delivery efficiency and temporal placement of transdermal patch. By analysing this, a designated time for use of transdermal patch could be known. For the present study, an appropriate period of patch using was less than one month. After one month, change with another by removing the previous one was needed.

Moreover, drug delivery efficiency also being affected by deepness of breast tumor and spatial placement of transdermal patch. These two parameters had indirect relationship. The deeper the tumor was grown in breast; lesser the drug concentration could be diffused to the targeted site, breast tumor. However, this could be solved the changing the spatial placement of transdermal patch on skin that near to tumor.

5 CONCLUSION AND RECOMMENDATIONS

This chapter summarizes the main points of this dissertation. It concludes all the important observation and information gained from the study. Recommendations for further research also suggested at the end of this report.

5.1 Conclusion

In conclusion, effects of simulation parameters on determining the drug's concentration and drug delivery efficiency were performed successfully in the present study. In this study, drug diffusivity was considered as important parameter in the drug delivery efficiency, as approved by the transportation work of the transdermal delivery system. Some other parameters (i. e. deepness of breast tumor, spatial and temporal placement of transdermal patch) were also taken into account. According to the results obtained, there was an optimal drug's concentration at the drug diffusivity of 10^{-5}. Below or above this optimal drug diffusivity, the drug delivery efficiency would be affected. Drug diffusivity at 10^{-5} could contribute to maximal drug delivering to the targeted cancer cells. There was an indirect relationship between deepness of breast tumor and spatial placement of transdermal patch. Deeper the tumor grown within breast, lesser drug's concentration could be diffused to it. However, this could be solved by changing the place of transdermal patch application due to the nearer the transdermal patch application to the tumor site, more efficiency of the drug delivery could be achieved. The temporal placement of transdermal patch also had significant affect on drug delivery efficiency. Drug release from patch would be reduced until there was no drug diffusing into the skin, and the period designated was normally less than one due to long placement of patch would cause irradiation to skin.

5.2 Recommendations

Improvement for the present study can be done as suggested below:-

- In this study, only diffusion condition was considered. However, there is still convective condition occurs between the transdermal patch and skin. Therefore, in future work, this model can be improved by accommodating the convective condition.
- The present simulation was carried out by using finite element modeling (FEM) with two-dimensional geometry. This model may be improved by constructing a more complex geometry.

Last but not least, drug dosage used when carry out the designation of transdermal patch should be taken into account in future research. Highest drug's concentration is not always good to patient because of the possibility to generate toxicity. For instance, a recommended dose of doxorubicin was $50mg/m^2$. (Kaoumpai, W. et. al., 2008) Higher dosing resulting in unaccepted skin and/or bloodstream toxicity. Thus, optimizing the drug's concentration in order to maximize local effective drug's concentration and minimize toxicity to skin and/or bloodstream can be done in the future work.

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APPENDIX A
DEGREE FINAL YEAR PROJECT TECHNICAL PAPER

Breast Cancer Drug Delivery Systems By Differential Delivery System Using Finite Element Analysis

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ABSTRACT: Breast cancer is the most common form of cancer affecting women in Malaysia. Conventional drug treatment for breast cancer, chemotherapy would destroy the cancer cells because of the medicine targets on rapidly dividing cells. However, healthy cells and tissues in blood, mouth, intestinal tract, nose, nails, vagina and hair also divide rapidly, they could be damaged. A more promising technology called transdermal patch has been introduced due to side effects are common expected results from conventional treatment. Therefore, the aim of this study was to treat breast cancer by delivering drug from transdermal patch precisely and safely to targeted cancer cell so that reducing the side effects and dosage of drug used. The objectives of this study were to determine the drug concentration at breast tumor, to investigate the relationship between drug diffusivity and drug delivery efficiency, and to evaluate the efficiency of drug delivery under other parameters (i.e. deepness of tumor, temporal and spatial placement of transdermal patch). Available software, COMSOL was used in this study. Drug concentrations that able to diffuse and reach tumor in breast were studied. The simulation results showed that there was optimal drug diffusivity for maximum concentration of drug reached tumor in breast. However, below and higher than this drug diffusivity optimal value, the delivery of drug concentration was poorer when the lesser. Production of microchannels in the skin by microneedle can increase the drug diffusivity and ensure delivery of pharmacologically effective concentration of drug to the targeted site, breast cancer cell. Deeper the tumor grown within breast, lesser drug's concentration could be diffused to it. However, this could be solved by changing the place of transdermal patch application. The nearer the spatial placement of transdermal patch to tumor growth in the breast on the breast skin increased the effectiveness of drug delivery to tumor. The longer the temporal placement resulted in higher drug concentration could be delivered to breast tumor. However, this constant concentration gradient only achieved for less than one month. After this, the concentration gradient would become zero. As a conclusion, the drug diffusivity, deepness of breast tumor, spatial and temporal placement of transdermal patch must be taken into account when engineering, constructing and applying the transdermal patch in order to achieve the maximum breast cancer treatment with reducing the undesired side effects.

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Key words: Breast cancer, chemotherapy, transdermal patch, drug, COMSOL

1. INTRODUCTION

Breast cancer is the most common form of cancer among women other than other skin cancer, and the number of cases for breast cancer is increased annually. About one in nineteen women in Malaysia are at risk. Breast cancer is also the leading cause of cancer-related death for women. In Peninsula Malaysia, the mortality rate per 100,000 showed an increase from 3.7 per 100,000 in 1982 to 5.8 per 100,000 in 1990. However, since only one-third of deaths in Peninsula Malaysia were medically certified, the mortality rate from breast cancer was actually higher. (Yip, C. H. and Ng, E. H., 1996).

Generally, chemotherapy is the common drug therapy for breast cancer. Many anticancer drugs are designed to simply kill cancer cells. They are often in a semi-specific fashion because the anticancer drugs target on rapidly dividing cells. Similar to cancer cells, the normal cells in blood, mouth, intestinal tract, nose, nails, vagina and hair also divide rapidly. Consequently, the distribution of anticancer drugs in healthy organs or tissues is especially undesirable due to the potential for severe side effects. This phenomenon greatly limits the maximal allowable dose of the drugs. However, low local drugs' concentration will cause less effect on destroying the cancer cells. Therefore, there is still a need for high or frequent drugs dosing.

To overcome such limitations, a new and more promising technology, transdermal technology has been introduced for breast cancer drug therapy. This application provides an alternative route for delivering drugs to cancer cells, which is through the largest organ of humans' bodies, skin. In this method, a transdermal patch is purposely engineered and constructed to allow the delivering of drugs precisely to the targeted cancer cells with fewer side effects. Site-specific drugs delivery is a concept that has the potential to increase local drugs' concentrations, and thereby produce more effective medicines with reducing the dosage of drugs used.

The new technology, transdermal patch allows the delivering of anticancer drugs to targeted cancer cell as effectively as possible without side effects and reducing the dosage of drugs used. However, transdermal application has limitation due to the remarkable barrier properties of the outermost layer of skin, stratum corneum. This layer is mainly consisted of lipids, has no blood flow, and thus plays a key role in limiting the diffusion of drugs to the bloodstream. For transdermal drugs delivery system to be effective, the drugs must obviously be able to penetrate this skin barrier and reach the targeted cancer cells. To achieve this, suitable modification has been made on the transdermal delivery system. It is hard to deny that drug diffusivity is a very important factor to be considered.

The aim of this study was to treat breast cancer by delivering drug from transdermal patch precisely to targeted cancer cells so that reducing the side effects and dosage of drugs used. This can be achieved by the following specific objectives:

1. To convert Materilaise's Interactive Medical Image Control System (MIMICS) image files into comsol,
2. To determine the drug concentration at breast tumor
3. To investigate the relationship between drug diffusivity and drug delivery efficiency, and
4. To evaluate the efficiency of drug delivery under other parameters (i.e. deepness of tumor, temporal and spatial placement of transdermal patch).

This study mainly focused on the efficiency of drug delivery from transdermal patch, which was evaluated by response parameter, drug concentration successfully reaching at the breast tumor. The study was carried out by using COMSOL software. Before implementing the COMSOL software, data collection for drug diffusivity and breast volume were needed. After data collection, Materilaise's Interactive Medical Image Control System (MIMICS) image files where converted by using COMSOL software. After converting the image files, simulation was run by using COMSOL software. The simulation was conducted with identified independent variables (i.e. drug diffusivity, deepness of tumor, temporal and spatial placement of transdermal patch). Simulation produced with different parameters was saved for further analyses. Graphs that relate the drug concentration at breast tumor were also developed. From the developed graphs, the association between the efficiency of drug delivery and drug concentration could be made.

This study had the significance to do a new strategy on developing a more promising technology to treat breast cancer. This study also important for eliminate the side effects or toxicities caused by conventional drug therapies. This was replaced by the application of new technology, transdermal patch. The other significance was including reducing the drug dosage used for breast cancer treatment. Reduce side effects and drug dosage used, thereby decreasing the cost of breast cancer treatment.

The problem of cancer in Malaysia is in a growing trend, and breast cancer is the most common cancer among women. 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. Breast cancer formed 30% and 31.1% of newly diagnosed cancer cases in women in 2002 and 2003. This was followed by cancer of the cervix, which only formed 12% and 12.9% of total female cancers in 2003 and 2003 respectively.

