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The Potential Application of Amplitude Modulated Ultrasound with Infrared Technique for Blood Glucose Level Determination in Non Invasive Manner

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ABSTRACT

The advent of a truly new noninvasive technology for blood glucose level determinations could revolutionize management of diabetes along with increased patient compliance, decrease burden on medical emergency and diabetes related complexities. Herein, we have investigated the potential of using amplitude modulated ultrasound with infrared techniques for blood glucose level determination in non invasive manner. This new noninvasive system with the operating wavelength of 940nm and ultrasound transmitter of 40 kHz has been used in 05 volunteers for the pilot studies. Standard procedures of the oral glucose tolerance test were conducted to check variations in the blood glucose levels. Blood samples for invasive blood glucose readings were obtained from the left hand fingers for every 15min up to 2 hours. Simultaneously noninvasive blood glucose readings were taken every 15min from the right hand fingers up to an entire time period of 2 hours. Overall 45 blood samples and 225 signals were recorded and examined in this pilot study. Close resembles observed between changes in the peak to peak voltage amplitude spectrum in frequency domain of noninvasively blood glucose measured values and the invasive method utilized here. The degree of similarity between the observed signal and the blood glucose level is owing to the novel utilization of the amplitude modulated ultrasound wave (standing wave). It enhances the sensitivity, specificity of near infrared optical method for noninvasive blood glucose determinations. This pilot study indicates the potentiality of the amplitude modulated ultrasound with infrared techniques for the noninvasive blood glucose determinations in human volunteers.

Key words: Noninvasive, Invasive, Blood glucose level, Diabetes, Modulated ultrasound, Infrared technique.

INTRODUCTION

Diabetes is a metabolic anarchy characterized by surplus of glucose in the blood and tissues of the living human body. Healthy supervision of blood glucose is mandatory to avoid long-term diabetes related complications to vital organs of the body. In this 21 century, Diabetes mellitus is one of the major endocrine ailments of concern that pose a serious life threat to human healthiness. In 2011, the worldwide prevalence of diabetics estimates around 350 million peoples[1] and it is expected to touch several other millions by 2025[2,3]. Healthy and effective monitoring of blood glucose levels are the primary prerequisite in the proper regulation of therapy programs for the diabetes subjects[2,4]. At present, the typical method of testing blood glucose involves lancet based

pricking of finger, placing a few drops of blood on an examination strip and putting that strip into a meter that displays the blood glucose levels. Meters differ in their characteristics, readability, portability, swiftness, dimension and price[5,6]. Problems associated with invasive techniques include pain, pricking related patient's mental agony, time consumption, cost per measurement, potential source for spreading infectious diseases, inability to monitor continuously[5-8]. The entire of these aspects, directs towards a requirement of a secure and suitable noninvasive blood glucose measurement.

The optical sensing of blood glucose in human body is currently a burning research topic of interest. To design and develop a healthy noninvasive method for blood glucose sensing, various optical method includes infrared absorption[9], near infrared scattering[10], Raman spectroscopy[11], fluorescent[12], thermal gradient spectroscopies[13], polarimetric[14], polarization heterodyning[15], photonic crystal[16], photoacoustic[17], photothermal[18], optical coherence tomography (OCT) techniques[19] and ultrasound-modulated optical technique[20]. In noninvasive glucose measurement using above-mentioned methods, common test sites include fingertips, cuticle, finger web, forearm, earlobes, eye etc[20]. Investigations also includes various skin layers (like subcutaneous, dermal, epidermal, combined dermal and epidermal), body fluids (like blood, ocular fluid, sweat, interstitial fluid) etc[2, 3, 20]. Extremely low signal produced by the glucose molecules leads to the design and development complexity of optical noninvasive blood glucose meter in the field of medical science. This phenomenon causes extremely low optical sensing and needs a lot of effort to increase the optical methods sensitivity and specificity for noninvasive blood glucose monitoring[6, 22].

The sensitivity and specificity enhancement of near infrared optical method for noninvasive blood glucose detection, the amplitude modulated ultrasound wave (standing wave) is used. This paper presents a new methodology and an experimental setup to detect blood glucose in noninvasive manner using amplitude modulated ultrasound and infrared techniques.

