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DEGREE OF M.sc IN BIOMEDICAL ENGINEERING

Study of Blood Glucose Measurement Based on Blood Resistivity

دراسه قياس نسبه الجلكوز في الدم إعتمادا علي مقاومه الدم

BY

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Dedication

This thesis is dedicated to:

To my wonderful parent.

To my husband.

My friends who encourage and support me.

To all people who i love deeply and for all the staff of biomedical engineering.

Acknowledgment

In the Name of Allah, the Most Merciful, the Most Compassionateallpraisebe to Allah, the Lord of the worlds; and prayers and peace be uponMohamed His servant and messenger.

First and foremost, I must acknowledge my limitless thanks to Allah, the Ever-Magnificent; the Ever- Thankful, for His help and bless. I am totally sure that thisworkwould have never become truth, without His guidance.

Iowe a deep debt of gratitudetoour university for giving us an opportunity tocomplete this work.

I am grateful to some people,who worked hard with mefrom the beginning till the completionof the present research particularly my supervisor Dr. fragoon.

I would like to take this opportunity to say warm thanks to all my beloved friends,who have been so supportive along the way of doing my thesis.

I also would like to express my wholehearted thanks to my family for their generous supportthey provided me throughout my entire life and particularly through theprocess of pursuing the master degree. Because of their unconditional love and prayers, I have the chance to complete this thesis.

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Abstract

Diabetic patients are generally advised to check their blood glucose level 5to 7 times per day. Since the all current existing conventional methods of home blood glucose tests are painful, intimidating, laborious, and expensive, since they require obtaining a blood sample by pricking a fingertip with a needle or lancet. Thus it is necessary to develop a non-invasive blood glucose method which could provide fast, painless, and convenient glucose monitoring to diabetic patients. Since a noninvasive method of monitoring blood glucose would present major advantages over current existing methods which are using invasive technologies.

This project presents a noninvasive technique for bioelectrical resistivity applying current pulse technique and curve fitting method. Simple circuit for current injection and voltage detection, circuit requires four electrodes two to current injection and two to voltage detection. The current source is presented with constant output current as low as 5.5mA. The voltage signal amplified and filtered to be used on microcontroller.

The Voltage detection and calculate of blood glucose from curve fitting technique(formulate equation using Mat lab). Successful simulation results using protus8 program.

المستخلص

ينصح مرضي السكري عموما بقياس نسبه السكر من خمس الي سبع مرات في اليوم. الي الان كل الطرق التقليديه في الوقت الراهن التي تستخدم في المنزل مؤلمه ومخيفه وباهظه الثمن بالاضافه الي انها تتطلب اخذ عينه بوخز الاصبع باستخدام ابره او اداه حاده.لذلك كان من الضروري استحداث طرق لقياس الجلكوز تكون غير مباشره وسريعه وغير مؤلمه ومريحهلمراقبه الجلكوز لمرضي السكري. الطرق الغير مباشره لمراقبه الجلكوز في الدم لها فوائد عديده بمقارنه مع الطرق التي تستخدم في الوقت الراهن.

هذا المشروع يقدم طريقه غير مباشره باستخدام المقاومه الكهربيه الحيويه بتطبيق نبضه تيار علي اصبع واستخدام تقنيه رسم المنحنيات . الدائره بسيطه وذلك عن طريق حقن التيار والتقاط الجهد الناتج.التيار المستخدم خرجه ثابت 5.5مللي امبير ذو تردد عالي لكي لا يحس بالالم باستخدام الكترودين واستقبال الجهد الناتج من مقاومه الدم للتيار المار بواسطه الكترودين ومن ثم ترشيح وتكبير الاشاره الناتجه ومن ثم تحويلها الي وحده التحكم لحساب نسبه السكر في الدم بواسطه المعادله المستخلصه من المنحني الرابط بين مقاومه الدم ونسبه السكر في الدم بواسطه برنامج الماتلاب .تمت محاكاه المشروع بواسطه برنامج البروتوس.

Abbreviation

IDDM	Insulin Dependent Diabetes Mellitus
NIDDM	Noninsulin Dependent Diabetes Mellitus
DCCT	Diabetes Care and Complication Trial
FIR	Far Infrared
NIR	Near Infrared
AHF	Anti Hemophilic Factor
IVIG	Intra Venous Immune Globulin
AICC	Anti_ Inhibitor Coagulation Complex
IC	Integrated Circuit
LCD	Liquid Crystal Display
ADC	Analog to Digital Converter
PIC	Peripheral Interface Controller
ROM	Read Only Memory
RAM	Random Access Memory
CMRR	Common Mode Rejection Ratio
FDA	Food and Drug Administration

Chapter one

Introduction

1.1 Overview

Diabetes mellitus is a medical condition in which the body does not adequately produce the quantity or quality of insulin needed to maintain normal circulating blood glucose.Insulin is a hormone that enables glucose (sugar) to enter the body's cells to be used for energy. Two types of diabetes are common. Type - Is also known as Insulin Dependent Diabetes Mellitus (IDDM) and accounts for 5-10% of all cases. Type - II or Non-Insulin Dependent Diabetes Mellitus (NIDDM) occurs in 90-95% of the diabetic population.

IDDM occurs in childhood. It requires insulin doses to maintain life, in addition to healthy practices. Frequent self-monitoring of blood glucose is crucial for effective treatment and reduction of the morbidity and mortality of diabetes[1]. Unmonitored diabetes can lead to severe complications over time, including blindness, kidney failure, heart failure, and peripheral neuropathy associated with limb pain, poorcirculation, gangrene and subsequent amputation.

These complications are largely due to poor glucose control. The Diabetes Care and Complications Trial (DCCT) demonstrate thatmore frequent monitoring of blood glucose and insulin levels could prevent many of the long term complications of diabetes [2]. However, the conventional blood (finger stick) glucose testing & monitoring are painful, inconvenient due to disruption of daily life. Also, it causesfear of hypoglycemia resulting from tighter glucose control and may be difficult to perform in long term diabetic patients due to calluses on the fingers and poor circulation. A glucose measurement with following qualities, i) non-invasive, ii) non-contact, iii) fast measurement capability, iv) painless measurements, v) convenience for glucose monitoring and vi) cost effective which could provide adequate control and greatly reduce the complications seen in these patients.

At present, the simplest and less painful method for glucose measurements are done by pricking a finger and extracting a drop of blood (50µl/dl) which is applied to a test strip composed of chemicals sensitive to the glucose in the blood sample.

Impedance plethysmography is a technique that measures pulsatile changes in limb electrical impedance to quantify arterial blood flow. Impedance can be

defined as the resistance that results when an alternating electric currentis introduced into a biological conductor, such as a limb.

Because blood is a good electrical conductor, total resistivity in the extremity decreases with each arterial pulse and reflects the change in blood volume for the tissue segment under consideration.

This project is to design a device for blood glucose levelmeasurement, in order to accomplishthis, it need a calculation for the amount of glucose level proportional to the blood resistivity.

That after determining the blood resistivity by using data acquisition device toacquire the signal from the finger, this device should be able to detect the electrical potential (voltage) change across the finger so that the change in resistance may be determined. It may need building an electrical circuit to perform signal processing include amplification of signal and filtering, Finally use microcontroller to calculate blood glucose from blood resistivity .

1.2 Problem statement

In addition to conventionalway for measuring sugar level depend on taking blood samples which can be subjected to contamination and cause pain to the patient, themost of invasive glucose monitoring techniques based on glucose oxidase which require a direct contact between glucose and some chemical reagents, they necessitate the extraction of glucose from the body. However, a non-contact, noninvasive method is impossible with any chemical based method. The only attraction is usinga spectroscopic method. In a spectroscopic technique is used an optical beam interacts withglucose within the human body. The generated signals are then analyzed and the results displayed.

Problems of optical measurements dependent on concentration changes in all body compartments measured, as well as changes in the ratio of tissue fluids (as altered by activity level, diet or hormone fluctuations) and this, in turn, effects the glucose measurement. Problems also occur due to changes in the tissue after the original calibration and the lack of transferability of calibration from one part of the body to another. Tissue changes include: body fluid source of the blood supply for the

body fluid being measured, medications that affect the ratio of tissue fluids, day-to-day changes in the vasculature, the aging process, diseases and the persons metabolic activity. However, the ratio of body fluids (intracellular, interstitial, plasma) are affected by factors such as activity level, diet or hormone fluctuations, but also by blood circulation, body temperature shift, metabolic activity and medication.

All these factors are capable of influencing the optical parameters and, consequently, impacting the blood glucose measurement. Moreover, day-to-day changes in vasculature and tissue texture as well as the aging process may affect the long-term stability of glucose monitoring.

1.3 Objectives

1.3.1 The general objective The aim of this project is to develop a new method to measure blood glucosenoninvasively because of problems of invasive methods that expose the blood to contamination and the patient to pain.

1.3.2Specific objectives

1- Design control circuit that measure blood glucose depend on blood resistivity
2- Test the control circuit by one of the simulation methods.
3- Implement the prototype of the suggested circuit.

1.4 Thesis layouts

The research was divided into six chapters:

Chapter oneis an introduction include the objective and the general idea of the project, then chapter two shows a theoretical background of the blood, chapterthree shows literature reviews, chapter four include the design and implementation of the project's prototype, chapter five shows the results obtained and its discussion, finally chapter sixinclude the conclusion and recommendations.