The number of deaths form breast cancer also showed an increasing trend, which were 260, 320 and 339 for the year of 1994, 1995 and 1998 respectively. And within these numbers, only 1/3 of all deaths in Malaysia were medically certified. This indicated that the awareness of breast cancer among women still low and not effective enough. Within the detected women with breast cancer, only 55.6% of Malaysian women presented with early stage breast cancer (Stage 0 – 1) compared with 72% of Singaporean women in 1990. (Yip, C. H. and Ng, E. H., 1996) From the year of 1993 to 2004, there were 30-40% of the patients presented in the late stage and although women are now presenting with smaller tumours, the decrease in size is not significant. (College Of Radiology Breast Health Information Centre, 2008).

The most common breast cancer drug therapy, also known as chemotherapy, in simplest sense, is a treatment with the aid of drugs that killing microorganisms or cancerous cells. The chemotherapy drugs can be swallowed by someone as tablets or capsules, or injected intravenously through the veins. When the drugs reach cancer cells, the drugs work by disrupting the growth of cancer cells.

However, when the drugs circulate in the blood, they not only reach cancer cells, but wherever they are in body. Many anticancer drugs are designed simply kill cancer cells. They have no the capability to distinguish between the cancer cells and normal cells. In contrast, they work by killing the cells that are actively growing and dividing into new cells. Cancer cells do grow and divide much more often than normal cells because most normal cells grow and divide in a precise, orderly way. Thus, cancer cells are more likely to be killed by the chemotherapy drugs. However, there are still some normal cells do divide and grow rapidly such as cells in hair follicles, nails, mouth, intestinal tract and bone marrow. Chemotherapy drugs can unintentionally harm these other types of rapidly dividing cells. As a result, the distribution of anticancer drugs in healthy and normal cells is especially undesirable due to the potential for severe side effects.

Materilaise's Interactive Medical Image Control System (MIMICS) is an interactive toolbox for the visualization and segmentation of stacked images (CT, microCT, MRI,…) and 3D rendering of objects. It provides the users the tools to convert the images to 3D objects and prepare these objects for different application domains.

Mimics Software is developed by Materialise NV a Belgian company that is specialized in additive manufacturing software and technology. Nowadays, engineers are playing a crucial role by supporting doctors and improving the quality of life of patients through optimized implants and devices, scientifically validated surgical procedures, studying surgical simulation, and more. Together, these Engineering professionals are working towards a better and healthier world.

COMSOL is all about flexible platform that allows even novice users to model all relevant physical aspects of their designs. Advanced users can go deeper and use their knowledge to develop customized solutions, applicable to their unique circumstances. With this kind of all-inclusive modeling environment, COMSOL gives us the confidence to build the model we want with real-world precision.

Certain characteristics of COMSOL become apparent with use. Compatibility stands out among these. COMSOL requires that every type of simulation included in the package has the ability to be combined with any other. This strict requirement actually mirrors what happens in the real world. For instance in nature, electricity is always accompanied by some thermal effect; the two are fully compatible. Enforcing compatibility guarantees consistent multiphysics models, and the knowledge that, even as the COMSOL family of products expands, we never have to worry about creating a disconnected model again.

COMSOL Multiphysics also has several problem-solving benefits. When starting a new project, using COMSOL helps us to understand our problem. You are able to test out various geometrical and physical characteristics of your model, so we can really hone in on the important design challenges. The flexible nature of the COMSOL environment facilitates further analysis by making "what-if " cases easy to set up and run. We can take our simulation to the production level by optimizing any aspect of our model. Parameter sweeps and target functions can be executed right in the user interface. From star t to finish, COMSOL is a complete problem-solving tool.

As we become a more experienced user of COMSOL, our confidence in computer simulation will grow. We will become a more efficient modeler, and the results will show it.

Transdermal patch is providing an effective alternative route for delivering drugs to cancer cells, which is through the largest organ of human bodies, skin. Transdermal delivery of medications was foreshadowed in earlier eras by the use of certain plasters and ointments. (Stanley, S., 2004)

Since the drugs are delivered directly from human's skin to bloodstream, it has provided a wide variety of advantages compared to chemotherapy. First of all, side effects associated with traditional delivery method could be eliminated due to site-specific delivery of drugs to the targeted site, cancer cells without circulating through the whole body like chemotherapy. The second benefit resulted from this shortened metabolic pathway of transdermal route is allowing for reduced pharmacological dosing. (Girish, C., 2006) Studies have shown that when formulations are delivered topically, as little as 5% of the drug can be make it to the cells where we need it when we taking a drug orally. This is because a large proportion of drug is destroyed and neutralized in stomach, intestine and liver before reaching bloodstream. On the other hands, transdermal technology ensures as much as 95% of a supplement reaches the cells it is needed. (Department of Pharmacology, University of Dublin)

Some other benefits of using transdermal application are including the transdermal patch provides the controlled release of drugs directly into the bloodstream through intact skin. By delivering a steady flow of drugs into the bloodstream for an extended period of time, transdermal system can avoid peak- and – effect of oral or injectable therapy and can enable more controlled effective treatment. Furthermore, transdermal patch application is convenient to use because it offers multi-day dosing and is flexible to terminate the drug administration by simply removing the patch from skin when there is toxicity observed. Last but not least, patients who have difficulty with swallowing pills or receiving injections, patch offers an effective alternative for them. The pros of transdermal appliction over chemotherapy are summarized in the table below (Table 1).

Chemotherapy	**Transdermal Application**
Form of delivery of drugs is oral route.	Provides an alternative route for delivering drugs, which is through skin.
Poor bioavaibility.	Site-specific drug delivery to obtain high local drug concentration.
Peaks and valleys in medication level.	Permits constant dosing.
A large proportion of drug are destroyed and neutralized in stomach, intestine and liver before reaching bloodstream.	Low circulating drug concentration avoiding the risk of side effects.
Gastrointestinal pathway, leading to a need for high and/or frequent dosing.	Allows for reduced pharmacological dosing due to the shortened metabolic pathway of the transdermal route.
Cost prohibitive and inconvenient.	Convenient, particularly when patches are applied once every several days.
As little as 5% of the	As much as 95% of a

drug can make it to the cells where we need it.	supplement reaches the cells where it is needed.

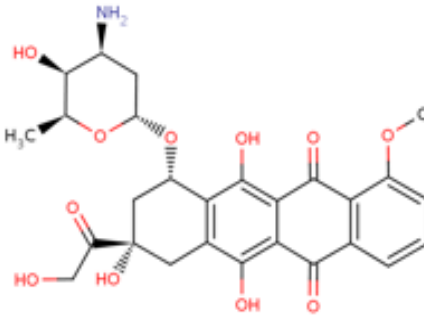
Table 1: Differences between transdermal application and chemotherapy.

2. EXPERIMENTAL

2.1 Introduction

To design a transdermal patch, which allowing the drugs delivery from the skin barrier into the application position that is targeted cancer cells, additional data needed were including drug diffusion data and breast volume data. For measuring the permeability of drugs through the skin, the drug concentrations at the application position is calculated by using the multi-physics software package, COMSOL, which was installed in computer.

2.2 Collection of drug diffusivity data

Property	Value
Standard diffusivity	**2.7×10^{-10} cm^2/s (Kaowumpai, W. et. al., 2008)**
Average Molecular Weight	**543.5193**
Chemical Formula	**$C_{27}H_{29}NO_{11}$**
Chemical Structure	

2.3 Collection of breast volume data

The method employed for breast volume calculation from the mammograms was that used by Katariya and colleagues and Hoe and colleagues, which is highly reproducible. The formula used for calculating the volume was that for the calculation of the volume of a cone (Senie, R. et. al., 1980):

$$\frac{1}{3}\pi r^2 h$$

where r was half the breast width and h the breast height.

2.4 Implementation in comsol

2.4.1 Steps for solving specified problem in comsol

1. Convert the MIMICS image file to COMSOL raw file (.mph)
2. Meshing: Create a structured mesh in the domain.
3. Defining material properties and initial conditions: Specify the diffusivity of the drug in the tissue. We will also enter the initial concentration of drug in the tissues as zero.
4. Defining boundary conditions: Supply the flux boundary condition for the patch and zero concentration boundary condition for the bottom edge of the tissue.
5. Specify solver parameters: Solve the problem for one week.
6. Postprocessing: Plot the drug concentration history as a function of time at point.
   Plot also the distribution of the drug in the domain after 3 days.
7. Save and exit: Finally, save the file and then exit.

2.4.2 Steps for monte carlo simulation

1. Open file: Open the file created in the last step.
2. Save as .m file: Save the COMSOL file, which is in .mph format originally, as a .m file.
3. Start editor and open .m file: Open a text editor to edit the .m file.
4. Modify the .m file in COMSOL script editor: Add commands in the .m file.
5. Run the .m file to perform Monte Carlo Simulations: Finally, run the file.

3. RESULT AND DISCUSSIONS

3.1 Efficiency of drug dilivery under drug diffusivity parameter

Under this parameter, there were total of nine different diffusivity values, in the range of 10^{-9} to 10^{-1} were used to run out the simulation. From the simulation, the drug's concentration reached the targeted site, breast tumor was found out for each and then tabulated into a table according to the diffusivity values.These data were then used to perform the analysis in order to know the relationship between drug diffusivity and drug delivery efficiency. The results are shown in Table 2.

Drug Diffusivity, D (cm^2/s)	Drug Concentration, c (mol/cm^2)
2.7×10^{-9}	$-1.004595 \times 10^{-13}$
2.7×10^{-8}	3.178387×10^{-14}
2.7×10^{-7}	4.417303×10^{-8}
2.7×10^{-6}	0.006829
2.7×10^{-5}	0.00932
2.7×10^{-4}	0.001227
2.7×10^{-3}	1.227515×10^{-4}
2.7×10^{-2}	1.227515×10^{-5}
2.7×10^{-1}	1.227515×10^{-5}

Table 2: Concentration of drug at breast tumor with different drug diffusivity, from 10^{-9} to 10^{-1}.