The organization of the paper is as follows: Section II describes the principle of glucose measurement using amplitude modulated ultrasound and infrared techniques. Section III depicts the system description along with the criteria of wavelength and transducer selection. In section IV, experimental results are furnished. Section V finally concludes the paper followed by the acknowledgment and reference portions.

MATERIALS AND METHODS

Principle of glucose measurement

The Amplitude Modulated Ultra Sound waves (standing wave) effect on the molecules of the blood medium and its optical measurement

The present investigation aimed to enhance infrared technique for noninvasive blood glucose measurement using amplitude modulated ultrasonic waves. These standing wave patterns generate molecular vibrations and oscillations in the focused zone within the blood medium. This standing wave (amplitude modulated ultrasound) causes molecular aggregations in the zone of its operation. These molecular aggregations assist in the determination of typical molecular infrared signatures present in the blood medium. Furthermore, the frequency of the modulating wave helps in arrangement of the target molecules (glucose) relating to its optical sensitive band in the infrared spectrum [25-31].

Ultrasonic manipulation of blood constituents

When amplitude modulated ultrasonic waves (standing wave) passes through the blood medium, the radiation force applied causes certain molecular vibrations and oscillations in it[21,25,26]. These forces are generated from the geometric orientations of ultrasonic standing waves often termed as acoustic pressure[27]. In the nodal region of the standing wave the molecular aggregation occurs[25]. The vector properties of these forces are maintained by the compressibility factor of the molecules present in the blood medium. The degree of compressibility depends on the molecules present in the blood medium. This phenomenon is coined as an acoustic contrast[25, 28-31]. The molecule present in the blood medium arranges itself into pressure nodes of the ultrasonic sound field. Moreover, the molecular vibrations and oscillations are influenced by certain factors like (i) molecular three dimensional properties (ii) extent of gravitational forces (iii) ultrasonic

waves modulating amplitude and frequency[21,25-31]. In the ultrasonic sound field, the particular definite molecule attains a location specific acoustic potential energy. These type of arrangements results in discontinuity in the phase of wave propagations[25, 28-31]. The regions of minimum acoustic potential got populated by the specific molecules. For blood molecules these regions are nearer to the pressure nodes, which are separated from one to another by distances of half a wavelength[25-31].

Small dimensional molecules when subjected to larger ultrasonic wavelength, the principally acting radiation forces F_r exerted on a volume V_c of the molecule, positioned from the pressure node by distance of z, is obtained from the gradient of the molecule acoustic potential energy[25-31] and is expressed as:

$$F_r = -\left[\frac{\pi p_o^2 V_c \beta_w}{(2\lambda)}\right] \cdot \phi(\beta, \rho) \cdot \sin(4\pi z/\lambda) \quad ...(1)$$

In this situation, the peak acoustic pressure amplitude is denoted as P_o and λ as the sound wavelength in the aqueous suspending phase medium. Here, β_w sign stands for the compressibility factor. The phenomenon is expressed as follows:

$$\phi(\beta, \rho) = \left[\frac{5\rho_c - 2\rho_w}{2\rho_c + \rho_w} - \left(\frac{\beta_c}{\beta_w}\right)\right] \quad ...(2)$$

Here β_c is referred as the molecular compressibility. Molecular densities are indicated by ρ_c and ρ_w signs for the molecules separately and the suspending blood medium respectively[25-31].

Acquisition of absorption spectra

Various factors needed to be considered when Infra Red spectrum analyses were performed. All the samples used show their unique IR light signatures in the path of light at a constant wave number. The legendary Lambert–Beer law is then applied to calculate the absorption A at a particular light wave number v.

$$A(v) = -\log I(v) / I_o(v) \quad ...(3)$$

Where I_0 represents the background intensity, I signifies the intensity at the particular wave number v of the real measurement[25,30-31].

The output signal thus acquired from the blood constituents with respect to these Amplitude Modulated Ultra Sound wave (standing wave) is picked up by the Infra-red light detector, subsequently the signal based information about the constituent blood molecules (specially glucose) is extracted using indigenously designed signal processing algorithm

Research design and methods

Blood glucose measuring system has been described in this section. A study was carried out to find out the suitable wavelength for maximum glucose detection. Subsequently the description of the experimental setup and testing methodology has been detailed.