Chapter two

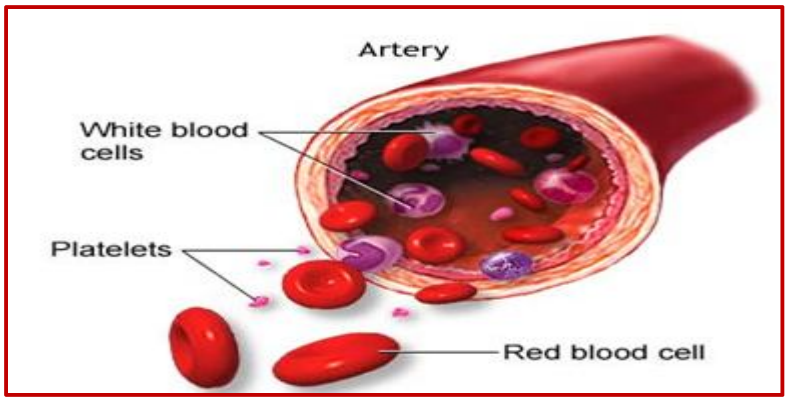
Theoretical background

2.1 The Blood

Is the familiar red fluid in the body that contains white and blood cells, platelets, proteins, and other elements. The blood is transported throughout the body by the circulation system.

Blood functions in two directions: arterial and venous. Arterial blood is the mean by which oxygen and nutrients are transported to tissue while venous blood is the means by which carbon dioxide and metabolic by products are transported to the lungs and kidneys respectively, for removal from the body

Blood may be transfused as whole blood or as one of its components. Because patients seldom require all of the components of whole blood, it makes sense to transfuse only that portion needed by the patient for a specific condition or disease. This treatment referred to as "blood component therapy", allows several patients to benefit from one unit of donated whole blood. Blood components include red blood cells, plasma, platelets, and cryoprecipitate ant-hemophilic factor (AHF). Up to four components may be derived from one unit of blood [11].



Figure(2-1) Blood Hematocrit.

2.1.1 Whole blood

Whole blood is a living tissue that circulates through the heart, arteries, veins, and capillaries carrying nourishment, electrolytes, hormones, vitamins, antibodies, heat, and oxygen to the body's tissues. Whole blood contains red blood cells, white blood cells, and platelets suspended in fluid called plasma.

If blood is treated to prevent clotting and permitted to stand in a container, the red blood cells which weigh more than the other components will settle to the bottom, the plasma will stay on top, and the white blood cells and platelets will remain suspended between the plasma and the red blood cells.

A centrifuge may be used to hasten this separation process. The platelet-rich plasma is then removed and placed into a sterile bag, and it can be used to prepare platelets and plasma or cryoprecipitate AHF. To obtain platelets, the platelet-rich plasma is centrifuge, causing the platelet to settle at the bottom of the bag. Plasma and platelets are then separated and made available for transfusion.

The plasma also may be pooled with plasma from other donors and further processed or fractionated to provide purified plasma proteins such as albumin, immunoglobulin (IVIG) and clotting factors.

Red blood cells are perhaps the most recognizable component of whole blood. Red blood cells contain hemoglobin, a complex iron containing protein that carries oxygen throughout the body and gives blood its red color. The percentage of blood volume composed of red blood cells is called the "hematocrit".

The average hematocrit of an adult male is 47 percent. There are about one billion red blood cells in two or three drops of blood and for every 600 red blood cells there are about 40 platelets and one white blood cell manufactured in the bone marrow, red blood cells are continuously being produced and broken down. They live for approximately 120 days in the circulatory system and are eventually removed by the spleen.

2.1.2 Red blood cells

Are prepared from whole blood by removing the plasma, or the liquid portion of the blood. They can revise the patient's hematocrit and hemoglobin levels while minimizing an increase in volume.

Patients who benefit most from transfusions of red blood cells include those with chronic anemia resulting from disorders such as kidney failure, malignancy or gastrointestinal bleeding and those with acute blood loss resulting from trauma or surgery. Since red blood cells have reduced amount of plasma, theyare well suited for treating anemia patients who have congestive heart failure or who are elderly or debilited, these patients might night tolerate the increased volume provided by whole blood.

Improvements in cell preservative solutions over the last 15 years have increased the shelf life of red blood cells from 21 to 42 days. Red blood cells may be treated and frozen for extended storage (up to 10 years).

2.1.3 Plasma

Is the liquid portion of the blood- a protein-salt solution in which red and white blood cells and platelets are suspended.Plasma which is 90 percent water constitutes about 55 percent of blood volume.

Plasma contains albumin (the chief protein constituent), fibrinogen (responsible in part, for the clotting of blood), globulins (including antibodies), and other clotting proteins. Plasma serves a variety of functions from maintaining a satisfactory blood pressure and volume to supply critical proteins for blood clotting and immunity. It also serves as the medium of exchange for vital minerals such as sodium and potassium, thus helping maintain a proper balance in the body, which is critical to cell function.

Plasma is obtained by separating the liquid portion of blood from the cells. Plasma is usually not used for transfusion purpose but is fractionated (separated) into specific products such as albumin, specific clotting factor concentrates and IVIG (intravenous immune globulin).

2.1.4Cryoprecipitated AHF

Is the portion of plasma that is rich in certain clotting factors including Factor VIII, fibrinogen, Von Willebrand factor, and Factor VIII. Cryoprecipitate AHF is removed from plasma by freezing and then slowly thawing the plasma. It is used to prevent or control bleeding in individual with hemophilia and Von Willebrand's disease which are common, inherited major coagulation abnormalities.

Its use in this condition is reserved for times when viral inactivated concentrates containing Factor VIII and Von Willebrand factor are unavailable and plasma components must be used. It may also be used as hemostatic preparation (fibrin sealant or fibrin glue) in surgery.

2.1.5 Platelets (thrombocytes)

Are very small cellular component of blood that helps the clotting process by sticking to the lining of blood vessels. Platelets are made in the bone marrow and survive in the circulatory system for an average of 9-10 days before being removed from the body by the spleen. The platelet is vital to life it helps massive blood loss resulting from trauma as well as blood vessel leakage that would otherwise occur in the course of normal day to day activity.

Units of platelet are prepared by using a centrifuge to separate the platelet-rich plasma from the donated unit of whole blood. The platelet-rich plasma is the centrifuged again to concentrate the platelets further.

Platelets also may be obtained from a donor by a process known as apharesis, or platelet pharesis. In this process, blood is drawn from the donor into an apharesis instrument which using centrifugation, separates the blood into its components, retains the platelet, and returns the remainder of the blood to the donor. The resulting component contains about six times as many platelets as a unit of platelets obtained from whole blood. Platelets are used to treat a condition called thrombocytopenia in which there is a shortage of it, and in patients with abnormal platelet function. Platelets are stored at room temperature for up to five days.

2.1.6 White blood cells

Are responsible for protecting the body from invasion by foreign substances such as bacteria, fungi, and viruses. The majority of white blood cells are produced in the bone marrow where they outnumber red blood cells by two to one. However, in the blood stream, there are about 600 red blood cells for every white blood cell. There are several types of white blood cells. Granulocytes and macrophages protect against infection by surrounding and destroying invading bacteria and viruses, and lymphocytes aid in immune defense.

Granulocytes can be collected by apharesis or by centrifugation of whole blood. They are transfused within 24 hours after collection and are used for infections that are unresponsive to antibiotic therapy. The effectiveness of white blood cell transfusion is still being investigated.

2.1.7 Plasma derivatives

Are concentrates of specific plasma proteins that are prepared from pools (many units) of plasma. Plasma derivatives are obtained through a process known as fractionation, developed during World War II, and are heat-treated and/or solvent detergent-treated to kill certain viruses, including HIV and Hepatitis B and C. Plasma derivatives include:

- Factor VIII Concentrate
- Factor IX Concentrate
- Anti-Inhibitor Coagulation Complex (AICC)
- Albumin.
- Immune Globulins including Rh Immune Globulin.
- Ant Thrombin III Concentrate.
- Alpha 1-Proteinase Inhibitor Concentrate.

2.2 Blood resistance

Resistance to blood flow through blood vessel, in tubes is generally determined by the diameter (radius r) of the tube as given by the following formula (Poiseuille's law).

$$\boldsymbol{R = 8VLq/\pi r\text{^}4} \textbf{ (2-1)}$$

Where:

V: viscosity of the fluid,L: length of the tube,R: radius of the tube.

Q:volumetric flow rate.

This relationship is accurate for rigid tubes (e.g. glass or steel) in blood vessels (which are not rigid) this mathematically relationship is applicable within limits. However, it is important to note that the main influence on variation of resistance is the diameter of the blood vessels (expressed as r4) adjustment of the diameter of the arterioles is the primary mechanism for the regulation of the peripheral resistance.In summary, the relationship between pressure, flow and resistance is similar to that in Ohm's law, which applies to electricity.

Ohm's law:

$$\mathbf{r = \frac{v}{i}(2\text{-}2)}$$

I: current,V: voltage,R: resistance.

