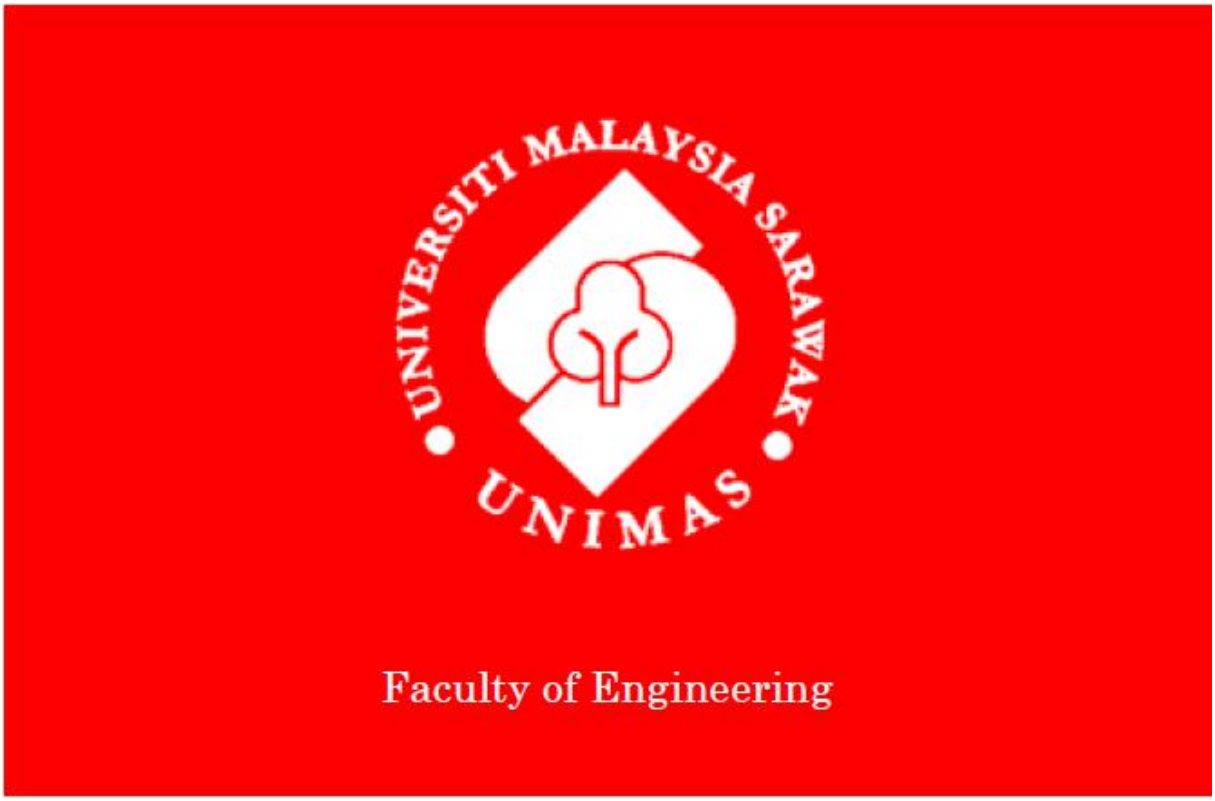

NON-NEWTONIAN BLOOD FLOW BEHAVIOUR IN MICROCHANNELS-APPLICATION IN MEDICAL INDUSTRY

YANA SHAHEERA BINTI YUNOS

Bachelor of Engineering with Honours
(Mechanical and Manufacturing Engineering)
2015

UNIVERSITI MALAYSIA SARAWAK

Grade:

Please tick (√)	
Final Year Project Report	√
Masters	
PhD	

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Ir. Dr. Mohd Danial Ibrahim Date

(Supervisor)

NON-NEWTONIAN BLOOD

FLOW BEHAVIOUR IN MICROCHANNELS-APPLICATION IN MEDICAL INDUSTRY

YANA SHAHEERA BINTI YUNOS

A dissertation submitted in partial fulfillment

of the requirement for the degree of

Bachelor of Engineering with Honours

(Mechanical and Manufacturing Engineering)

Faculty of Engineering

Universiti Malaysia Sarawak

2015

Dedicated To My Beloved Family and Friends...

ACKNOWLEDGEMENT

First and foremost, I thank Allah and both of my parents, Mr. Yunos Bin Aili and Mrs. Lily Suriany Binti Mohd. Yussof for continuously gives me strength and guidance to finish up my thesis and undergo my Degree of Bachelor of Engineering with Honours in Mechanical and Manufacturing Engineering. Not to be forgotten, I would like to take this opportunity to express my deep gratitude to my supervisor of the project, Dr. Mohd Danial Bin Ibrahim for his patience, advices, supervision, guidance and continuous support throughout my final year project.