Wavelength selection and transducer properties

The composition of blood and tissue is complex in nature and there optical property varies accordingly. Moreover, blood glucose provides very weak signal and also got affected by the overlapping phenomenon of the water and the surrounding media respectively. The wavelength selection criteria must be rigid and robust for blood glucose measurement in noninvasive manner.

The molecular extinction coefficients of oxygenated hemoglobin and melanin and the absorption coefficient of water are shown in Fig. 1. It indicates melanin, water and oxygenated hemoglobin plays a major role in variation of optical properties of tissue over the wavelength spectrum. The absorbance pattern of the major intracellular absorbers like melanin, water, oxygenated hemoglobin is very small in the red and the near infra Red regions. The scarcity of the well-organized one-photon absorbers causes the biological cells and tissues to be virtually optically transparent in the wavelength spectral domain from 700nm to 1100nm. For this phenomenon, wavelength spectral domain from 700nm to 1100nm is described as optical window for the living biological tissues. The light enters up to certain millimeters in this so-called optical window region of the living biological tissues [32-33].

From Fig. 2 it can be depicted that at wavelength 1037nm, the absorption of glucose is high but absorption profile of water at this wavelength is also maximum[33].

The absorption spectra for oxyhemeglobin and deoxyhemeglobin in the wavelength range of 1000nm to 1200nm are unalike in nature. But this dissimilarity of absorption phenomenon is moderately less in the range of 900 to 980nm as indicated by the Absorption profile of Oxy-Hemoglobin and Reduced Hemoglobin at Red-Near infrared region in Fig. 3.[34]. Light absorption profile changes with respect to the magnitude of blood oxygenation[34, 35].

The tissue optical window phenomenon indicates that a wavelength around 940nm is more effective for blood glucose measurements. The reduced interference from the surrounding media and similar molecules at this wavelength plays a vital for its considerations in the measurement of blood glucose. The IR LED diode and its receiver at 940nm are available readily in the present market conditions. This factor also drives us for using this particular wavelength of light.

As per the specifications supplied by the manufacturers, the ultrasonic transducer is of 0.30" height X 0.43" diameter, built in the aluminum casings. They come in pairs with main operating frequency noted as 40.0±1.0KHz, with 2000pF±20% of capacitance property. 20 Vrms is the maximum tolerable input voltage as specified.

Block level Description

Figure 4 illustrates the block diagram of the experimental setup. The experimental setup is based on amplitude modulated ultrasound wave (standing wave) and near infrared (NIR) optical technique unit. The Synchronous square wave generator connects the infrared LED (Light Emitting Diode) to provide the square wave pulses to it. The infrared unit delivers square pulsed mode light to the finger holder block. The amplitude modulating signals were produced from the modulating signal of sine wave generator and the high frequency carrier wave from the carrier generator blocks respectively. The light source: point of focus and the ultrasonic wave: direction of propagation is geometrically perpendicular in their orientations. The infrared light source is focused on the ultrasonic zone of impact, to obtain the resultant amplitude modulated ultrasound light signal. The IR detector sensitive in the infrared region detects the signals produced due to the above phenomenon. Signal amplifier block amplifies the desired signal. The acquired signal is then processed by MATLAB software. It also automates the process of collecting the amplitude modulated ultrasound wave based light waveform data from Digital Storage Oscilloscope (DSO) at specified intervals. Infrared light detector senses the amplitude modulated ultrasound based light signal embedded with blood glucose information. Precautions had been taken to achieve good SNR (signal to noise ratio) and to reduce the effect of random noise, external interferences, etc. After signal processing, the blood glucose level is displayed.

Volunteers Profile

A team of 05volunteers (03men and 02women) aged 21 years or more (average: 28 years) were studied in these pilot study. The human volunteers were healthy and fit, without any chronic episodes of medications, belongs to different parts of the country. Institutional ethical committee approved the pilot study. Volunteers had signed their respective consent form for the experimental procedures.

Experimental protocol

To check the functionality of the noninvasive blood glucose detection experimental setup, the standard procedures of the Oral Glucose Tolerance Test (OGTT)[2] was carried on the 05 volunteers.