Similarly:

$$\boldsymbol{f}\textbf{=p/r (2-3)}$$

P: pressureF: flow

2.3 Definition of Glucose

Glucose is a molecule with the chemical formula $C_6H_{12}O_6$. In human body, food is converted into sugar and provides energy to all tissues and organs through blood circulation. In terms of its chemical composition, human blood sugar consists of D-glucose that exists mainly in the water base of blood plasma. The daily variation of glucose concentration in the human body is in the range of 60 - 160 mg/dl. Arterial and capillary blood taken from the fingertip have an identical glucose content, while the glucose level of venous blood is lower than the corresponding arterial value (1 - 17 mg/dl in healthy subjects and up to 30 mg/dl in diabetic patients). Besides, blood glucose also exists in other bio fluids such as intracellular fluid, interstitial fluid, humor, saliva, sweet and urine. Researchers have established that, in the steady state condition, the glucose level in the intracellular and interstitial fluid is identical with the concentration of glucose in the blood. It is also known that the glucose level in humor correlates strongly with the glucose content of blood, while the glucose level in saliva, sweet and urine does not. It is the basic energy source for cellular metabolism.

Glucose concentration varies between different anatomic regions and in different parts of the of the blood circulation [11].

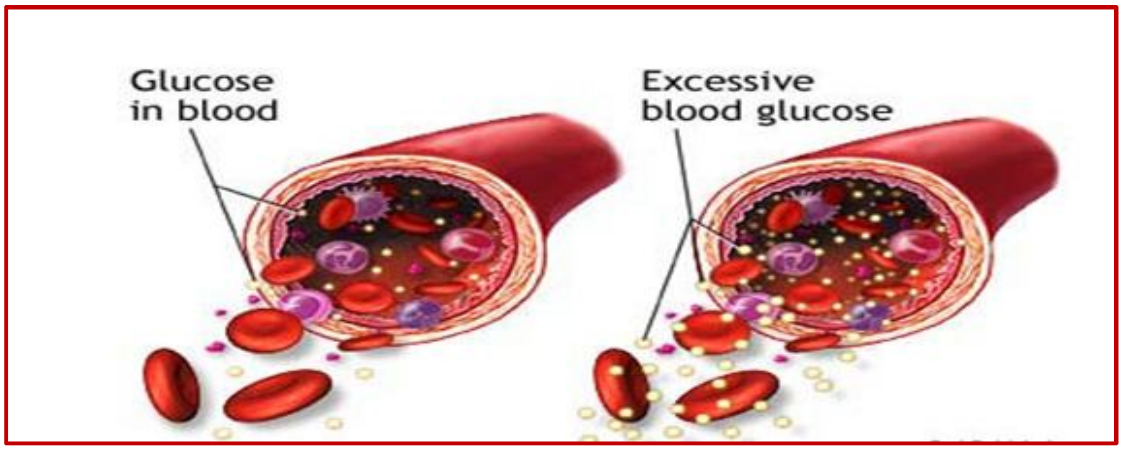


Figure (2-2)glucose in blood vessels.

2.4 Diabetes

Diabetes mellitus is a group of metabolic diseases characterized by high blood sugar (glucose) levels that result from defects in insulin secretion, or action, or both. Diabetes mellitus, commonly referred to as

Diabetes (as it will be in this article) was first identified as a disease associated with “sweet urine”, and excessive muscle less in the ancient world.

Elevated levels for blood glucose (hyperglycemia) lead to spillage of glucose into the urine, hence the term sweet urine. Normally, blood glucose levels are tightly controlled by insulin, a hormone produced by the pancreas.

Insulin lowers the blood glucose level when the blood glucose elevates (for example: after eating food). Insulin is released from the pancreas to normalize the glucose level. In patients with diabetes, the absence or insufficient production of insulin causes hyperglycemia.Over time, diabetes can lead to blindness, kidney failure and nerve damage. These types of damage are the result of damage to small vessels, referred to as micro-vascular disease [11].

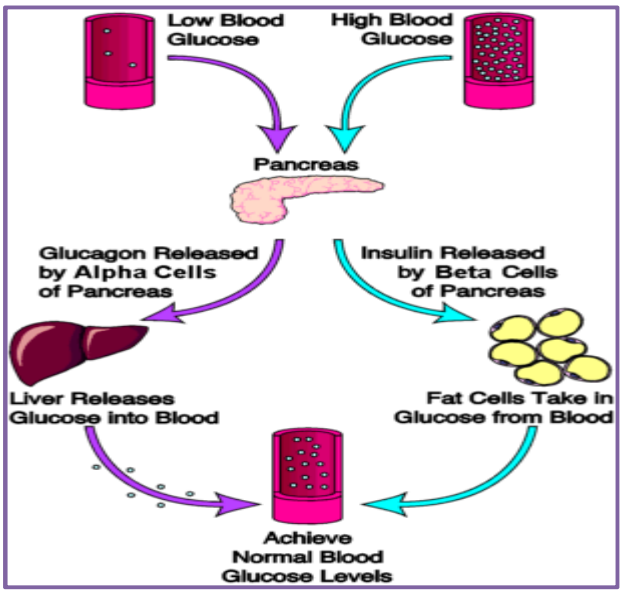


Figure (2-3) Glucose Controlled By Insulin.

2.5 Type of diabetes

Type 1 diabetes is usually diagnosed in children and young.
Adult, and was previously known as juvenile diabetes. In type 1diabetes, the body does not produce insulin. Insulin is a hormone that is needed to convert sugar (glucose), starches and other food into energy needed for daily life.

Type 2 diabetes is the most common form of diabetes

In type 2 diabetes, either the body does not produce enough insulin or the cells ignore the insulin. Insulin is necessary for the body to be able to use glucose for energy. When you eat food, the body breaks down all of the sugars and starches into glucose, which is the basic fuel for the cells in the body. Insulin takes the sugar from the blood into the cells. When glucose builds up in the blood instead of going into cells.

2.6 Noninvasive Blood Glucose Monitoring methods

The concentration of glucose in the blood may soon be measured noninvasively, without puncturingthe ringer to obtain a drop of blood. Current prototype devices for this purpose requiregreater accuracy and miniaturization to be commercially viable. No such device has beenapproved for marketing by the U.S. Food and Drug Administration. The technology used fornoninvasive blood glucose monitoring involves either radiation or fluid extraction. With radiationtechnology, an energy beam is 1) applied to the body, 2) modified proportionate to the concentration of glucose in the blood, and 3) measured. The blood glucose concentration isthen calculated. With fluid extraction technology, a body fluid containing glucose in a concentrationproportionate to the blood glucose concentration is extracted and measured. Theblood glucose concentration is then calculated.
The most promising technologies are 1) near infraredlight spectroscopy, 2) far-infrared radiation spectroscopy, 3) radio wave impedance, 4)optical rotation of polarized light, 5) fluid extraction from skin, and 6) interstitial fluid harvesting.
Each method has features predictive of commercial viability, as well as technical problemsto overcome.

2.6.1 NIR spectroscopy

NIR spectroscopyis the only noninvasive blood glucose monitoring technology ever reviewed by a public Food and Drug Administration (FDA) panel for marketing approval.

Although approval was not granted, press coverage of the hearing in 1996 (1) resulted in heightened public awareness of the competition to produce a noninvasive blood glucose monitoring system and of NIR spectroscopy as a technology that might make such monitoring possible (2). The term "near-infrared light" refers to the use of an external light source with wavelengths in the infrared spectrum near the wavelengths of visible light. An NIRsource can pass through or be reflected by a body part. Glucose and other body constituents absorb a small amount of the light at each wavelength (3).

Spectroscopy, an established technology used to measure energy containing many wavelengths, detects the amount of NIR absorbed at each wavelength by comparing a reference beam with the detection beam that has passed through or is reflected by the body (4,*)).

With spectroscopy, a data processing technique known as chemo metrics or multivariate analysis simultaneously analyzes the amount of light absorption at selected wavelengths for each blood glucose level. A polynomial formula is generated that converts the sum of the relative contributions of absorption at the selected wavelengths to the blood glucose concentration (6). This technology is used in oximetry to measure the oxygen saturation of blood.

The major problem with using NIR spectroscopy for blood glucose monitoring is the necessity for frequent recalibration. NIR spectroscopy does not measure one signal specific for glucose, but rather many signals that are neither specific for glucose nor linked to glucose levels in a linear fashion.

Glucose is responsible for <0.1% of NIR absorbed by the body (7). Water, fat, skin, muscle, and bone account for the vast majority of NIR absorption. Perturbations in the amounts of these substances can alter NIR absorption and thus invalidate the calibration formula for correlating light absorption with blood glucose concentrations that was generated during the calibration process. Other

situations that could also require recalibration include: I)use of medications that absorb NIR, 2) alterations in blood levels of hemoglobin or other proteins that absorb NIR, 3) alterations in body temperature, and 4) alterations in state of hydration or nutrition (6,7). Studies of glucose measurement in vivo using NIR spectroscopy have been disappointing.

2.6.2 FIR spectroscopy

A second technology for noninvasive blood glucose monitoring spectroscopically measures absorption of FIR contained in natural thermal emissions or body heat. FIR spectroscopy is the only type of radiation technologythat does not require an external energy source. The term "thermal emissions" refers to deep layers of the human body emitting thermal radiation or body heat with wavelengths in the FAR spectrum far from the wavelengths of visible light. The peak wavelengths of thermal energy emitted by a 37° human body are 5,000-12,000 nm, in the FIR range of the electromagnetic spectrum. Among these wavelengths, glucose strongly absorbs energy in a band (theFIR "glucose band") around 9,400 nm (8). When FIR passes out of the body, glucose in the blood absorbs part of the radiation.

Absorption of thermal energy in the FIR glucose band by blood glucose in tissue is related in a linear fashion to blood glucose concentration. Thermal energy absorption of FIR in the glucose band by blood glucose can be spectroscopic ally determined by comparing measured and predicted amounts of thermal energy at the skin surface.