From the data shown in the table above, it quantitatively showed that there was an optimum for the doxorubicin concentration at diffusivity of 2.7 X 10^{-5} cm^2/s. Lower or higher than this optimal diffusivity, the drug concentrations found at breast tumor were lesser compared to the drug concentration at diffusivity of 2.7 X 10^{-5} cm^2/s. However, between both set of values, the drug diffusivities bigger than optimal diffusivity had higher drug concentrations than the drug diffusivities smaller than optimal diffusivity.

3.1.1 Discussion on efficiency of drug dilivery under drug diffusivity parameter

Overall, the highest drug concentration was found at diffusivity of 2.7 x 10^{-5} cm^2/s. This was not in expectation because it against the original believing that higher the drug diffusivity is, the higher the drug concentration will be obtained at breast tumor. The highest of drug concentration here could be explained by the balance between diffusion and drug release rate from the reservoir system

Once the transdermal patch was applied, the drug release rate from the reservoir would be maximal. But, over some time, the drug release rate from matrix system underwent a slight decline because of progressive increase in length of the diffusional pathway as the drug is being depleted. With most well-designed matrix systems, this decline is insignificant and provides a pseudo zero-order or apparently constant drug release rate during the designated period of patch use. (Ratna, M., 2004) These best to describe why there was an optimal drug diffusivity, but the higher the drug diffusivity is, the higher the drug concentration will diffuse to breast tumor.

The initial release of large amount of drug from the matrix system caused the declination of drug release rate from reservoir for the progressive length in the diffusional pathway. As a result, the drug concentration reached on the breast tumor would be significantly reduced.

A best result could be accepted here was at the diffusivity if 2.7 x 10^{-5} cm^2/s, known as optimal drug diffusivity. Well, to achieve this diffusivity, this drug, doxorubicin may can replaced by another drug with diffusivty of 10^{-5} cm^2/s. Other device also can be used to enhance drug diffusitivity and there still a need for furthering the research.

3.1.2 Discussion on efficiency of drug delivery under temporal placement of transdermal patch parameter

With the reservoir system, there is a tendency for the drug molecules to diffuse into the control membrane over time and saturate it. As explained earlier, constant concentration gradient is important for most well designed patch. There needs to be a significantly large amount of drug in the device in order to maintain a uniform concentration gradient over the duration of patch use. When drug concentrations in the patch are depleted significantly, the drug release rate begins to drop, and the zero-order rate is no longer maintained. Most patches should be removed before reaching this stage. This means there is still a significant amount of drug remaining in the patch after it is ‘used up’. (Ratna, M., 2004)

After one month, the concentration gradient turned to zero. Therefore, there was a need to remove and change the patch with another patch. Besides, longer placement and larger surface area of skin being contacted with the transdermal patch, these will cause skin irritation of patients. Thus, it is not encouraged for a patch to be put on the skin for too long. Moreover, there is a risk that the patch will become detached and subsequently supply inadequate medicinal product to the body. Hence, changing with another is needed for solving these stated problems. According to EVRA™ Product monograph, 1.8% of patches needed to be replaced due to detachment and 2.8% due to partial detachment in a large clinical study using EVRA®.

3.2 Efficiency of drug delivery under deepness of breast tumor parameter

To investigate the relationship between drug delivery efficiency and deepness of tumor within breast, drug concentration for two different location of tumor in the same breast volume were analyzed, and the results obtained are shown in the Table 3

Deepness of Breast Tumor	Drug Concentration, c (mol/cm^3)
Top of the breast	0.012219
Bottom of the breast	0.056516

Table 3: Concentration of drug at tumor that grown at the top and bottom of breast.

3.2.1 Discussion on efficiency of drug delivery under deepness of breast tumor parameter

The concentration gradually declined from the maximum to the minimum with an apparent iso-contour distribution of concentration. The drug distribution had high concentration around the corner of patch and stratum corneum. These results confirmed that the interphase drug concentrations have a direct connection with the diffusion path. The concentration of drug had a uniform front, where the diffusions around the corner between the patch and stratum corneum showed greater local drug concentration, which was presented by red colour. In contrast, local drug concentration at the end from patch and stratum corneum was shown by blue colour, which was the minimal.

3.3 Efficiency of drug delivery under spatial placement of transdermal patch

To relate drug delivery efficiency to spatial placement of transdermal patch on skin, drug concentration at tumor was analyzed when placing the trransdermal patch at different site of breast, one at the top of breast and one at the bottom of breast and the results were tabulated in the Table 4.

Spatial Placement	Drug Concentration, c (mol/cm^3)
Top of the breast	0.012219
Bottom of the breast	0.061773

Table 4: Concentration of drug at tumor when patch aplied at different locations.

3.3.1 Discussion on efficiency of drug delivery under spatial placement of transdermal patch

In studying the effect of deepness of breast tumor on drug delivery efficiency, deeper the breast tumor was grown would cause lesser drug concentration being diffused and reached on tumor was discovered. Therefore, applying patch on different position of breast had been examined on the drug delivery efficiency.

From the results, poorer of drug concentration could be diffused when the deeper of the breast tumor was. However, this could be solved by applying the transdermal patch on different location due to the nearer of patch to the tumor, the drug concentration able to diffuse to the tumor will be higher. So, when the tumor was grown at the bottom of breast, the patch could be placed at the bottom of breast for better drug delivery and in otherwise.

4. CONCLUSION

In conclusion, effects of simulation parameters on determining the drug's concentration and drug delivery efficiency were performed successfully in the present study. In this study, drug diffusivity was considered as important parameter in the drug delivery efficiency, as approved by the transportation work of the transdermal delivery system. Some other parameters (i. e. deepness of breast tumor, spatial and temporal placement of transdermal patch) were also taken into account. According to the results obtained, there was an optimal drug's concentration at the drug diffusivity of 10^{-5}. Below or above this optimal drug diffusivity, the drug delivery efficiency would be affected. Drug diffusivity at 10^{-5} could contribute to maximal drug delivering to the targeted cancer cells. There was an indirect relationship between deepness of breast tumor and spatial placement of transdermal patch. Deeper the tumor grown within breast, lesser drug's concentration could be diffused to it. However, this could be solved by changing the place of transdermal patch application due to the nearer the transdermal patch application to the tumor site, more efficiency of the drug delivery could be achieved. The temporal placement of transdermal patch also had significant affect

on drug delivery efficiency. Drug release from patch would be reduced until there was no drug diffusing into the skin, and the period designated was normally less than one due to long placement of patch would cause irradiation to skin.

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APPENDIX B1

BREAST IMAGES FOR SIMULATION RUN OF 1-13

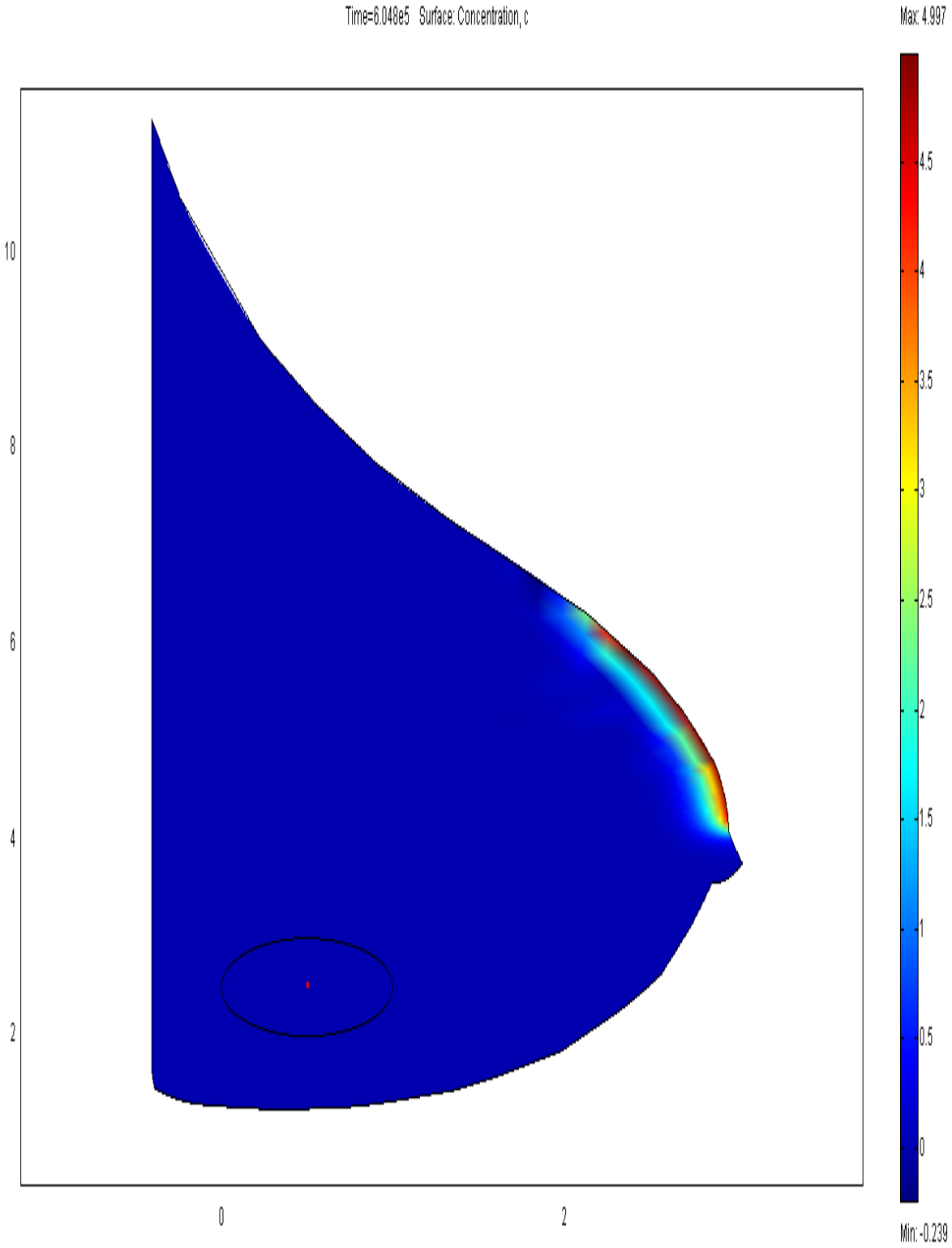

Figure B1.1: Drug's concentration after one week using drug diffusivity of 2.7 x 10^{-8} cm^2/s.

