SIMULATION ON TRANSDERMAL PATCH FOR BREAST CANCER THERAPY BY USING COMSOL

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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.

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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LIST OF SYMBOLS

C	Concentration
c	Centimeter
D	Diffusion Constant
Da	Dalton
ɗ	Delta
g	Gram
h	Height
mm	Millimeter
mol	Mole
r	Radius
s	Second
t	Time
µm	Micrometer
z	z-axis
Π	Pi
%	Percentage
>	More than

LIST OF ABBREVIATIONS

AC	Doxorubicin and Cyclophosphamide
e.g.	Example given
FEC	Epirubicin, Cyclophosphamide and Fluoruocil
i.e.	That is
MMM	Methotrexate, Mitozantrone and Mitomycin
SI	International System of Units

CHAPTER 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 determine the drug concentration at breast tumor,

2. To investigate the relationship between drug diffusivity and drug delivery efficiency, and
3. 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, 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.

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 OVERWIEW 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 2002 and 2003 respectively (Figure 2.2).

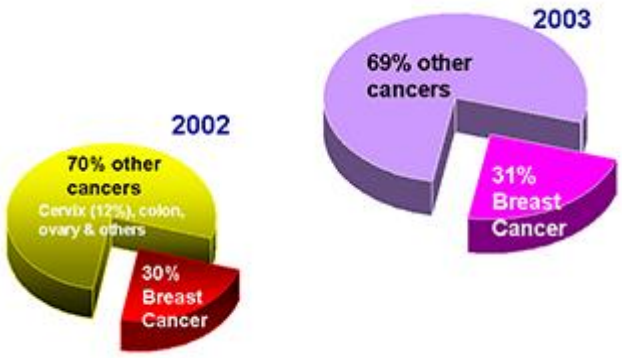

Figure 2.2: Percentage of different kinds of cancer in Malaysian women, in the year of 2002 and 2003.

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.
- Nausea.

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 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.

2.4 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 2.3).

Figure 2.3: Components of transdermal patch, which consisted of five main key elements such as liner, drug, adhesive, membrane and backing.

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)

2.5 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 capillary 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.

2.5.1 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 2.4). 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.