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ABSTRACT

Blood is a complex suspension that demonstrates non-Newtonian rheological characteristics. The study of hemorheology has been of great interest in the fields of biomedical engineering and medical researches for many years. Micro-channel such as micro-needle has been an expanding medical technology in recent years due to their ability to penetrate tissue and deliver therapy with minimal invasiveness and patient discomfort. Micro-channel geometries have been used to study the inertial focusing behaviour of particles suspended as variations in design have allowed for enhanced fluid delivery. This manuscript focuses on the fluid flow aspects of the design which has four different shape of channel, characterizing the contributions to hydraulic resistance from the geometric parameters of the micro-channels and the inner surface roughness of the channel which is made from different type of material. Simulations using COMSOL consisted of measuring the flow rate of blood through a relevant range of channel lengths, channel diameters, shape of channel and also material of the channel. The objectives of the study are to investigate the theoretical principles of a blood as a non-Newtonian fluid used for measuring velocity inflow of micro-needles of different type of inner design with different properties and to investigate the effect of non-Newtonian on the blood rheology and flow patterns. The discussion will also include the comparisons of flow velocity in the micro-needle in delivering drug and blood. The micro-needle geometry is successfully designed to improve the flow performance and potentially the micro-needle to deliver drug and blood efficiency.

ABSTRAK

Darah adalah satu penggantungan yang kompleks untuk menunujukkan karakter-karakter *non-Newtonian.* Pembelajaran tentang reologi darah telah memberi impak yang besar dalam kejuruteraan bioperubatan bertahun lamanya. Salah satu contoh saluran mikro yang telah lama mengembang di bidang teknologi perubatan adalah *micro-needle* yang faktot utamanya adalah mampu menembusi tisu-tisu dan menghantar terapi dengan kesakitan yang minimum dang mengurangkan ketidakselesaan pesakit. Geometri saluran mikro telah lamadigunakan untuk mengkaji kelakuan dalaman zarah yang mengalir dalam variasi rekabentuk yang meningkatkan perjaanan pepejal dalam saluran mikro. Tesis ini fokus kepada pengaliran pepejal dalam empat rekabentuk saluran dan menggunakan dua jenis bahan untuk membezakan dari segi kekasaran permukaan. Simulasi untuk mengukur kadar aliran darah di dalam saluran yang berbeza panjang saluran, garis pusat saluran, bentuk dalaman saluran dan jenis bahan saluran dengan menggunakan COMSOL. Objektif pembelajarn ini adalah untuk mengkaji prinsip teori darah sebagai pepejal *non-Newtonian* dengan mengukur aliran masuk halaju dalam *micro-needle* yang mempunyai pelbagai sifat dan menyiasat kesan *non-Newtonian* terhadap reologi darah dan corak aliran. Perbincangan juga termasuk tentang perbandingan halaju aliran dalam *micro-needle* untuk mengalirkan ubat dan darah. Bentuk *micro-needle* telah berjaya di ubah suai untuk meningkatkan prestasi aliran dan kebolehan *micro-needle* untuk mengalirkan ubat dan darah dengan berkesan.

CHAPTER 1

INTRODUCTION

1.1 Background

Injecting drug and blood withdrawing techniques are obtained either from arteries or veins. By using hypodermic needle to penetrate human skin until reach the arteries or veins is surely uncomfortable and painful. From the beginning of the realization of painless needle from mosquito's mechanism of blood withdrawal, lots of research is done to improve the efficiency of the micro-needles for drug delivery and blood withdrawal from various sizes of needle and designs. From hypodermic needles to the current conventional micro-needle, the advancement of the researches leads to the technologies of micro-needles in improving the flow and performance while completing the task of penetrating the human outermost skin to withdraw blood or injecting fluid drug into the blood stream (Khumpuang et al., 2007).

1.1.1 Introduction to Microfluidics/Microchannels

Micro-fluidics is a multidisciplinary field intersecting engineering, physics, chemistry, biochemistry, nanotechnology and biotechnology with practical applications to the design of systems in which small volumes of fluids are handled that characterized by the study and manipulation of fluids at millimeters length scale. The application of microfluidics is among the greatest engineering challenges of the century and includes drug discovery efforts. The idea of microfluidics is that fluids that can be precisely manipulated using a micro-scale device which is micro-needle with technologies first

developed by the semiconductor industry and later expanded by the micro-electromechanical system (MEMS).