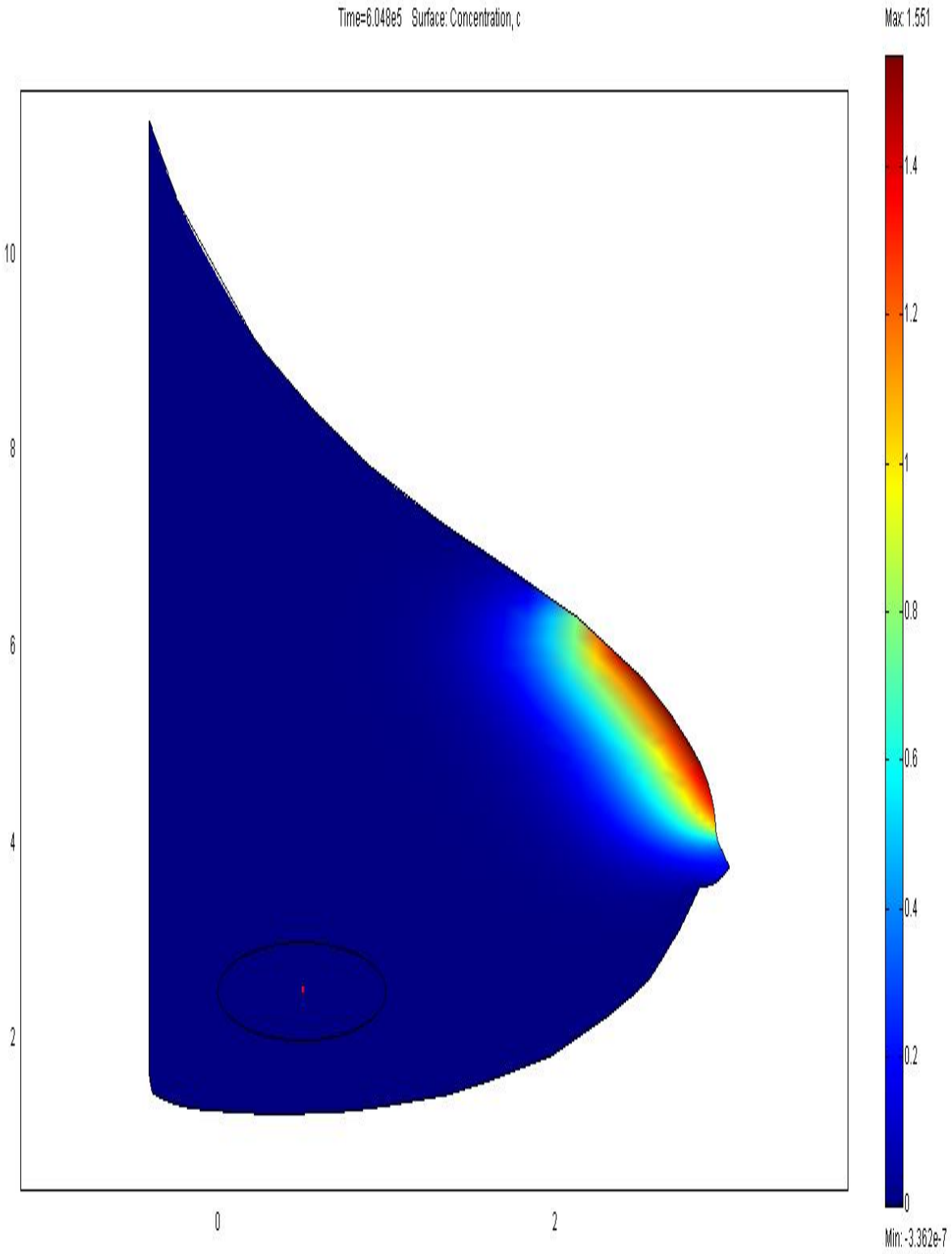

Figure B1.2: Drug's concentration after one week using drug diffusivity of 2.7 x 10^{-7} cm^2/s.

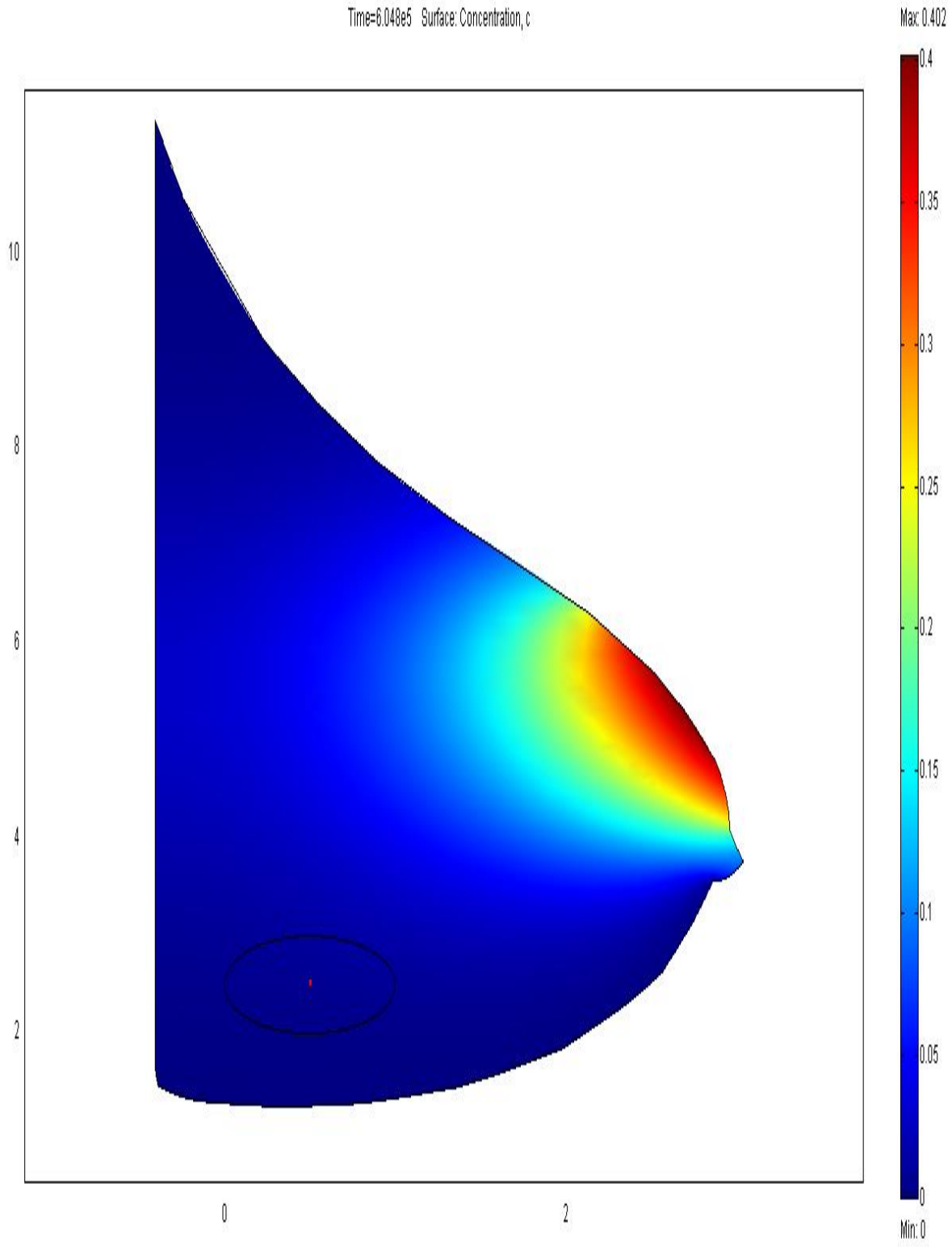

Figure B1.3: Drug's concentration after one week using drug diffusivity of 2.7 x 10^{-6} cm^2/s.