The predicted amount of thermal energy radiated can be calculated by the Planck distribution function (9). Simultaneous measurement of thermal energy absorption outside the FIR glucose band determines the reference intensity, which is a necessary variable for calculating the blood glucose concentration. The percentage of thermal energy absorption can be arithmetically converted to a blood glucose concentration. No in vivo data has been published about the accuracy of this method for measuring blood glucose. This technology is used in tympanic thermometry to measure body temperature.

FIR spectroscopy for blood glucose monitoring has two problems. First, the signal size of human thermal emissions is very small. Second, the prototype device incorporates cryogenically cooled infrared detectors.Replenishment of the cryogenic fluid, currently liquid nitrogen, is inconvenient.

2.6.3 Radio wave impedance

A third technology for noninvasive blood glucose monitoring measures the impedance of radio waves. The components of a device using this technology will be inexpensive because they will be off-the-shelf and not custom miniaturized versions of bench-top equipment.

Impedance is the total opposition to an alternating current flowing through a material. Impedance is proportional to the differences in both amplitude and phase of a detection beam compared to a reference beam (10). When a radio wave beam is applied to an aqueous solution, a nonionic solute such as glucose interacts with the energy to attenuate the amplitude and shift the phase of the beam, resulting in increased impedance proportionate to the solute concentration. In blood, glucose is the nonionic solute present at the highest molar concentration.

With the use of a conversion factor, the concentration of glucose in blood can be calculated from a measurement of the impedance to radio wave energy of a body appendage such as a fingertip. No in vivo data has been published about the accuracy of this method for measuring blood glucose.

This technology is used to measure the moisture content of agricultural crops (11).Radio wave impedance technology for blood glucose monitoring has two problems. First, impedance is also affected by factors other than glucose, which must be accounted for to determine the relationship between impedance and blood glucose concentration. These factors include concentration of electrolytes in the blood, finger width, and body temperature. Second, an inexpensive disposable finger clip may be necessary to conduct the radio waves.

The recurring costs of any disposable attachment could be a psychological deterrent to frequent use of a monitor.

2.6.4 Optical rotation of polarized light

A fourth technology for noninvasive blood glucose monitoring measures the optical rotation of polarized light. This process is known as polarimetry. When polarized light passes through a fluid that contains glucose, the plane of polarization rotates proportionate to the glucose concentration (12). A beam of infrared polarized light can be passed through a body compartment, and the amount of optical rotation can then be measured. This method would be used to measure the glucose content of the aqueous humor of the eye (13). In rabbits the aqueous humor glucose concentration has been demonstrated to correlate with the blood glucose concentration (14).

In polarimetry, a beam splitter divides a polarized light beam into a reference beam and a detection beam that passesthrough the body. The beams are then compared to determine the amount of phase shift produced by passage through the body. A blood glucose level is calculated by applying a conversion factor to the phase shift. No in vivo data has been published on the accuracy of such a method formeasuring blood glucose.

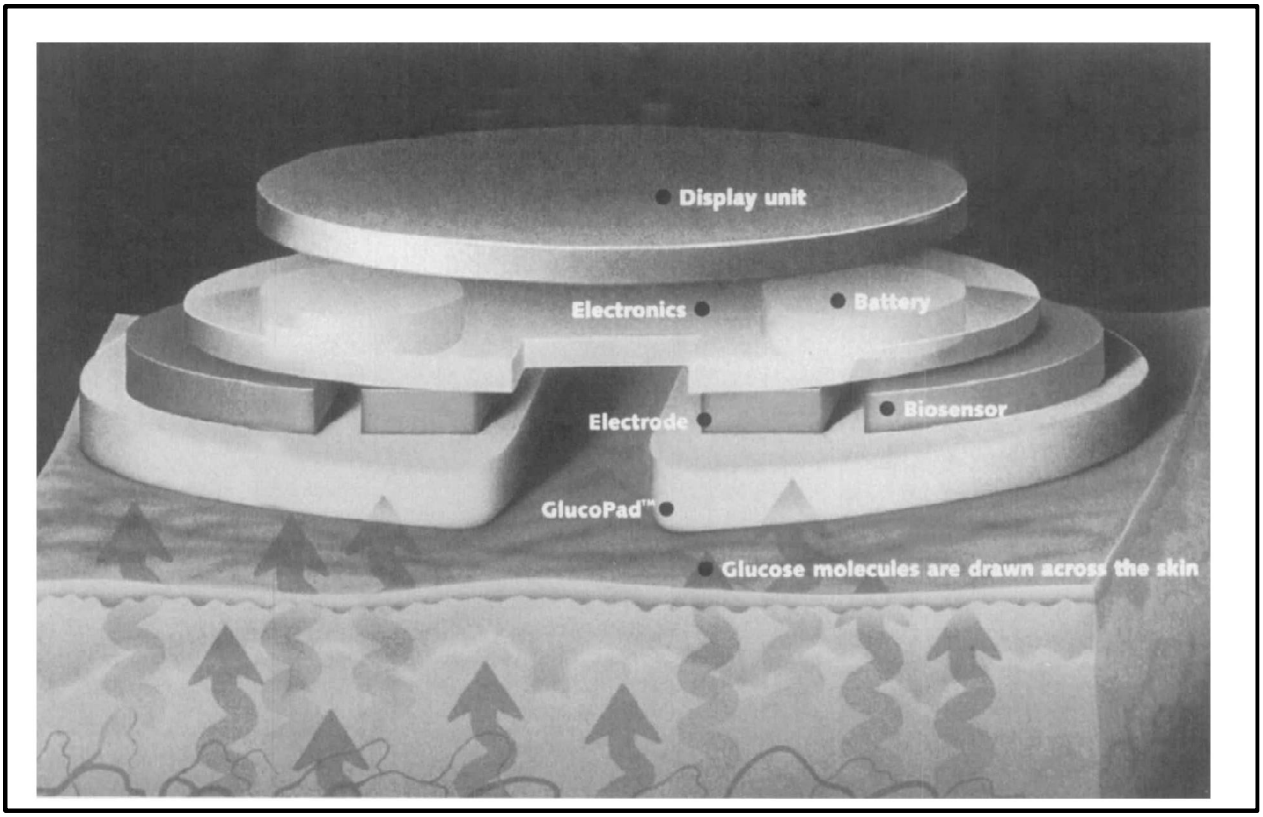


Figure (2-4) Schematic diagram of the glucose monitoring system.

2.6.5 Fluid extraction from skin

A fifth technology for noninvasive blood glucose monitoring extracts and measures tissue fluid from skin. This technology, also known as reverse iontophoresis, is accurate and produces multiple measurements over a 24-h period (16). A device using this technology would measure trends in blood glucose concentrations and could beprogrammed to control an insulin delivery system, which would create an artificial pancreas.

Fluid extraction from skin is the only noninvasive blood glucose monitoring technology capable of measuring blood glucose levels continuously without patient effort.Reverse iontophoresis involves creation of an electrical current applied to the skin.The current pulls out salt, which carries water, which in turn carries glucose. Thus, glucose is extracted from the skin, where it can be absorbed and its concentration measured. The glucose concentration of this extracted fluid is proportionate to that of blood (17,18).

Iontophoresis, from which reverse iontophoresis derives, is an effective drug-delivery technology.

There are several problems with fluid extraction from skin as a method for blood glucose measurement. First, there is a lag time of at least 20 min from the beginning of a fluid extraction cycle until a blood glucose level can be reported. If the blood glucose level is falling rapidly, severe hypoglycemia may not be ascertained and a patient might fail to take corrective action. Delayed recognition of a rapidly rising blood glucose level is less dangerous. The time required to complete a measurement makes the technology unsuitable for a physician's office or hospital, where rapid screening of blood glucose levels is desired.

Second, the technology necessary to measure extracted fluid glucose levels must be very accurate because the glucose concentration in this fluid is —1/1,000 that of blood glucose and the fluid glucose level is converted to blood glucose with a conversion factor. Third, the prototype device requires recalibration at least weekly andcannot be shared by a second person without a 60-min equilibration period followed by recalibration. Fourth, there may be a few minutes of mild discomfort or formication on first applying such a device to the skin, but these symptoms should then resolve.

Fifth, the device has not been tested in patients with diabetic thick skin or during exercise-induced sweating, where the fluid extraction rate could be altered. Sixth, wrist skin could be adversely affected by prolonged reverse iontophoresis. Seventh, the prototype device is currently too large for commercial use and must be miniaturized.

A noninvasive blood glucose monitoring system is being developed that will resemble a wristwatch (Fig. 2-4). The device will consist of 1) a display unit that shows the time and the blood glucose levela glucose pad, which is a disposable pad in which extracted fluid glucose triggers an electrochemical reaction and that must be replaced every 24 h; *3)* a pair of electrodes that transmit current to the skin; 4) a biosensor that measures electron emissions; and 5) a computer that stores data. This system will extract fluid from skin using reverse iontophoresis.A blood glucose level could be reported as often as three times per hour.

A programmable alarm will sound if high or low panic values are exceeded. The device will be powered by a single AAA battery. A prototype of thereverse iontophoresis system has been reported to produce clinically acceptable.

Results for 95% of its measurements (16). Such accuracy is comparable to that of currently available blood glucose monitors (19). The mean absolute error of the measurements was 13%, and there was a correlation coefficient of 0.89. Measurements were performed during a glucose tolerance test and an insulin infusion to determine whether rapidly rising or falling extractedfluid glucose levels significantly lag behind serum glucose levels. Such a problem was not apparent in this series (16).