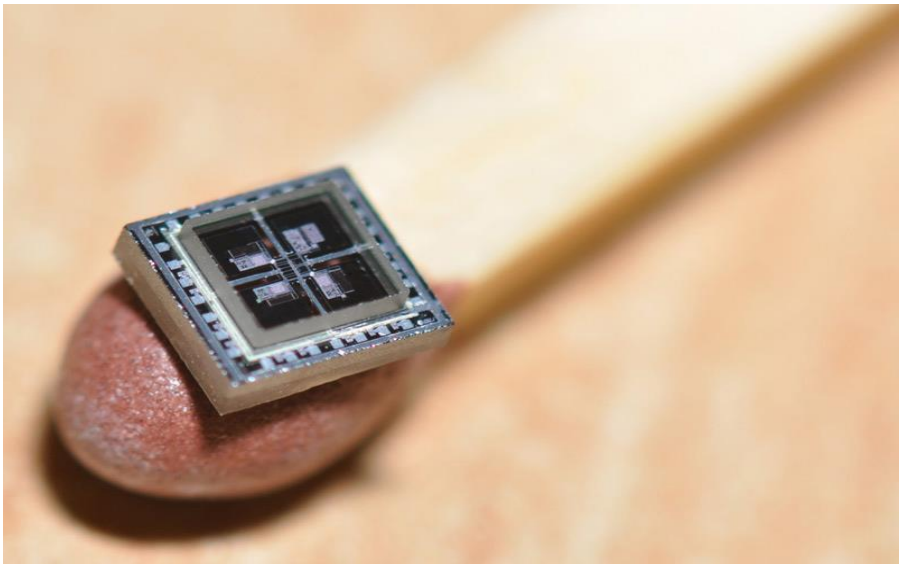

Figure 1.1 Micro-mechanical systems (MEMS) chip (International Electrotechnical Comission, 2014)

The terms of micro-fluidic and micro-channel came from the invention of the micro-needle which is inspired by female mosquito's bloodsucking mouthparts, proboscis. A female mosquito sucks blood by flexing and relaxing certain muscles in proboscis which makes the drawing of blood creates a suction or negative pressure into its proboscis. When a mosquito lands on us, it inserts its proboscis several millimetres deep into the skin which is less than the width of human hair and very sharp so it can be easily inserted into tissue with minimal damage to the surrounding tissue. With the discovery of the mechanism, a painless hypodermic needle or micro-needle is invented by engineers in India and Japan which mimics the way a female mosquito sucks blood. The needle could be used to draw blood, insulin pump, glucose-level monitor for diabetics and other drug delivery devices.

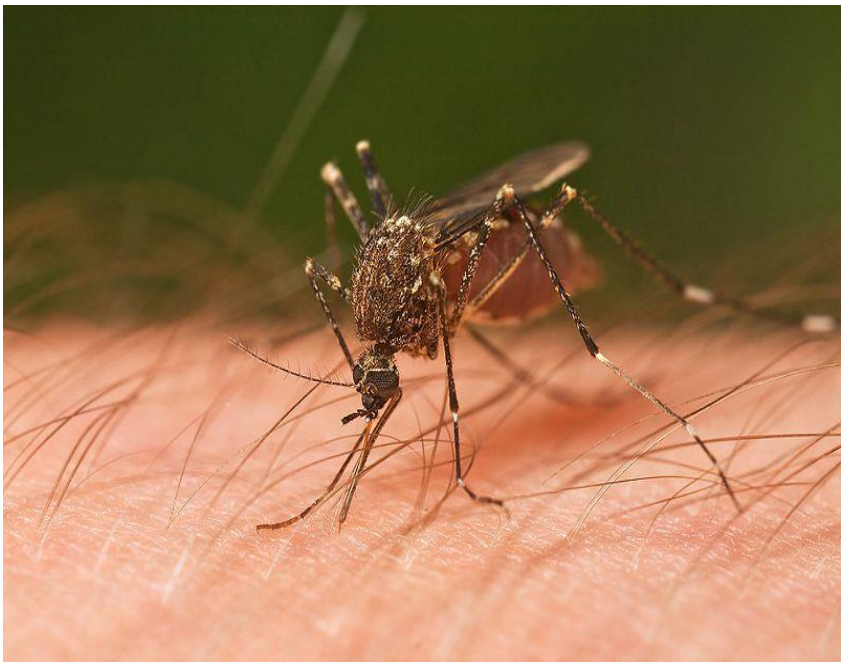

Figure 1.2 Blood sucking female mosquito (AskNature, n.d.)