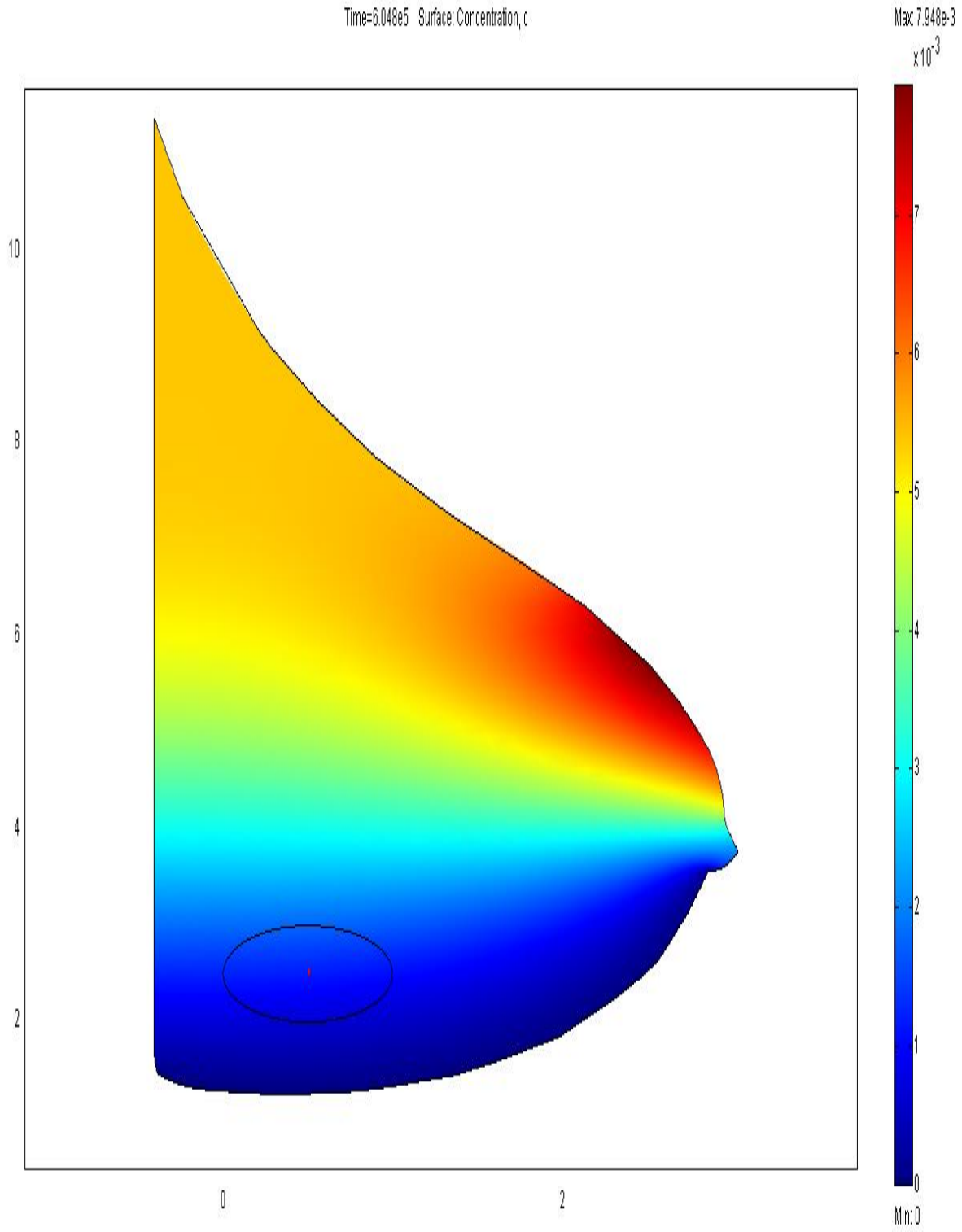

Figure B1.4: Drug's concentration after one week using drug diffusivity of 2.7 x 10^{-4} cm^2/s.

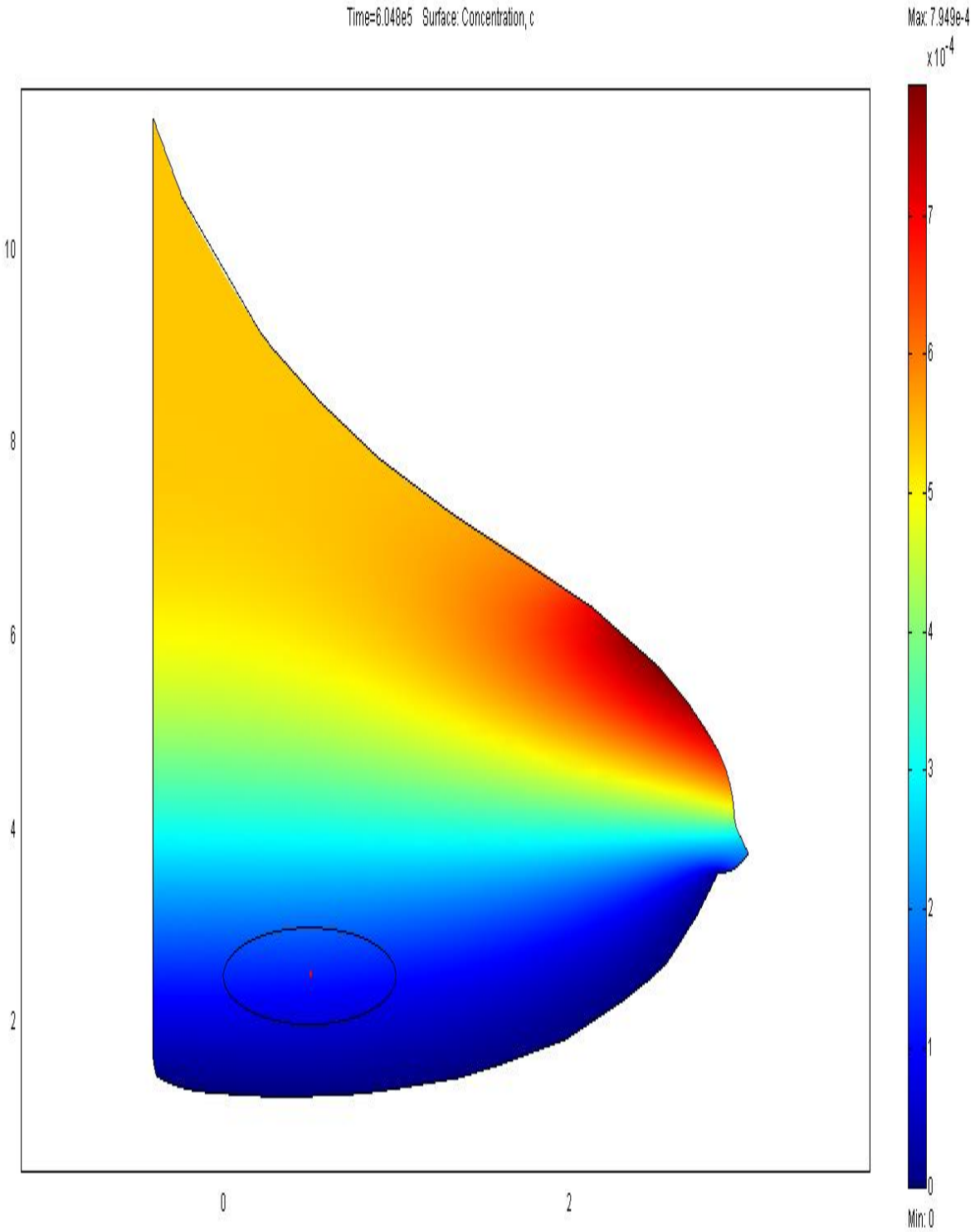

Figure B1.5: Drug's concentration after one week using drug diffusivity of 2.7 x 10^{-3} cm^2/s.

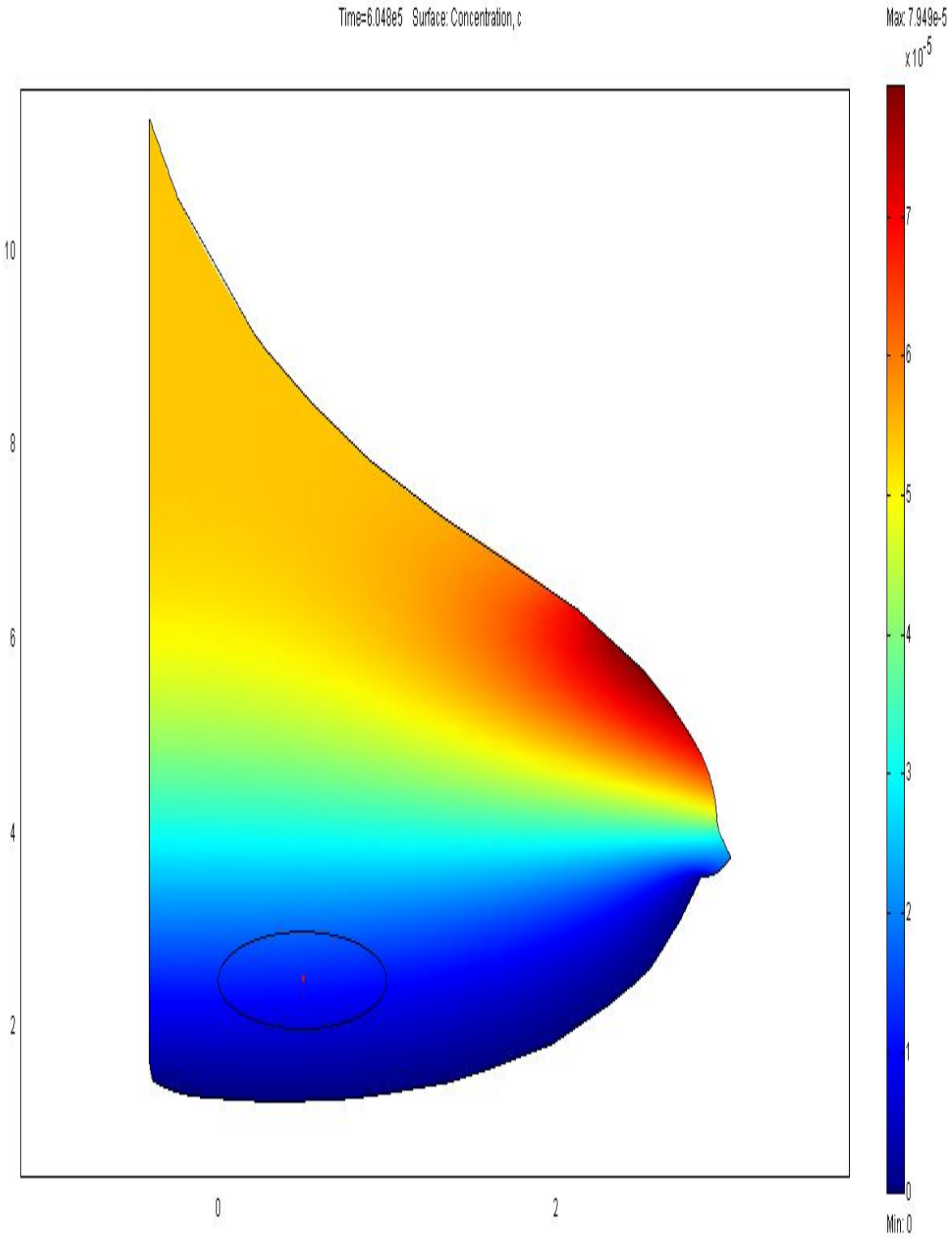

Figure B1.6: Drug's concentration after one week using drug diffusivity of 2.7 x 10^{-2} cm^2/s.