2.6.6 Interstitial fluid harvesting

A sixth technology for noninvasive blood glucose monitoring involves transcutaneous harvesting and measurement of interstitial fluid from skin. Prototype devices using this technology are accurate and are handheld.

Various methods can be used to extract and measure interstitial fluid.
Unlike the aforementioned five noninvasive technologies, which produce neither skin trauma nor pain, transcutaneous harvesting of interstitial fluid may be accomplished with nearly no skin traumaand with minimal sensation. This technology is therefore classified not as noninvasive, but rather as nearly noninvasive (20).

Transcutaneous harvesting of interstitial fluid produces no significant breaks in the skin surface, in contrast to minimally invasive technology, which involves insertion of an indwelling subcutaneous glucose sensor (21,22). There is such similarity between transcutaneous interstitial fluid harvesting technology and noninvasivetechnologies that this nearly noninvasive technology is being included in the present review of noninvasive monitoring. The process of collecting interstitial fluid, compared to blood, is less inconvenient in terms of 1) pain, 2) skin trauma, 3) site restriction (sampling is not limited to the fingertips), and 4) risk of contamination by a pathogenic agent into or from the circulation (23). Furthermore, it is simpler to assay glucose in interstitial fluid than in blood because with interstitial fluid an erythrocyte sequestration step is not necessary Interstitial

fluid harvesting involves extraction of fluid from the skin followed by direct measurement of the fluid glucose concentration.

If the sample volume is greater than 3 pies, then currently available blood glucose measurement technologies may beused. In the future, the minimum sample volume for commercial blood glucose monitors may be as little as 1. The concentration of interstitial fluid glucose has been shown to be equivalent to that of serum glucose when the serum glucose level is stable (24-27).

In the literature, if there is a rapid shift in the serum glucose level, then the equilibration process between blood and the interstitium results in a 5- to 15-min lag before the interstitial fluid glucose concentration also changes (28).

There are two problems with interstitial fluid technology for blood glucose monitoring. First, most interstitial fluid systems use disposable assay systems intended for one-time use. The expense of these disposables could impede frequent use of the monitor. Second, because of the potential lag time, as with extracted skin fluid technology, some treatment decisions may be based on inaccurate measurements if blood glucose levels are shifting rapidly.

Six promising technologies are being intensively evaluated as tools to detect blood glucose levels noninvasively .These technologies include: 1) NIR spectroscopy 2) FIR spectroscopy 3) radio wave impedance, 4) optical rotation ofpolarized light, 5) fluid extraction from skin, and 6) interstitial fluid harvesting.

There are technical problems to solve before any of these methods can become commerciallyviable. Large prototype devices must be made more accurate and small enough for use initially as a home or office deviceand eventually as a portable device. A noninvasive blood glucose monitor would be a powerful new tool for improving the lives of people with diabetes.

Chapter three

Literature reviews

3.1 NIR technique

Shinde and Scholar (2011) design technique based on occlusion spectroscopy. The experimental setup comprises of Infrared transmitter and receiver and finger as the body site. With properpositioning of the finger, over systolic pressure is applied to the finger to occlude the blood flow for a period of30 seconds. The response of the optical signal thus obtained is studied by performing the FFT analysis usingspectrum analyzer. The frequency spectrum is windowed for certain range using hanning window. The difference in the peak frequencies is observed for two conditions i.e. Before occlusion and After occlusion. The interesting results obtained show frequency variation depending on the health condition of the subject. A considerable frequency variation was observed for diabetic patients, very low frequency change for BP patients and no variation in frequency for healthy patients [29].

3.2 Optical technique

Hong etal. (2007)designtechnique using advanced opto-electronic technology. optical glucose sensing technique using the optical rotatory effect of glucose have many advantages over currently existing invasive and noninvasive methods, since the method is based on shining a brief pulse of light into the front of the eye. Highly coherent light source, accurate optical components, and sophisticated analyzing system will be involved in this study. The optical glucose sensing method introduced in this study can be miniaturized using current integrated optics, electronics, and advanced micro fabrication technologies and has the potential to provide a low cost, fast, and compact noninvasive glucose sensor for the diabetic patients within near future[30].

3.3 Interstitial Fluid technique

Brian J.wenzel and his team (2001) make comparison of glucose concentration in, and capillary and venous blood during rapid changes in blood glucose levels.

The relationship between glucose concentrations in interstitial fluid (ISF) and blood has generated great interest due to its importance in minimally invasive and noninvasive techniques for measuring blood glucose. The relationship between glucose levels in dermal ISF, and capillary and venous blood was studied with the dermal ISF samples obtained using the suction blister technique. The study was conducted with intensely managed diabetics whose blood glucose levels were manipulated so as to induce rapid changes in blood glucose levels. Glucose levels in the three compartments exhibited high correlations both when individual subjects were considered separately and when data from all subjects were combined. No significant time lag during glucose excursions was observed among the ISF, and capillary and venous glucose levels[31].

3.4 Bio impedance measurement technique

Sagar and Hossain (2012)there designis accomplished in two sections comprising of current injection & voltage detection and impedance estimation as shown in Fig(3-1) The first section involves two major hardware parts of impedance measurement system: 1) current source and 2) voltage sensor. The second section involves the software to transform the voltage and current in frequency domain to estimate impedancespectroscopy and impedance parameters Re(extracellular), Ri(intracellular) and Cm subsequently[32].Once the potential across biological tissues is fetched, voltage spectrum is found using FFT in Mat-lab [32].

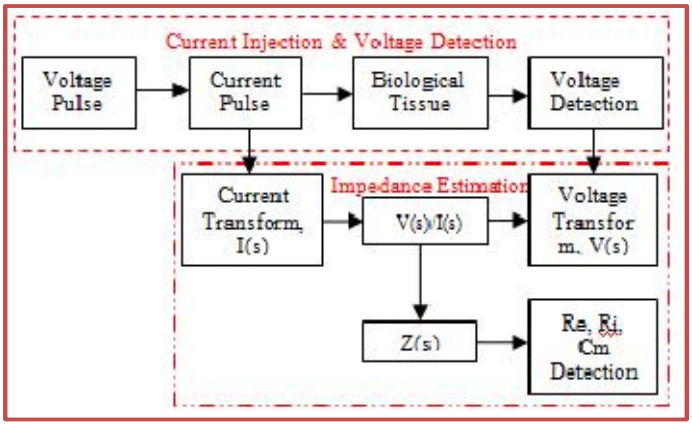


Fig (3-1).Block diagram of bio-impedance measurement system

3.5 Metabolic Heat Conformation Method

Fei Tang et al. (2008) design non-Invasive glucose measurement by use of metabolic heat conformation method.

The homoeostatic circadian rhythm of the human body depends on the correlation between metabolic heat, local oxygen supply level and glucose level. Glucose and oxygen are supplied to the cells in the body through the blood circulation system. The oxidation of glucose is related to the generation of energy which can be emitted into the environment in the form of heat, so the quantity of dissipated heat is correlated to the quantity of dissipative glucose and oxygen. The MHC method is based on this. Since the quantity of supplied oxygen is the function of the degree of blood oxygen saturation and the blood flow rate in the capillary vessel, the quantity of dissipated heat will be

$$H = f(G, BF, O)$$

This system consists of three temperature sensors, two humidity sensors, an infrared sensor and an optical measurement device. The glucose level can be deduced from the quantity of heat dissipation, blood flow rate of local tissue and degree of blood oxygen saturation. The methodology of the data process and the measurement error are also analyzed. The system is applied in a primary clinical test.

Compared with the results of a commercial automated chemistry analyzer, the correlation coefficientof the collected data from the system is 0.856. Result shows that the correlation coefficient improves when the factor of heat dissipated by evaporation of the skin is added in. A non-invasive method of measuring the blood flow rate of local tissue by heat transmission between skin and contacted conductor is also introduced. Theoretical derivation and numerical simulation are completed as well. The so-called normalized difference mean (NDM) is chosen to express the quantity of the blood flow rate. The correlation coefficient between the blood flow rates by this method and the results of a Doppler blood flow meter is equal to 0.914[3].

Chapter Four
Design
And Implementation

4.1 Basic Concept of Design

The glucoselevel measurement methods for patient diabetes implemented to facilitate periodically measuring of glucose dependant on taking sample and applied different processes according different methods such as optical and chemical. These methods have many disadvantages like blood manipulation and painful.The design will focus on non-invasive blood glucose level measurement; it needs a calculation for the amount of glucose level proportional to the blood resistivity according to the relationship between the blood viscosity and glucose level.