Micro-channel is a channel with dimensions ranging from millimetres (mm) down to micrometers (μm) and well defined as a channel having a hydraulic diameter of 1mm. Micro-channels are commonly used in heat transfer in micro-heat exchanger and fluid control in micro-fluidics. Designs for micro-needle have been thrown around the science world in the past but the previous designs used a much smaller needle length and more brittle material, silicon dioxide. The future micro-needle design uses titanium for much more snap resistant needle so the needle is strong enough to penetrate as far as 3mm into skin and reach capillary blood vessels during injections. Its size compared to earlier models also means that the surface tension effects are exploited further and the same capillary flow that helps the blood to be draw into and out the micro-needle.

1.1.2 Drug Delivery History in Medical Application

Drugs have been long used to improve health and extend lives. The practice of drug delivery has changed dramatically in the last few decades and even greater changes are anticipated in the near future. Engineers not only contributed substantially to our understanding of the physical barriers to efficient drug delivery such as transport in the circulatory system and drug movement through cells and tissues but also contributed in

development of a number of new modes of drug delivery that have entered clinical practice.

Drug delivery systems control the rate at which a drug is released and the location in the body where it released. Some systems can control both. But due to the interacting parts of the body there are unacceptable side effects that are not the target of the drug. Side effects limit the ability to design optimal medications for many diseases such as cancer, neurodegenerative diseases and infectious diseases.

The first generation of drug delivery in 1950-1980 is focused on developing oral and transdermal sustained release systems and establishing controlled drug release mechanisms. Drug delivery system field began in 1960s to 1970s and 1980s when macroscopic controlled drug delivery devices and implants were designed for delivery as mucosal inserts such as eye or vagina, as implants such as sub-cutaneous or intra muscular, as ingestible capsules such as G-I tract, as topical patches on the skin.

The second generation in 1980-2010 was dedicated to the development of zero-order release systems, self-regulated drug delivery systems, long-term depot formulations and nanotechnology-based delivery systems. In 1980s and 1990s, the microscopic degradable polymer depot systems were commercialized. The nanoscopic era began with systems proposed in 1970s then used in 1980s and came of age in 1990s which are presently evolving into many exciting and clinically successful products in 2000s. The latter part of the second generation was largely focused on studying nanoparticles formulations.

Drug delivery towards a productive third generation requires an open dialogue without preconceived ideas of the past. The drug delivery field needs to take a bold approach to designing future drug delivery formulation primarily based on today's necessities to produce the necessary innovations.

1.2 Objective

The objective of this project is

- To improve velocity of drug and blood in micro-needle
- To find the best flow performance of drug and blood in design micro-needle.

To achieved the objective various of micro-needles are designed

- Two different materials of micro-needle
- Four inner design of micro-needle
- Three different length of micro-needle
- Two different diameter of micro-needle

Comparisons of the velocities flow are then compared to find the best drug and blood flow performance in micro-needles. The materials used for micro-needle gives impact to the flow of fluid due to the difference surface roughness. In rough channel, the friction factor is higher than in smooth channel causing pressure drop increased significantly. This happens when frictional force is caused by resistance to flow as the fluid flows through the tube. These caused the pressure gradient in the channel increased significantly. The higher value of friction and pressure will caused the flow velocity to decrease. Moreover, decreasing the width of channel also increase the pressure drop in the channel.

The relation between surface roughness, diameter, length and shape will eventually affect the efficiency of the flow performance of blood and drug delivery in micro-channel. By improving the flow of fluid in micro-needle to find the best flow performance, patients that need an in-vivo treatment will be able to use micro-needles to deliver drug or blood into human skin with more volume and direct to the blood vessel compared to conventional micro-needles which only penetrate human skin where the drugs need to diffuse for body to absorb drugs while keeping the basic fundamental concept of mimicking a female mosquito feeding from a host. Being able to control slip length can achieve significant increase in volumetric flow rate of fluid requiring small pressure gradient.

CHAPTER 2

LITERATURE REVIEW

This chapter is about the details study of the skin structure of human, non-Newtonian fluid rheology, blood as non-Newtonian fluid, Navier's slip condition and fluid-wall interaction. The discussion of the human skin structure will allow us to understand about the anatomy of our skin layers and its function. A fundamental study of non-Newtonian rheology and blood as non-Newtonian fluid is also explained more in this topic which will be handful in analyzing flow profile in the micro-needle. The last part in this topic is the study of fluid-wall interaction and the relation of Navier's slip that allows us understand the parameters on the effects of the fluid flow in the micro-needles.

2.1 Microneedle developments

Hypodermic injection is a very good route for drug and vaccine delivery due to accessibility, avoidance of first pass effect and the potential for self-administration. However, there is several advantages including accidental needle sticks, pain, transfer of microbes into the puncture wound and needle phobia. Efforts to bypass the stratum corneum are aimed at altering the medication molecule to make it more lipid soluble which will enhance drug penetration. Transdermal patches have been used for several decades but newer forms offer improvements in efficacy. The original patches often failed to bond to the skin effectively and sometimes irritating patient's skin. In attempt to increase transport across the stratum corneum, chemical skin permeation enhancers were added.