The steps followed for carrying out OGTT as given below:

The trials were held in the morning and the volunteers were instructed to fast (water is allowed) for 8–12 hours prior to the tests.

Step 1 Fasting blood glucose level of the volunteers has been measured at 0min by our noninvasive blood glucose meter based on amplitude modulated ultrasound with infrared technique and by an established invasive blood glucose detection method.

Step 2 Solution of 75gm (approx.) of glucose in 100ml (approx.) of water was given to the subjects for drinking within a 5min time frame after step 1.

Step 3 This stage involves acquisition of noninvasive and invasive blood glucose readings at every 15min up to a total period of 2 hours.

Experimental Procedures

The renounced software toolbox is utilized for all the data processing and programming. During each experiment five sets of signal data was recorded. In the Fast Fourier Transform (FFT) domain, peak to peak voltage amplitude of these consecutive signals is obtained. These peak to peak amplitude values of the 05 successive FFT data based signals were averaged, standardized and utilized as a key function for the real blood glucose concentration indicator.

RESULTS

The study had shown that the potential use of amplitude modulated ultrasound with infrared technique can be used for this purpose. In this study noninvasive blood glucose readings were acquired from human subjects. Calibrations were done by invasive glucose detection method to validate these noninvasive readings. A total of 45 blood samples for blood glucose measurements and 225 data based signals were recorded and examined in this pilot study. Table 1 shows the settings used for the experiment. Figure 5 depicts the observed signal of a volunteer at 0 min, 60min and 120min. whereas figure 6 depicts the voltage amplitude spectrum of the observed signal of the same volunteer at 0 min, 60min and 120min respectively. The time sequence relationship between the invasive blood glucose readings and the noninvasive blood glucose readings of a volunteer had been given in Fig. 7. We attuned the prediction partiality by the first reference blood glucose content, i.e., the expected data was attuned to the calculated value. The obtained full data sets for blood glucose content are presented

Table 1: Setting used for the Experiment

S. No	Parameter	Value
1.	Infrared LED operating wavelength	940nm
2.	Ultrasound operating frequency	40.0±1.0 kHz
3.	Interval between two readings	
	(a) Noninvasive readings	15min
	(b) Invasive readings	15min
4.	Total Time	120min

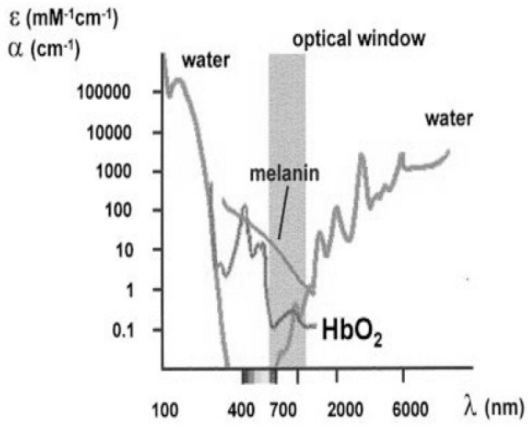

Fig. 1: Absorption spectra of major intracellular absorbers in the wavelength range from 100nm to 6000nm [32]

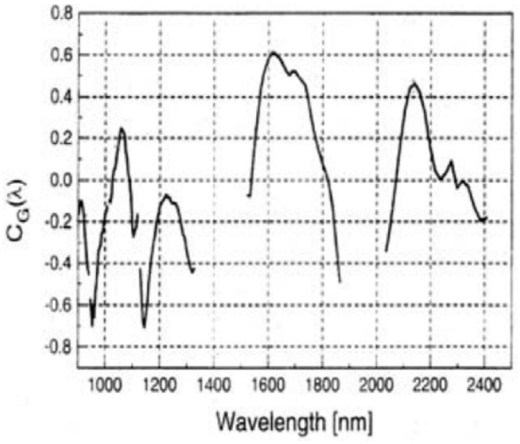

Fig. 2: Absorption profile of Glucose in the NIR (near infrared) wavelength range from 1000nm to 2400nm [33]