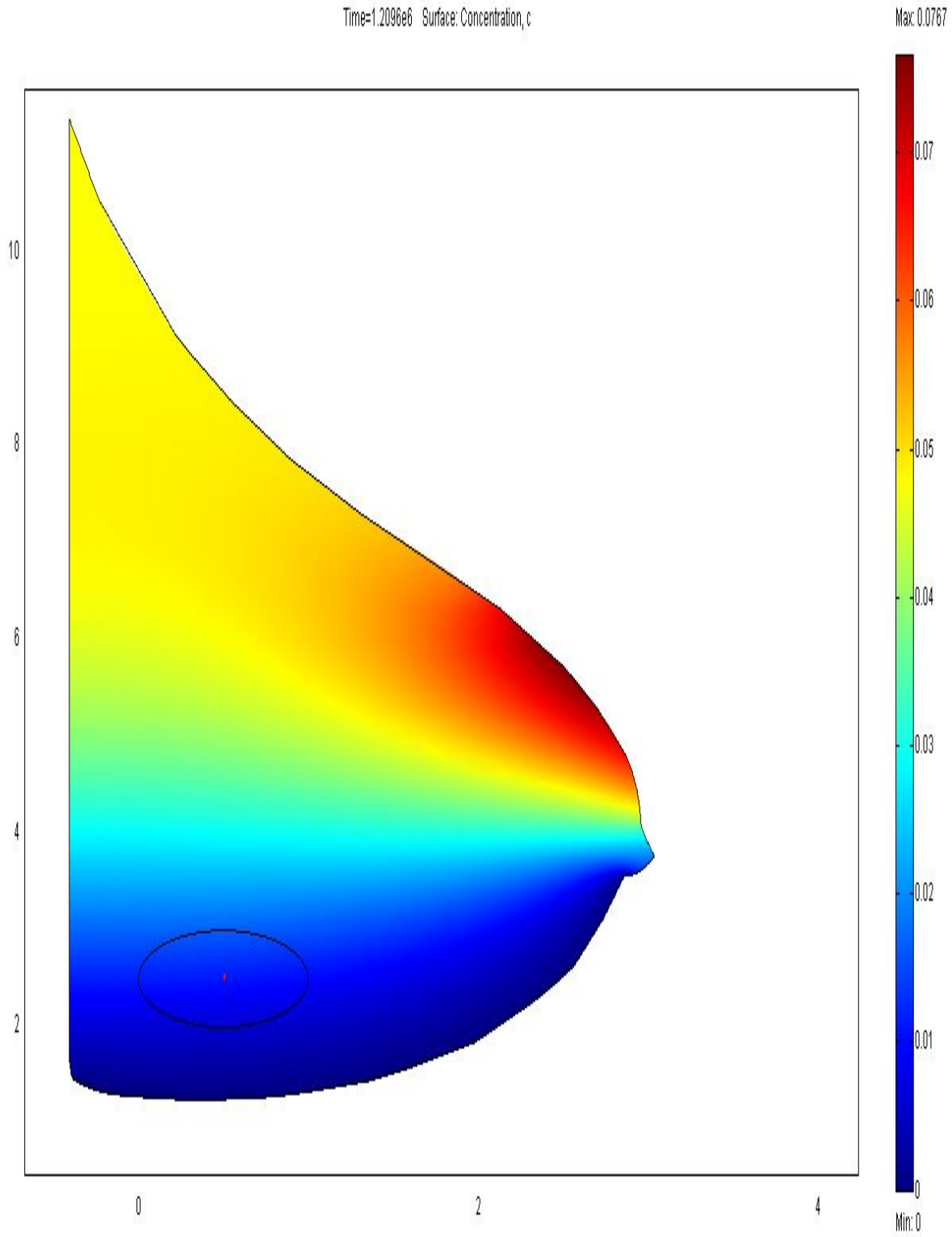

Figure B1.7: Drug's concentration after two weeks using drug diffusivity of 2.7 x 10^{-5} cm^2/s.

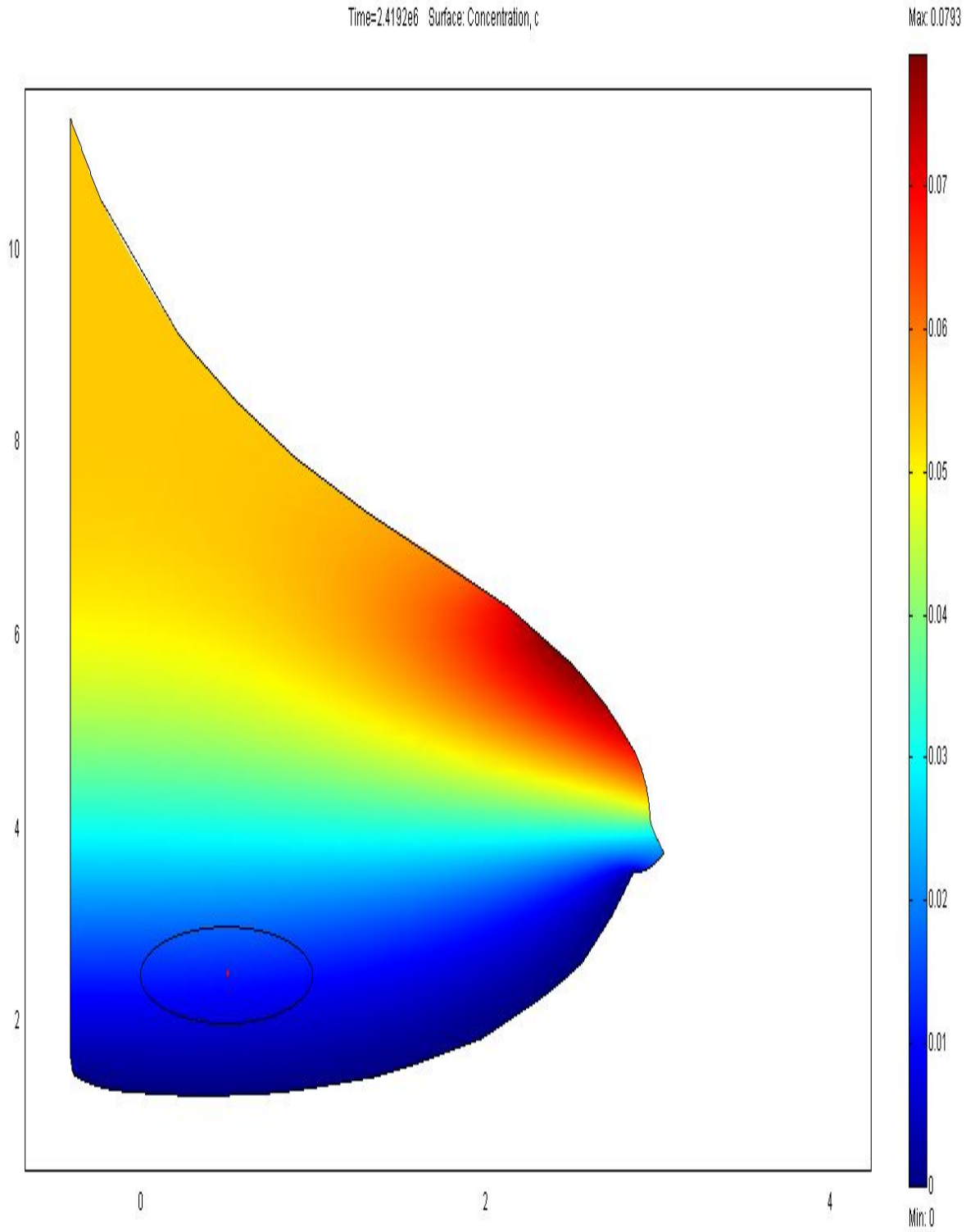

Figure B1.8: Drug's concentration after one month using drug diffusivity of 2.7 x 10^{-5} cm^2/s.