The use of micro-needles is another recent area of research in transdermal drug delivery. Most early studies of micron-scale needles were performed with solid micro-needles. Micro-needles are inserted at a depth of 1mm within the skin yielded rapid insulin absorption and an adequate reduction of glucose level. In previous studies and researches, the solid micro-needles were pressed into the skin or scraped against the skin to create microscopic holes. These tiny holes increased skin permeability by up to four orders of magnitude. A transdermal patch was then applied to the treated area.

Figure 2.1 Improved micro-needle patch

Nowadays, technique of the usage of micro-needle is to encapsulate a dry coating of vaccines or drugs onto solid micro-needles and insert them into the skin. Within one minute, the coating is absorbed and the micro-needle is removed and discarded.

Small bore micro-needles can deliver insulin, a relatively small molecule, through the skin in amounts adequate for managing the patient's glucose levels. Today, micro-needle is the best suited for facilitating the treatment of diabetes patients. Diabetes affects approximately 250 million individuals worldwide. Insulin replacement is the primary form of treatment for type 1 diabetes and can also be used in advanced cases of type 2 diabetes.

2.2 Skin Structure of Human

Human skin is the largest organ of the human body and one of the complex tissues of the human body which include several layers which has different functions, components and structure. Figure 1 shows the layers of human skin and the thickness of each layer. Skin can be categorized into four main layers which is fat layer also called as hypodermis, dermis, epidermis and the outermost layer of tissue is called stratum corneum. Skin also a kind of material which is non-homogeneous, anisotropic, non-linear visco-elastic material (F.M. Hendriks et al.). The first contact of the body with needles is stratum corneum. It is a thin, flexible and bio-polymer layer which interconnected to corneocytes.

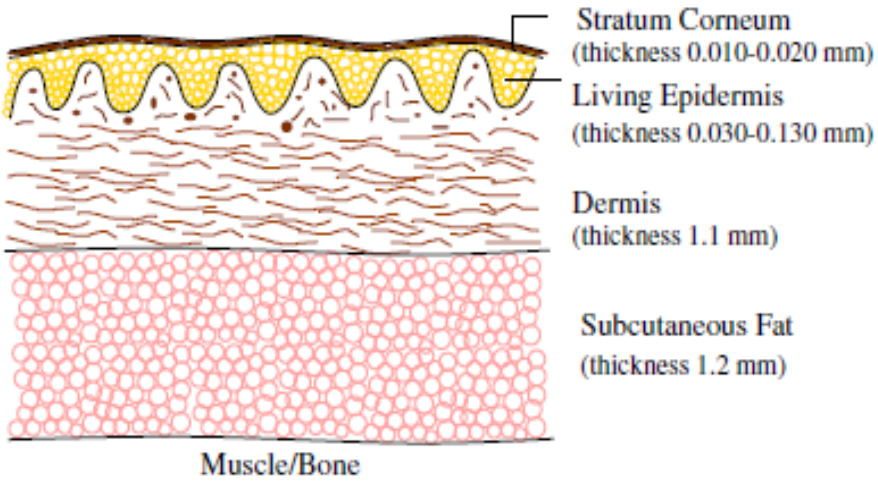

Figure 2.2 Cross section of human skin

Human skin in each part itself is different in their young modulus as it is claimed to double with age and differ in each part of human body. The level of hydration of human skin is affected by the young modulus and also the level of pain when the needle is about to penetrate the skin as human double with age, the young modulus in each part of human body skin is different. (Julien Van Kuilenburg, 2012)

Stratum Corneum, the outermost layer of human skin, serves as barrier as in preventing other fluid to absorb into and out of human body system such as water. According to Julien Van, this layer is composed of cornified dead cell which is 20-40μm thick. (Julien Van Kuilenburg, 2012)

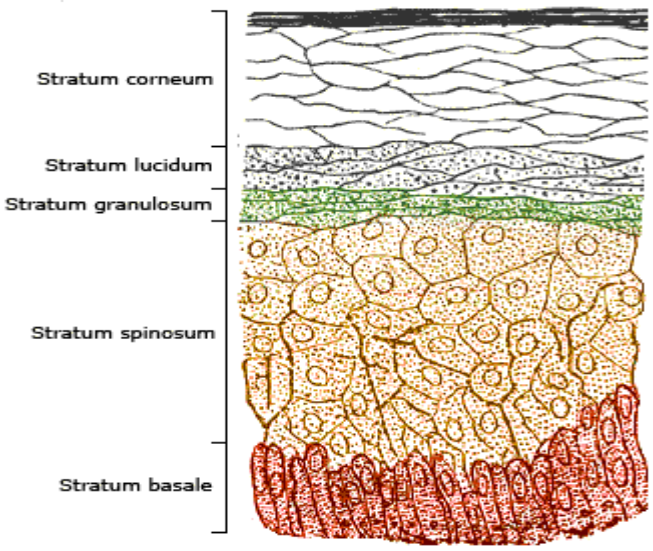

Figure 2.3 Structure of stratum corneum (Who Needs Vitamin D?, n.d.)