4.2 Prototype Implementation

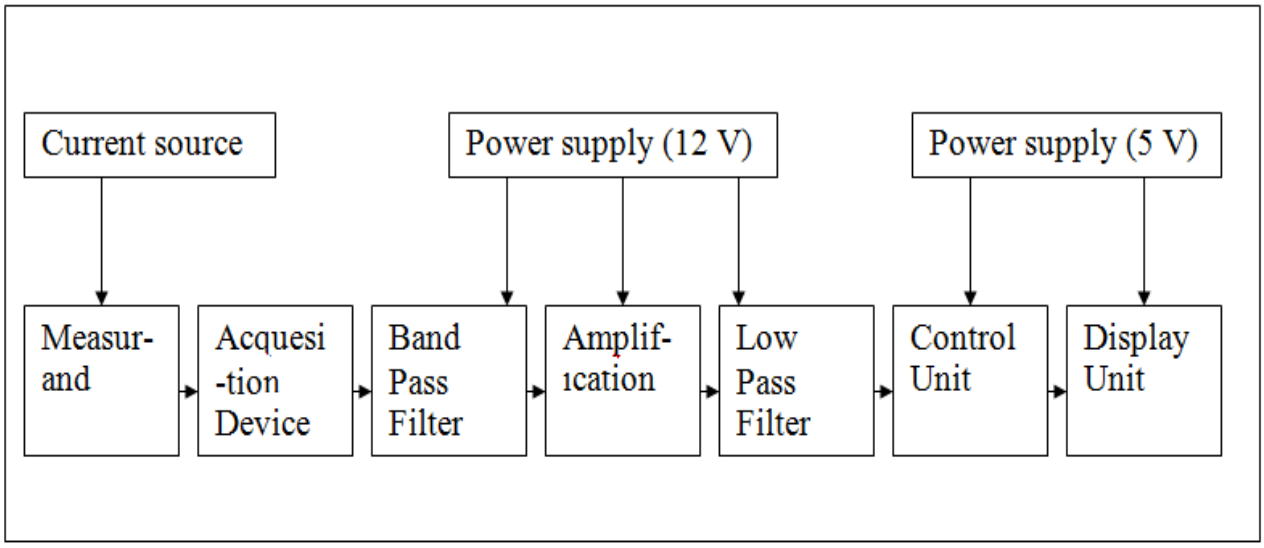


Figure (4-1) Implemented Prototype Block Diagram

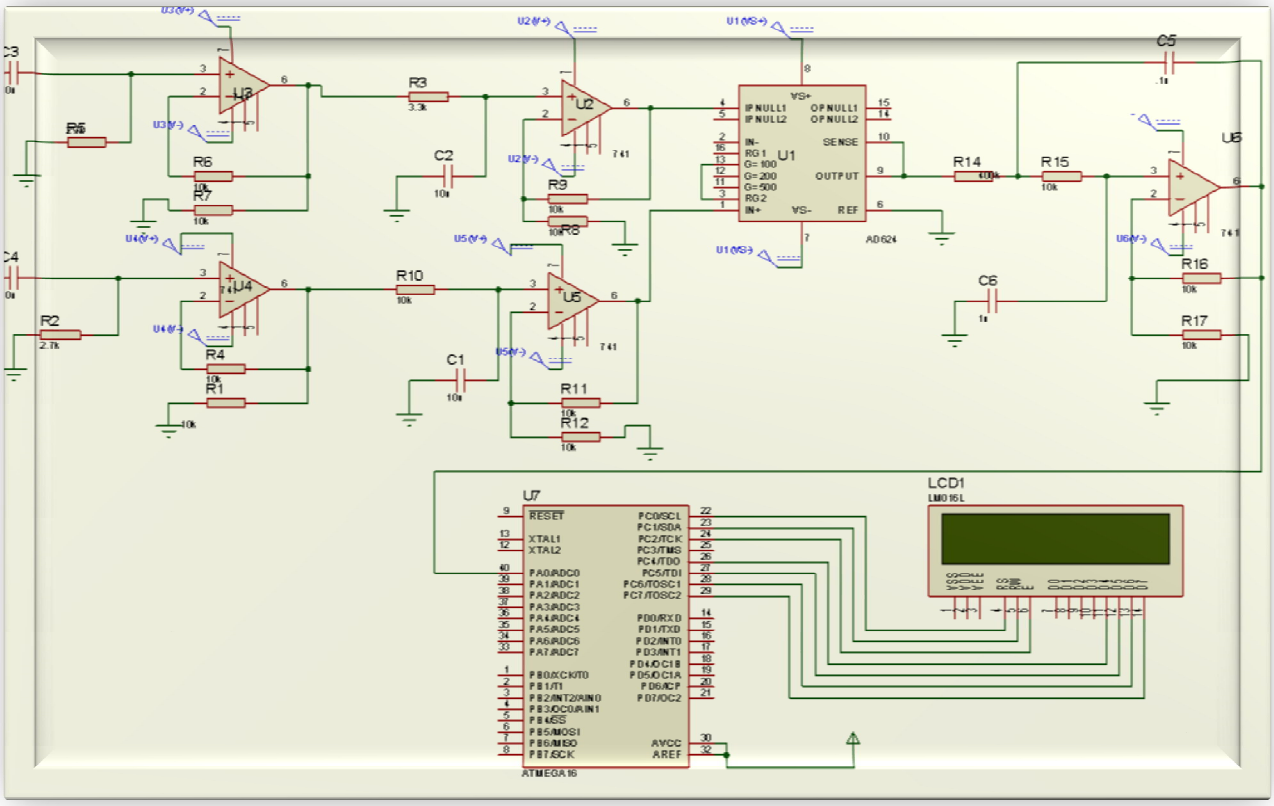


Figure (4-2) prototype circuit diagram

4.2.1 Prototype element

Power supply (5V and 12V)

The design was being depended on power supply with (DC) output provide voltage (5V and 12V), the output voltage (5V) was supplied each of microcontroller and display unit.

The output (12V) was supplied instrumentation amplifier all the ground of each power supply was grounded together.

Current source

The measurand was connected with current source from wave form generator to provide 5.5 m A and 50 KHz [5].

Data acquisition device (electrodes)

The electrodes consist of alight weight metalled screen or plate held away from the subject by a flat washer which is connected to the skin, these electrodes were made of silver impregnated silastic rubber and were found to be comfortable to wear.

These electrodes should be able to detect the electrical potential (voltage) change across the finger so that the change in resistance may be determined. In this project used four electrodes, two electrodes to pass current through the finger and two electrodes to measure the voltage output across the finger.

A current used 1mA at 50 kHz should provide a safe current that will not harm the test subject, yet still allow for an adequate voltage drop to appear across the finger. The exact current value will change between subjects due to variations in body resistance.

Band Pass Filter

A band pass filter passes a limited band of frequencies and rejects all frequencies below and above the selected band .it can be made bycascading low pass and high pass filters [10].

In this project built band pass filter with center frequency 50 KHz to receive the carrier signal from patient and calculate the value of resistance and capacitance by:

$$F=1/2\pi RC \qquad (4\text{-}1)$$

F= Cutoff frequency.
R=Resistance.
C= capacitance.

As Shown below:

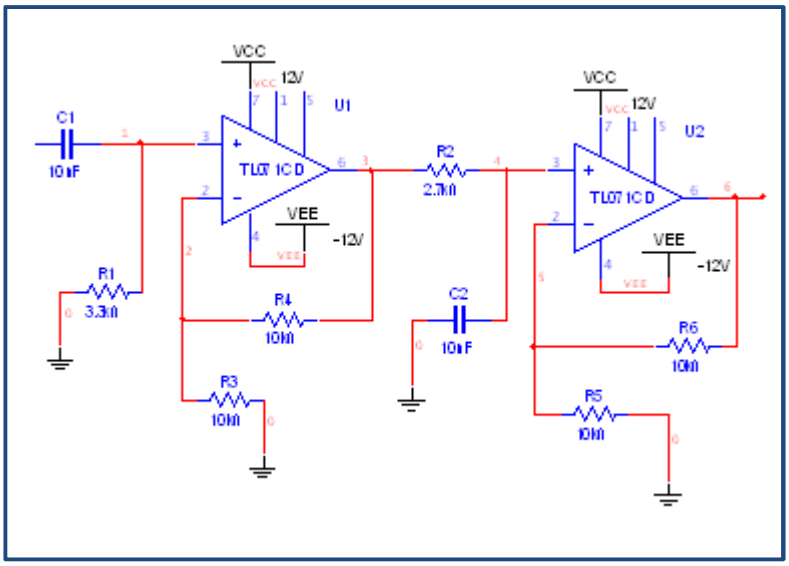


Figure (4-3) band pass filter

Amplification circuit

The AD624 is a high precision, low noise, instrumentation amplifier designed primarily for use with low level transducers, including load cells, strain gauges and pressure transducers. An outstanding combination of low noise, high gain accuracy, low gain temperature coefficient and high linearity make the AD624 ideal for use in high resolution data acquisition systems.

The AD624C has an input offset voltage drift of less than 0.25 µV/°C, output offset voltage drift of less than 10 µV/°C, CMRR above 80 dB at unity gain (130 dB at G = 500) and a maximum nonlinearity of 0.001% at G = 1. In addition to these outstanding dc specifications, the AD624 exhibits superior ac performance as well. A 25 MHz gain bandwidth product, 5 V/µs slew rate and 15 µs settling time permit the use of the AD624 in high speed data acquisition applications.

The AD624 does not need any external components for pretrimmed gains of 1, 100, 200, 500 and 1000. Additional gains such as 250 and 333 can be programmed within one percent accuracy with external jumpers. A single external resistor can also be used to set the 624's gain to any value in the range of 1 to 10,000.