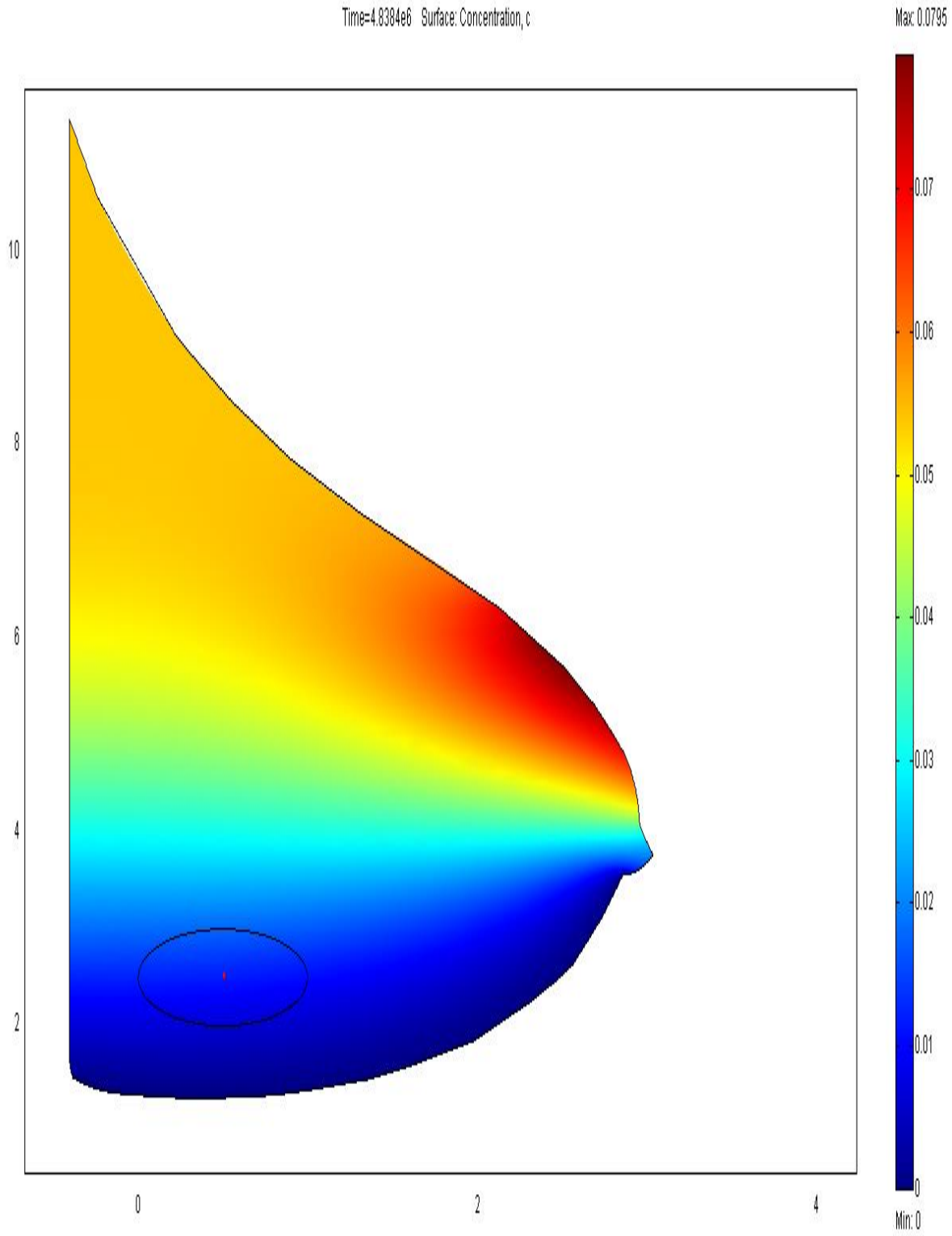

Figure B1.9: Drug's concentration after two months using drug diffusivity of 2.7 x 10^{-5} cm^2/s.

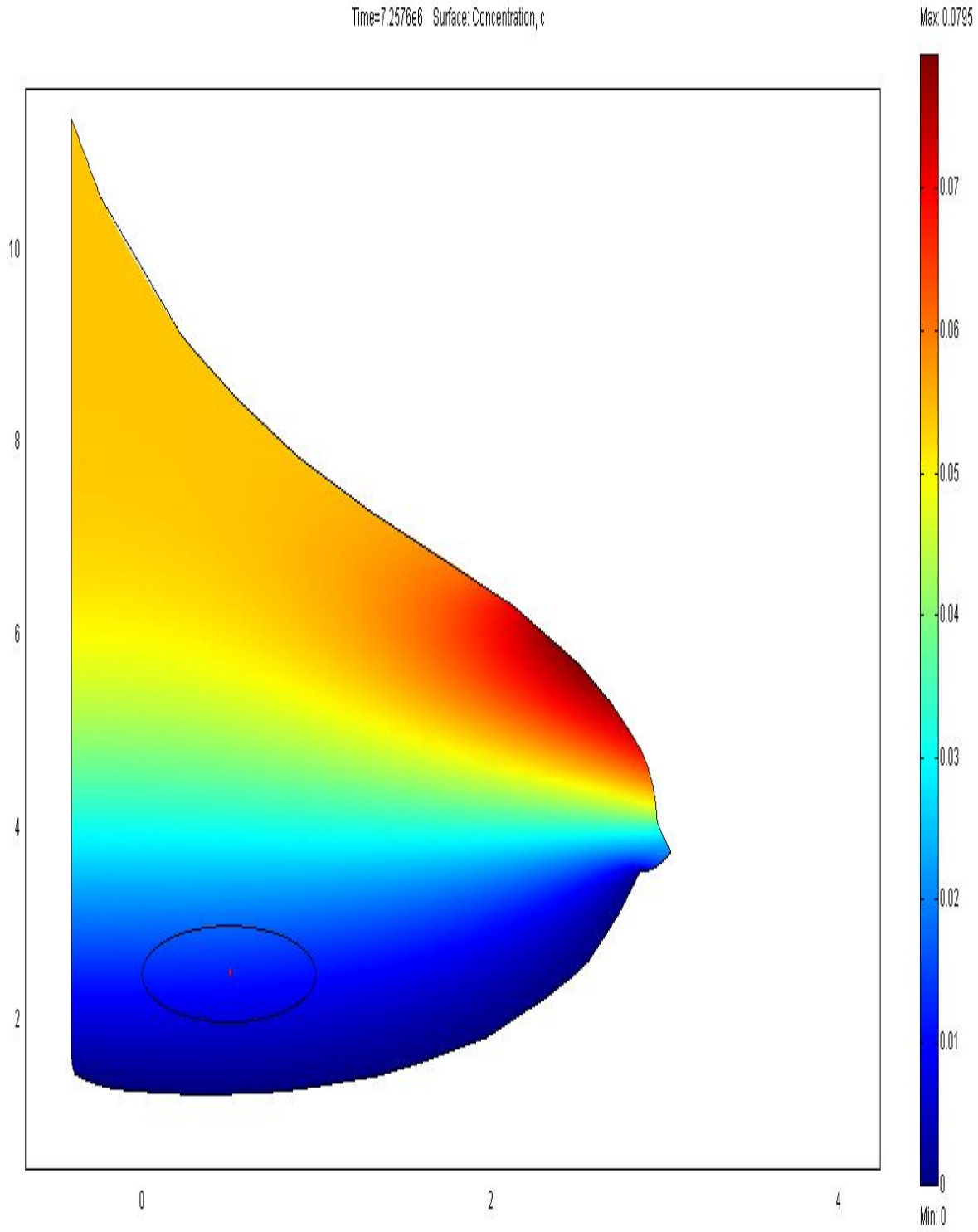

Figure B1.10: Drug's concentration after three months using drug diffusivity of 2.7 x 10^{-5} cm^2/s.