The structure of stratum corneum is very complex as it serves to couple the organism to the environment. In previous research, stratum corneum had been used in simulation since it is the initial contact with micro-needles. Since the significant point developing a micro-needle to rupture the stratum corneum to make the delivery more successful but only to drug by diffusing through the skin.

2.3 Non-Newtonian Fluid Rheology

The subject of rheology is devoted to the study of the behavior of non-Newtonian fluid. A non-Newtonian fluid is a fluid whose viscosity is variable based on applied stress or force. Usually non-Newtonian fluids consist of high molecular weight liquids as well as liquids in which fine particles that are suspended. The physical behavior of non-Newtonian fluid is always depends on the forces acting on it from time to time.

The slope of the shear stress versus shear rate curve will be not constant as we change the shear rate (Subramanian). When the viscosity decreases with increasing shear rate, the fluid is called shear thinning. In the opposite case where the viscosity increases as the fluid is subjected to a higher shear rate, the fluid is called shear thickening. Shear

thinning behavior is more common than shear thickening and will be discussed more in next sub-topic. Shear thinning fluids also are called pseudoplastic fluids.

2.3.1 Behaviours

A typical shear stress versus shear rate plot for a shear thinning fluid will looks like this.

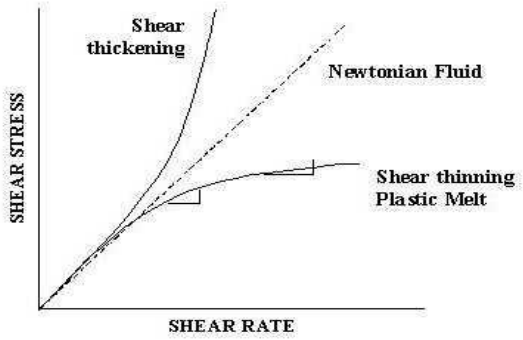

Figure 2.4 Relationship between shear stress and shear rate in shear thinning fluid (Shear, n.d.)

Figure 2 shows the relationship between shear stress and shear rate in shear thinning fluid. As shown in the graph above, the shear stress increases with the increasing of the shear rate. In Figure 3 below shows the relationship between shear rate and viscosity in shear thinning fluid. It shows that the viscosity decreases with increasing of shear rate.

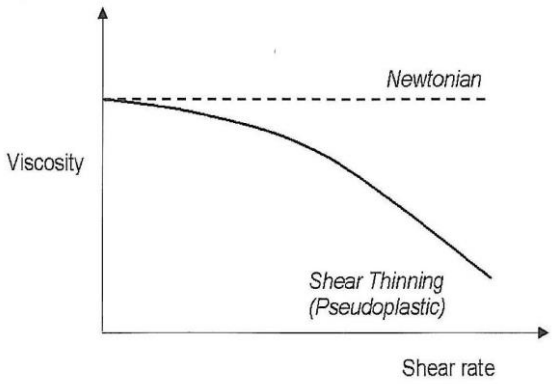

Figure 2.5 Relationship between shear rate and viscosity in shear thinning fluid (Chemical and Materials Engineering, 2005)

To relate both of the figure above, shear thinning fluid shows that when the shear rate increases the shear stress also increasing while the viscosity is decreasing.