The pin configuration shown below

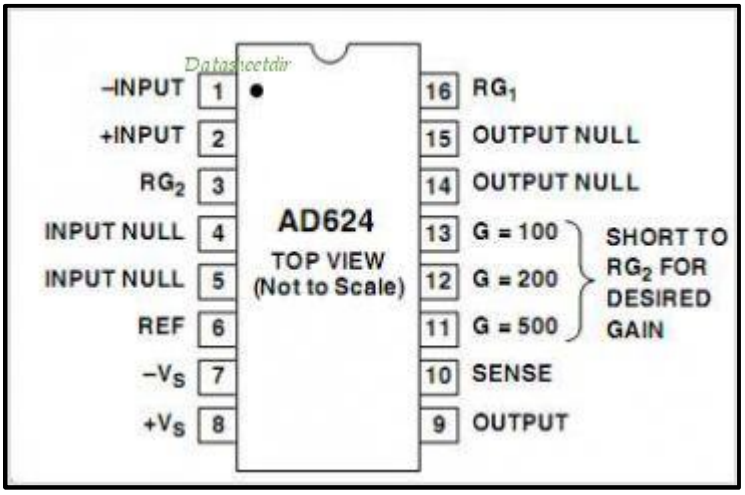


Figure (4-4) pin configuration of (AD524) Instrumentation Amplifier[14].

Low pass filter

A low pass filter passes limited frequencies and rejects all frequencies above the selected frequency. In this project used low pass filter with cutoff frequency 10 Hz. This cutoff was chosen because the voltage pulses are expected to be at a frequency of 1-2 Hz [5], so anything above this is not wanted, and calculate the value of resistance an capacitance by using:

$$F=1/4\pi RC \qquad (4\text{-}2)$$

F= Cutoff frequency
R=Resistance.
C= capacitance.

Shown below:

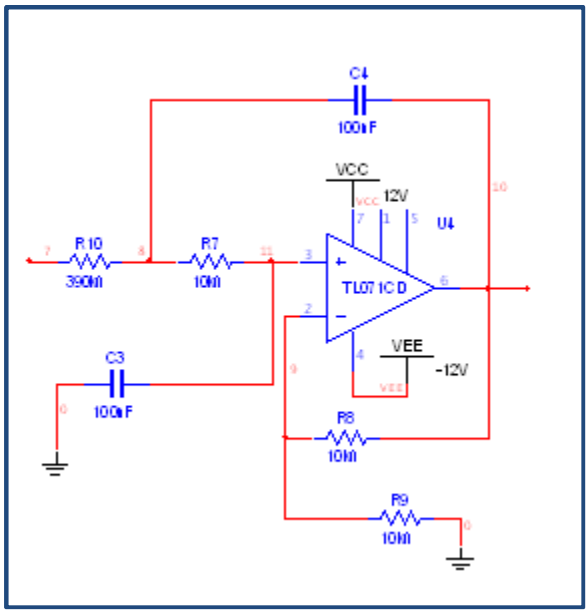
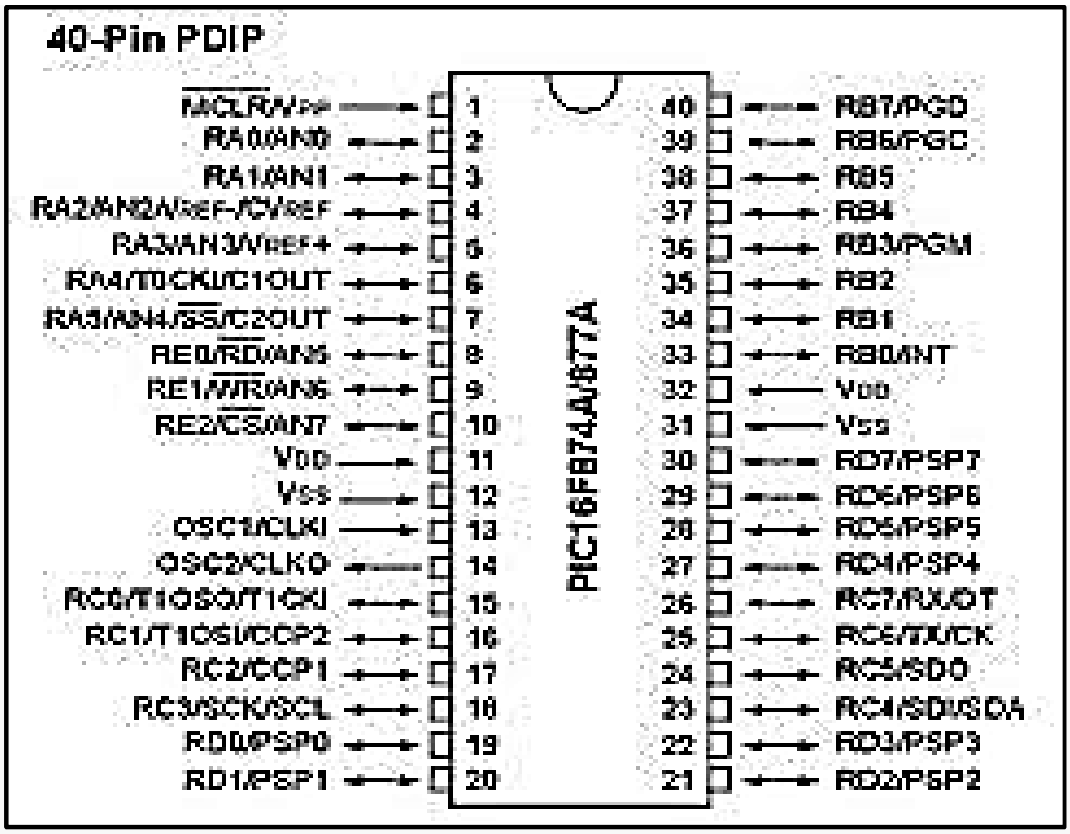


Figure (4-5) low pass filter.

Control unit (microcontroller)

A microcontroller is a complete computer system on a single chip. It is more than a Read-Only Memory (ROM), a Read-Write Memory (RAM), some input/output ports, and some peripherals, such as, counters/timers, analog-to-digital converters, digital-to-analog converters, and serial communication ports. It is highly integrated chip that contains all the component which was comprised the control operation.PIC is a family of modified Harvard architecture microcontrollers made by Microchip Technology, derived from the PIC1650 originally developed by General Instrument's Microelectronics Division. The name PIC initially referred to "Peripheral Interface Controller"(appendix A).PICs are popular with both industrial developers and hobbyists alike due to their low cost, wide availability, large user base, extensive collection of application notes, availability of low cost or free development tools, and serial programming (and re-programming with flash memory) capability.It arranged as in the pin configuration shown below:



Figure(4-6)pic16f877a pin configuration

The design of prototype was based on using two ports of microcontroller, port (A) was used as input to represent the value of input voltage. Port (B) as output to display the value of blood glucose level.

Microcontroller (pic16f877a) was programmed using micro C language to calculate the blood glucose by using the following steps:

-Digital to analog converter to transfer the input analog signal to digital form.

-Calculate the blood resistivity by dividing the maximum voltage with the input current which was given to the patient.

-Calculate blood glucose level from the equation that formulate from the curve that connect glucose to blood resistivity using Mat lab.

-Display the blood glucose by using LCD.

Display unit

LCD devices rely on the fact that the molecules of a nematicliquid crystal have the ability to rotate the plane of polarized light, so that when placed between crossed polarizer's, light may pass through the liquid crystal layer.

The amount of light transmitted depends on the orientation of the molecules within the layer, which in turn can be controlled by application of an electric field.

The LCD screen consists of two lines with 16 characters each every character consists of 5x8 or 5x11 dot matrix. Display contrast depends on the power supply voltage and whether messages are displayed in one or two lines. For this reason, varying voltage 0-Vdd is applied on the pin marked as Vee. Trimmer potentiometer is usually used for that purpose Some LCD displays have built in backlight.

In this project used LCD (LMB 162 ABC_4) to display the result shown below.

Figure (4-7) LCD (LMB 162ABC_4)

4.2.2 Operation stages

The prototype was design to displaythe value of blood glucose .the display operation passes through five stages. These stages are:

Stage one

The first stage was begun with flowing the current from current source (wave generator) to measurand through finger by using current value (5.5mA) with frequency (50KHz) sinusoidal wave, during current passes through the blood generated electrical potential(voltage)this voltage acquired by two defibulator electrodes.

Stage two

In the second stage detected the carrier signal which carried the desired signal by using band pass filter with center frequency (50 KHz).

Stage three

In this stage the signal from previous stage amplified using instrumentation amplifier (AD624) with set gain value 20.

Stage four

In this stage passes only frequencies (10Hz) of blood impedance to arterial blood pulsations by using second order low pass filter.

Stage five

In the final stageused micro C language to programthe microcontroller (pic16f877) to calculate the value of blood glucose and display the result in LCD (LMB 162 ABC_4)(appendix A).