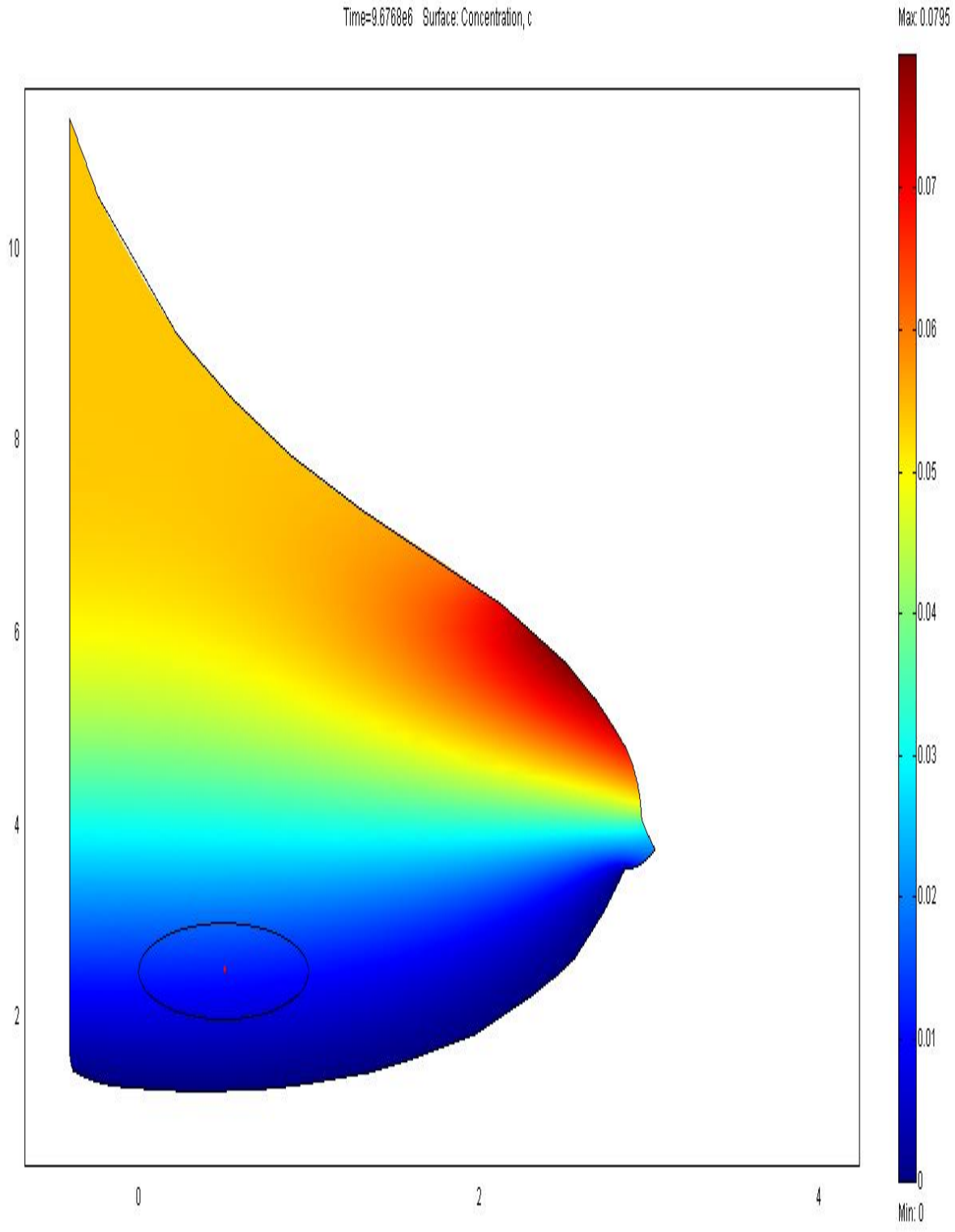

Figure B1.11: Drug's concentration after four months using drug diffusivity of 2.7 x 10^{-5} cm^2/s.

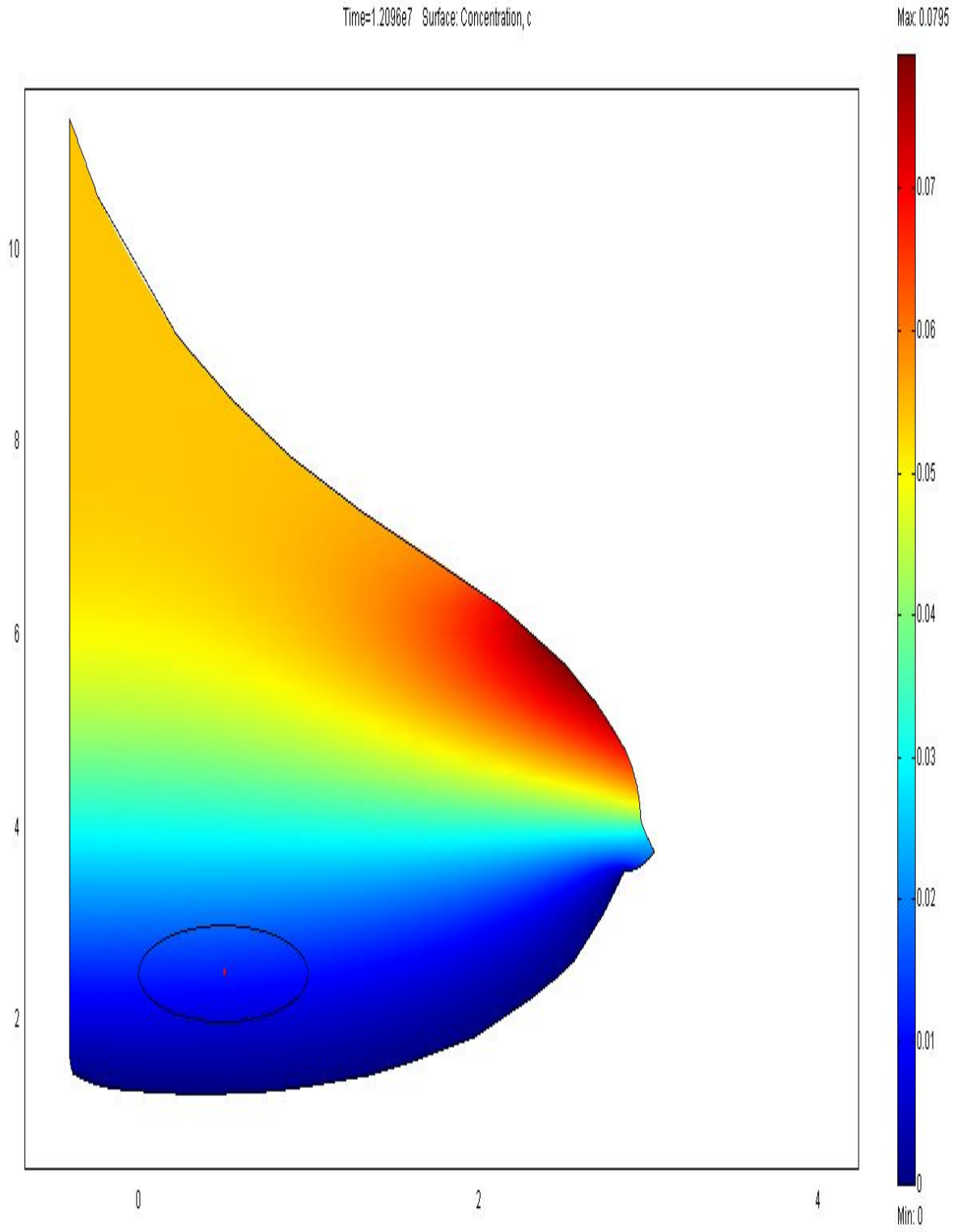

Figure B1.12: Drug's concentration after five months using drug diffusivity of 2.7 x 10^{-5} cm^2/s.

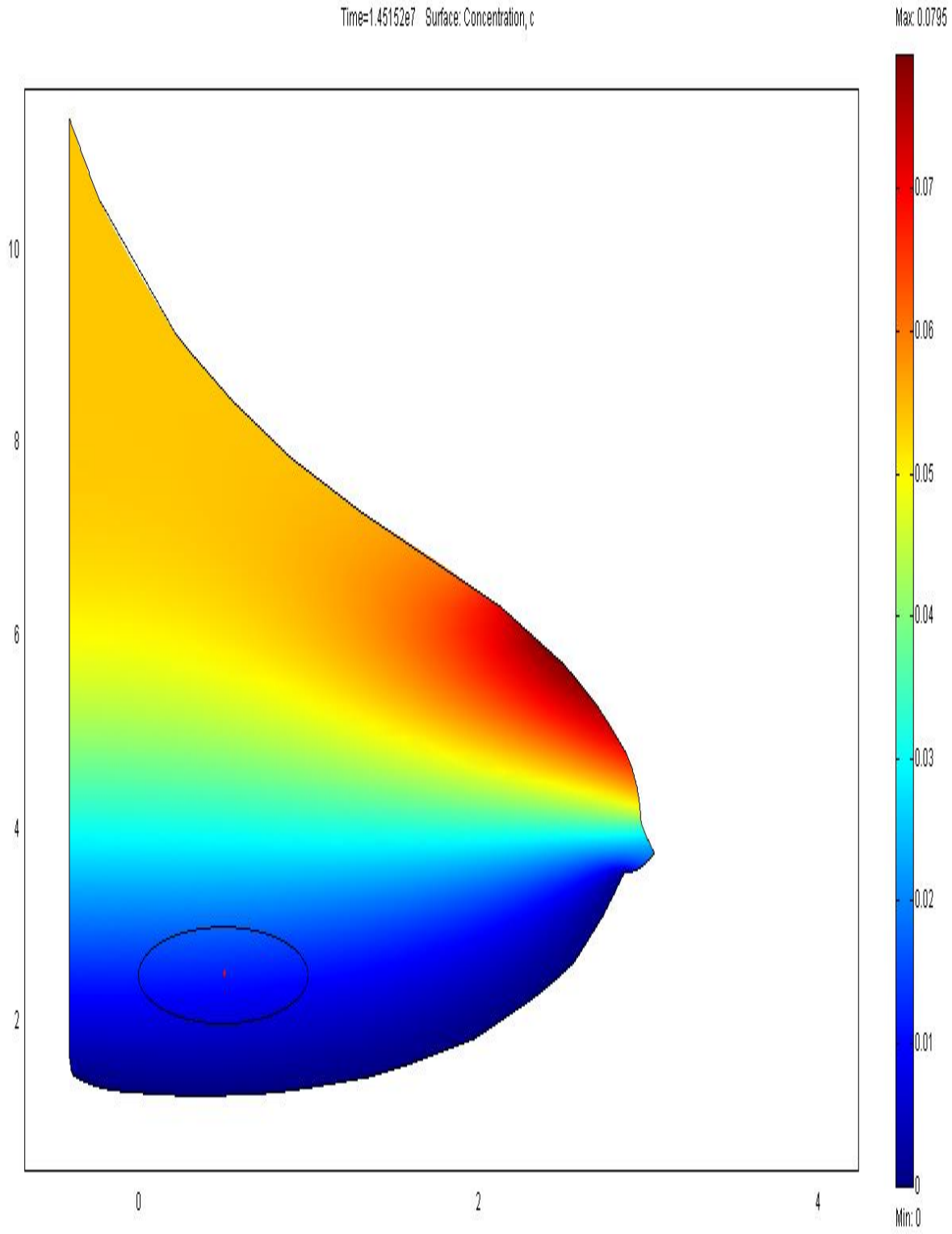

Figure B1.13: Drug's concentration after six months using drug diffusivity of 2.7 x 10^{-5} cm^2/s.