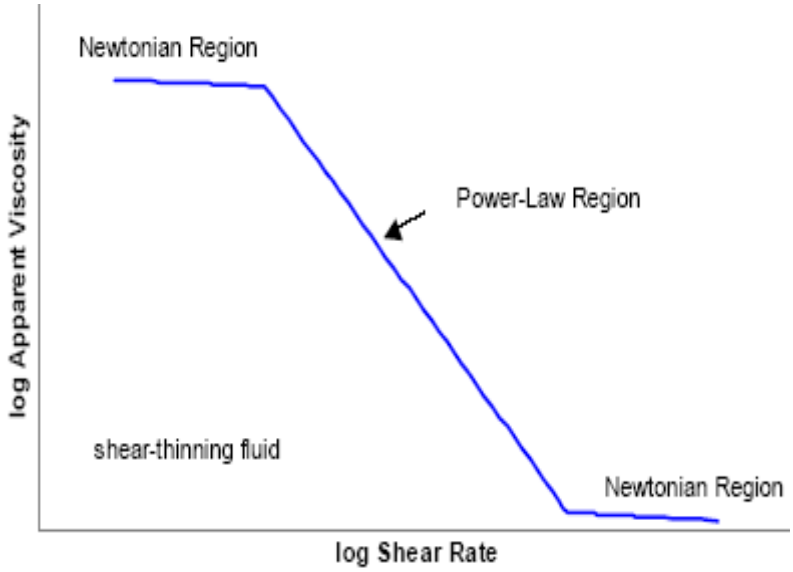

Figure 2.6 Newtonian region (BroadPulse Corporation, n.d.)

Many shear thinning fluids will exhibit Newtonian behaviour at extreme shear rates, both low and high. The figure above shows the regions where the apparent viscosity is approximately constant which are known as Newtonian regions. The behaviour between these regions can usually be approximated by a straight line on these axes. For instance, some classes of fluids exhibit time-dependent behaviour. Under a given constant shear rate, the viscosity may vary with time.

Examples of shear thinning fluids are polymer melts such as molten polystyrene, polymer solutions such as polyethylene oxide in water and paints. When the paint is sheared with a brush, it flows comfortably but when the shear stress is removed, the viscosity increases and no longer flows easily. The solvent then evaporates soon and the paint sticks on the surface. The behaviour of the paint is a bit more complex because the viscosity changes with time at a given shear rate.

2.3.2 Fluid Properties

Non-Newtonian fluids can be described in an act of action where if we punch a bucket full of non-Newtonian fluid such as cornstarch, the stress introduced by the incoming force causes the atoms in the fluid to rearrange such that it behaves like a solid, our hand will not go through. If we shove our hand into the fluid slowly, however it will penetrate successfully. If we pull our hand out abruptly, it will again behave like solid and we can literally pull a bucket of the fluid out of its container. In this way, non-Newtonian fluids help us to understand the wide variety of fluids that exists in the physical world.

When combined with an oscillating plate, non-Newtonian fluids demonstrate other unusual properties, like protruding "fingers" and holes that persist after creating them. An oscillating plate applies stress on a periodic basis, rapidly changing the viscosity of the fluid and putting it in an odd middle ground between a liquid and a solid. At the same time, there are examples where placing a bowl of corn starch near a vibrating speaker to see the interesting patterns that are created on the surface of the mixture. (General Electric Company, 2009)

To define it scientifically, a non-Newtonian fluid is a fluid whose flow properties are not described by a single constant value of viscosity. Many polymer solutions and molten polymers are non-Newtonian fluids, as are many commonly found substances such as ketchup, starch suspensions, paint, and shampoo. In a Newtonian fluid, the relation between the shear stress and the strain rate is linear, the constant of proportionality being the coefficient of viscosity. In a non-Newtonian fluid, the relation between the shear stress and the strain rate is nonlinear, and can even be time-dependent. Therefore a constant coefficient of viscosity cannot be defined.

2.4 Blood as Non-Newtonian Fluid

Blood is heterogeneous multi-phase mixture of solid corpuscles which contains red blood cells, white blood cells and platelets suspended in liquid plasma which is an aqueous solution of proteins, organic molecules and minerals. The rheological characteristics of blood are determined by the properties of these components and their components and their interaction with each other as well as with the surrounding structures.

Figure 2.7 Red blood cells (erythrocytes)

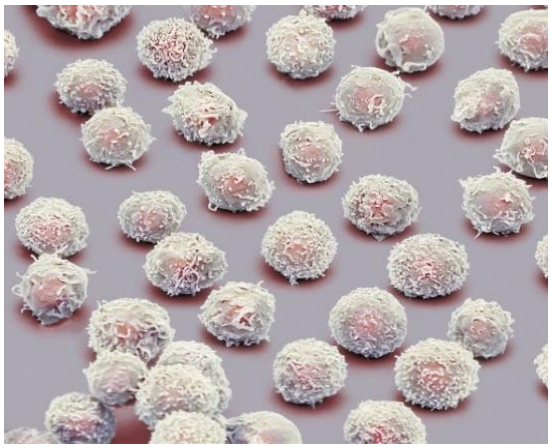

Figure 2.8 White blood cells (leukocytes)