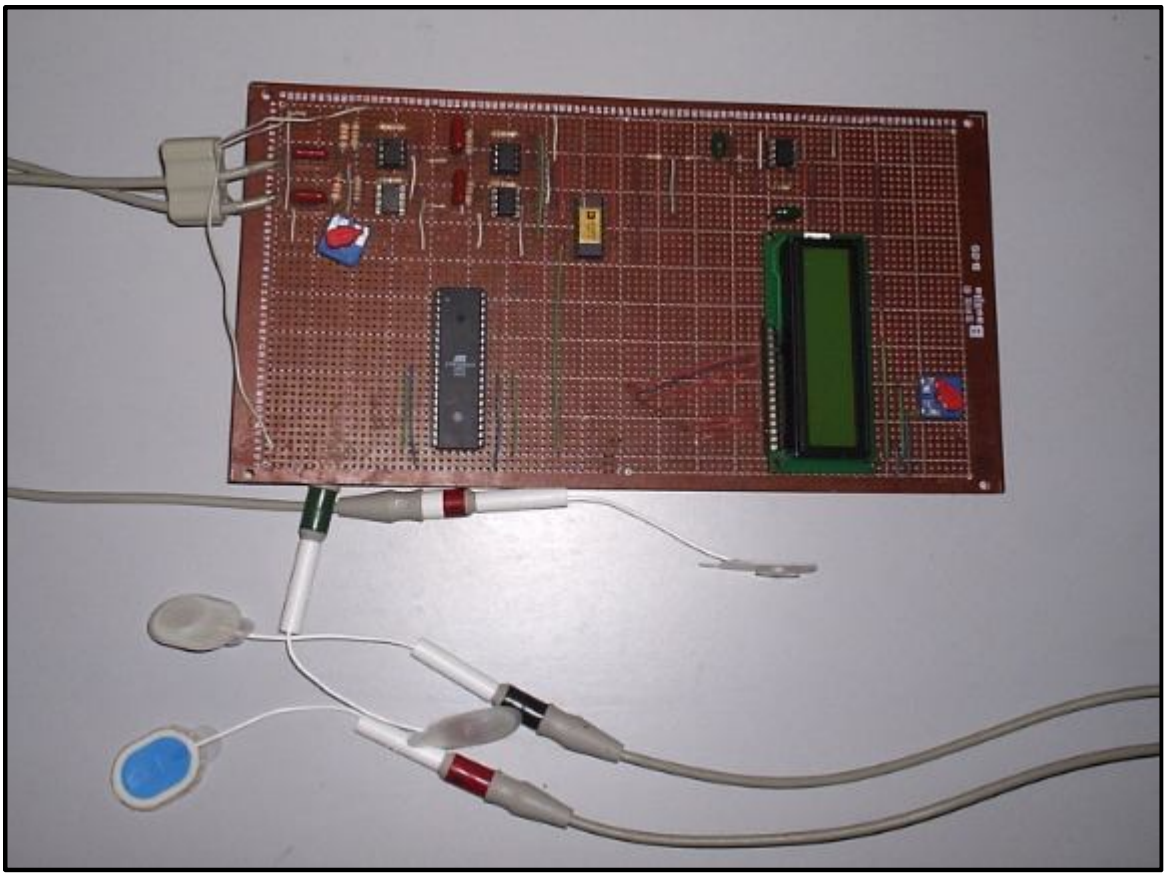


Figure (4-8) implementation of prototype

Chapter five

Result and discussion

5.1 Result

-The blood resistivity circuit was tested on seven diabetes patient in Sudan University. The test was done glucose level and blood resistivity at the same time. Table (5-1) and show the result of the test.

Table (5-1) blood resistivity versus blood glucose level of diabetic patients

Patient number	Blood resistivity(ohm)	Blood glucose level
1	2.72	235 mg/dl
2	2.36	117 mg/dl
3	2.00	100 mg/dl
4	2.18	110 mg/dl
5	1.09	6 mg/dl
6	1.90	4.5 mg/dl
7	1.09	7 mg/dl

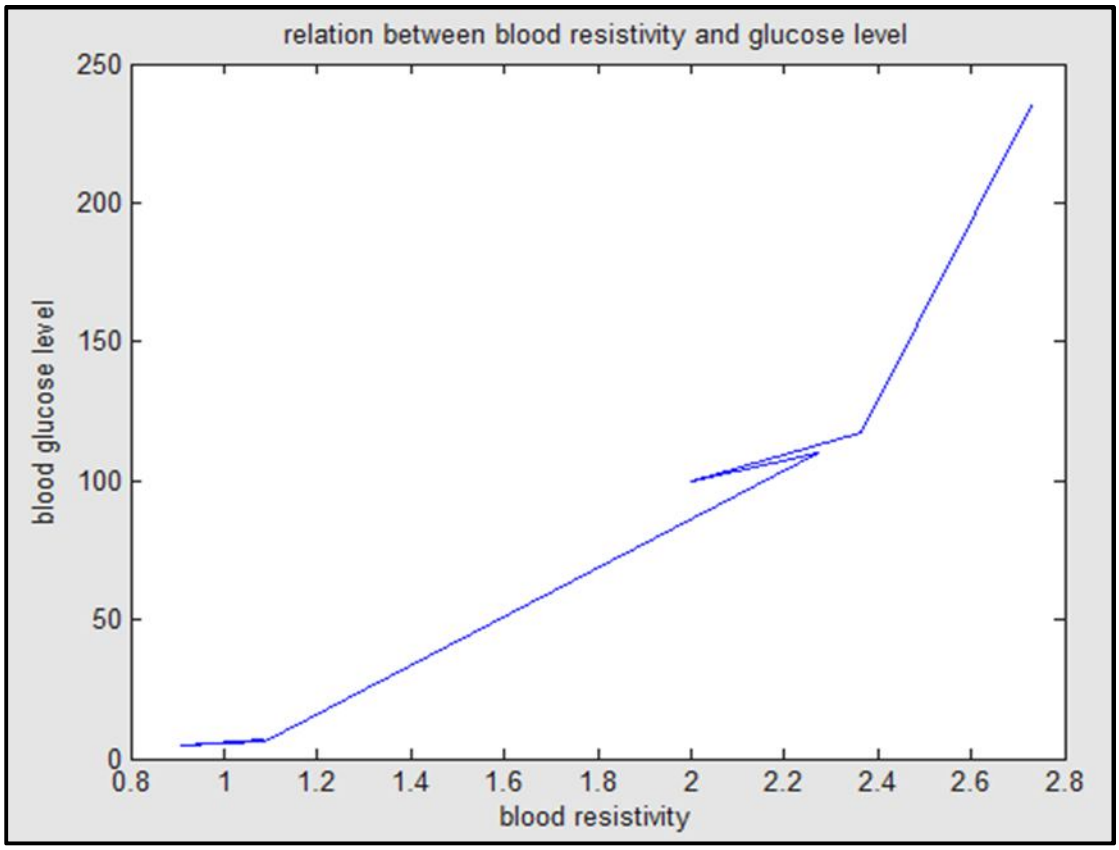


Figure (5-1) proportion between blood resistivity and glucose level

The X axis represent the bloodresistivity, Y axis represent the bloodglucose level

$y = 100.3 * 2^{x} - 177.5x + 83.46$ … … … … … … … … ….(5-1)

Where:

Y=blood glucose level x=blood resistivity

-The control circuit was designed.

-The simulation runs successfully.

5.2 Discussion

According to this result there is a clear direct proportion between the blood resistivity and glucose level, in both cases of diabetes high and low level of glucose.

The voltage or impedance measurement does not provide any direct information as to how much current travels through intracellular versus extracellular volumes, in blood versus muscle, or in fat versus fat-free tissues. Current paths in the body used by impedance will generally differ from person to person because of differences in body size, shape, electrolytes, fluid distribution, or other aspects of the body's composition. These characteristics vary within an individual, and almost any change in body size, shape, or composition will have at least a small effect on impedance.

Chapter six

Conclusion

And recommendation

6.1Conclusion

Diabetes mellitus is a complex group of syndromes that have in common a disturbance in the body's use of glucose, resulting in an elevated blood sugar. Once detected, sugar diabetes can be controlled by an appropriate regimen that should include diet therapy, a weight reduction program for those persons who are overweight, a program of exercise and insulin injections or oral drugs to lower blood glucose. Blood glucose monitoring by the patient and the physician is an important aspect in the control of the devastating complications (heart disease, blindness, kidney failure or amputations) due to the disease. Intensive therapy and frequent glucose testing has numerous benefits.

With ever improving advances in diagnostic technology, the race for the next generation of bloodless, painless, accurate glucose instruments has begun. However, many hurdles remain before these products reach the commercial marketplace. An instrument must be designed that accurately detects glucose concentration. Correlation and clinical interpretation of this value, in respect to the patient's true glucose value, is imperative for optimum therapy and disease management.

The project is a design of non- invasive device to help the measurement of blood glucose level. It is directed to solve the dangerous facing of contamination and cause of pain;it aims to produce useful and successful way of measurement.

The project is a design of signal acquisition, processing and display system for calculating blood glucose level.

6.2 Recommendation

This project represents a useful way to measure the blood glucose level for the diabetic patient by non- invasive way ,this project also it can help to measure another type of blood disease depend on the specific characteristics of these diseases .

From this study there are recommendations for further studies,

-Design of current source that suitable to gain the best reading that is nearest to real readings.

-The readings of blood glucose the was limited, develop of software to increase the range of readings

- Develop the circuit to connect it to pc of patient and then the patientconnect to doctor pc.

-Develop the circuit to record the result during the day.

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Pic16f877 programme:

```
sbitLCD_RS_Direction at TRISB0_bit;
sbitLCD_EN_Direction at TRISB1_bit;
sbit LCD_D7_Direction at TRISB7_bit;
sbit LCD_D6_Direction at TRISB6_bit;
sbit LCD_D5_Direction at TRISB5_bit;
sbitLCD_D4_Direction at TRISB4_bit;
void main()
 {
char txt[15];
floatx,y,z,m;
LCD_Cmd(_LCD_CURSOR_OFF);
trisb=0;portb=0;trisa=1;porta=0;
lcd_init();
ADC_Init();
while(1)
   {
LCD_Cmd(_LCD_CURSOR_OFF);
       x=Adc_read(0);
       y=36*x/1023/20;
       z=1000*y/5.5 ;
       m=100.3*2^z-177.5*z+83.46;
floattostr(m,txt);
lcd_out(1,1,"blood glucose is:");
lcd_out(2,1,txt              );
delay_ms(100);
   } }
```