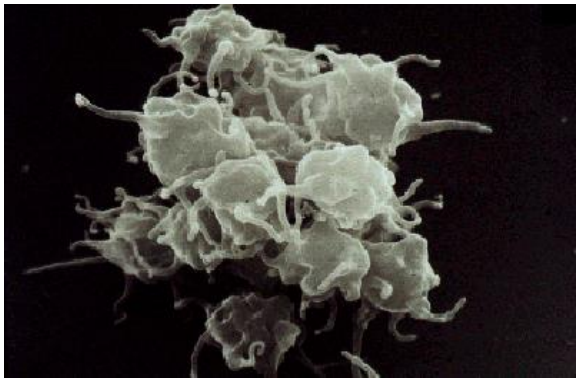

Figure 2.9 Platelets (thrombocytes)

The blood rheology is also affected by the external physical conditions such as temperature. However, in living organisms in general and in large mammals in particular, these conditions are regulated and hence they are subject to minor variations that cannot affect the general properties significantly. Other physical properties, such as mass density, may also play a role in determining the blood overall rheological conduct. The rheological properties of blood and blood vessels are affected by the body intake of fluids, nutrients and medication. Although in most cases the effect is not substantial except possibly over short periods of time and normally does not have lasting consequences.

2.4.1 Viscosity

The viscosity of blood is determined by several factors such as the viscosity of plasma, hematocrit level, blood cell distribution and the mechanical properties of blood cells. The blood viscosity is also affected by the applied deformation forces, extensional as well as shearing and the ambient physical conditions.

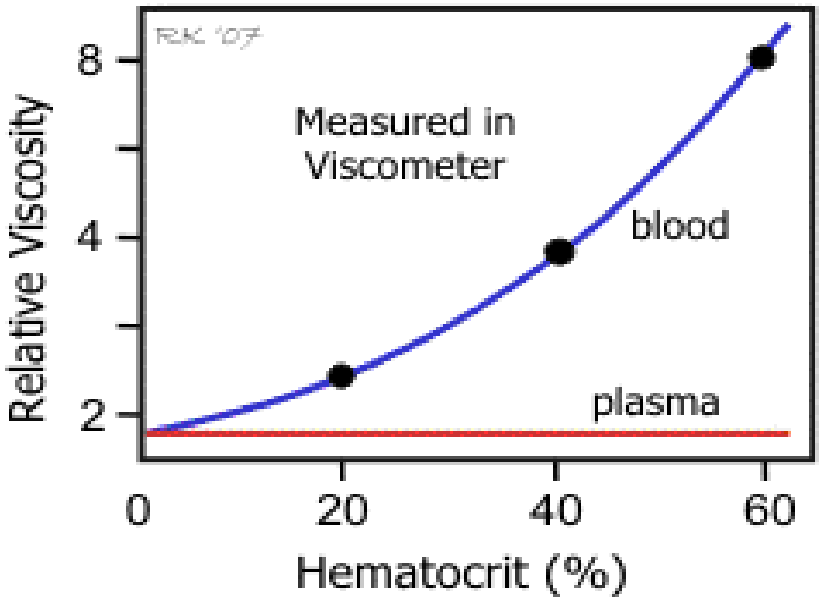

Figure 2.10 Viscosity of blood (Klabunde, 2010)

Although plasma is mostly water, it contains other molecules which causing molecular interaction between these components. It is not surprising that plasma has high viscosity than water even though water is behaved as Newtonian fluid.

The plasma is essentially a Newtonian fluid, the blood as a whole behaves as a non-Newtonian fluid showing all signs of non-Newtonian rheology which includes deformation rate dependency, viscoelasticity, yield stress and thixotropy. Most Newtonian effects originate from the red blood cells due to their high concentration and distinguished mechanical properties such as elasticity and ability to aggregate forming three-dimensional structures at low deformation rates.

2.4.2 Yield Stress

Blood demonstrates yield stress which arises from the aggregation of red blood cells at low shear rates to form the above-mentioned three-dimensional micro-structures that resist flow. Studies have indicated that yield stress is positively correlated to the concentration of fibrinogen protein in blood plasma and to the hematocrit level. Other factors such as the concentration of minerals also have contributions. Many of the blood rheological characteristics in general and non-Newtonian are also influenced by the fibrinogen level.

The yield characteristic of blood became negligible when hematocrit level falls below a critical value. Yield stress contributes to the blood clotting of injuries, healing and also to the formation of blood clots and vessel blockage in some pathological cases such as strokes. In experimental studies, shows the value of yield stress indicates that it is not significant and has no tangible effect on the flow profile at the biological flow ranges in large and medium size blood vessels. The magnitude of yield stress and it effect could be aggravated by certain diseased states related to the rheology of blood, like polycythemia vera or the structure of blood vessels such as stenoses.

The magnitude of the yield stress of human blood appears to be at the order of 0.05 dyne/cm^2 or 5 mPa (Stoltz, 1999) and is almost independent of temperature in the range of 10-37°C.