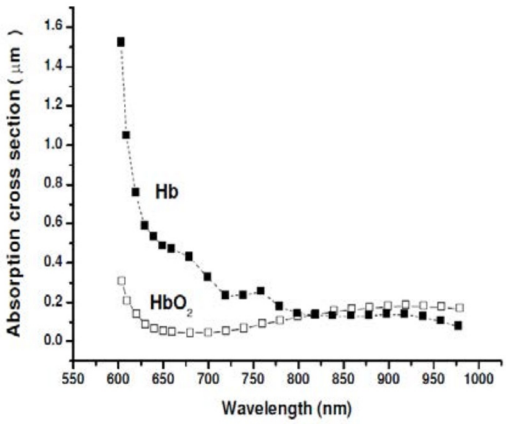

Fig. 3: Absorption cross-section of Oxy-Hemoglobin and Reduced Hemoglobin at R-NIR region [34].

using the Clarke error grid analysis in Fig. 8. [36-41]. Figure 8 presents the result for Clarke error grid analysis obtained using the data sets as obtained from the volunteers. The data plots included are, for the A zone: 91.11%, B zone: 08.88%, C zone: 0%, D zone: 0%, and E zone: 0%. Here all the prediction plots exist in zones A and B. To improve these predictions below 100 mg/dl and above 250mg/dl, noise reduction and accurate blood glucose content measurement is essential.

DISCUSSION

Diabetes mellitus is a complex metabolic disorder characterized by a common feature of uncontrolled blood glucose level. Once diagnosed with a diabetic mellitus, controlled diet regimen, overweight reduction, physical exercise and insulin

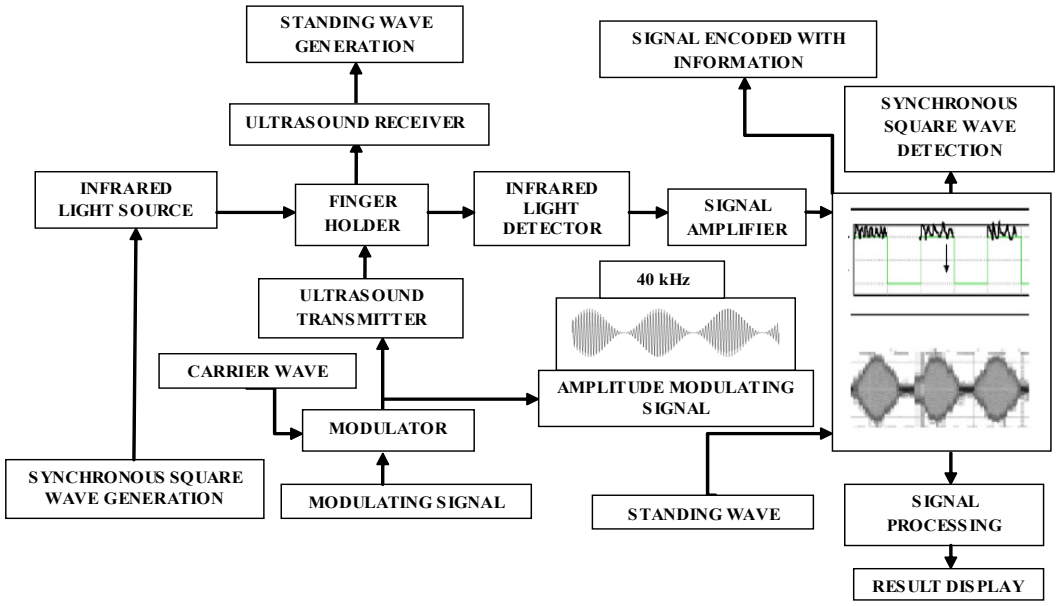

Fig. 4: The schematic diagram of the noninvasive blood glucose sensing experimental setup with Amplitude Modulated Ultrasound and Infrared Technique used in the clinical studies

injections or oral drugs are administrated to control hypo or hyper blood glucose levels. Controlled blood glucose levels prevent the patients from the medical emergencies like heart disease, blindness, renal failure or body part amputations. Utmost care for blood glucose level and proper medications in diabetes plays a vital role. Improvements in the medical diagnostic technology had introduced with the next generation of bloodless, painless, noninvasive blood glucometers. Continuous noninvasive glucometers can prevent medical emergencies arisen due to hypo and hyper glycemic conditions.

The OGTT based results of our pilot study performed over the human volunteer's shows

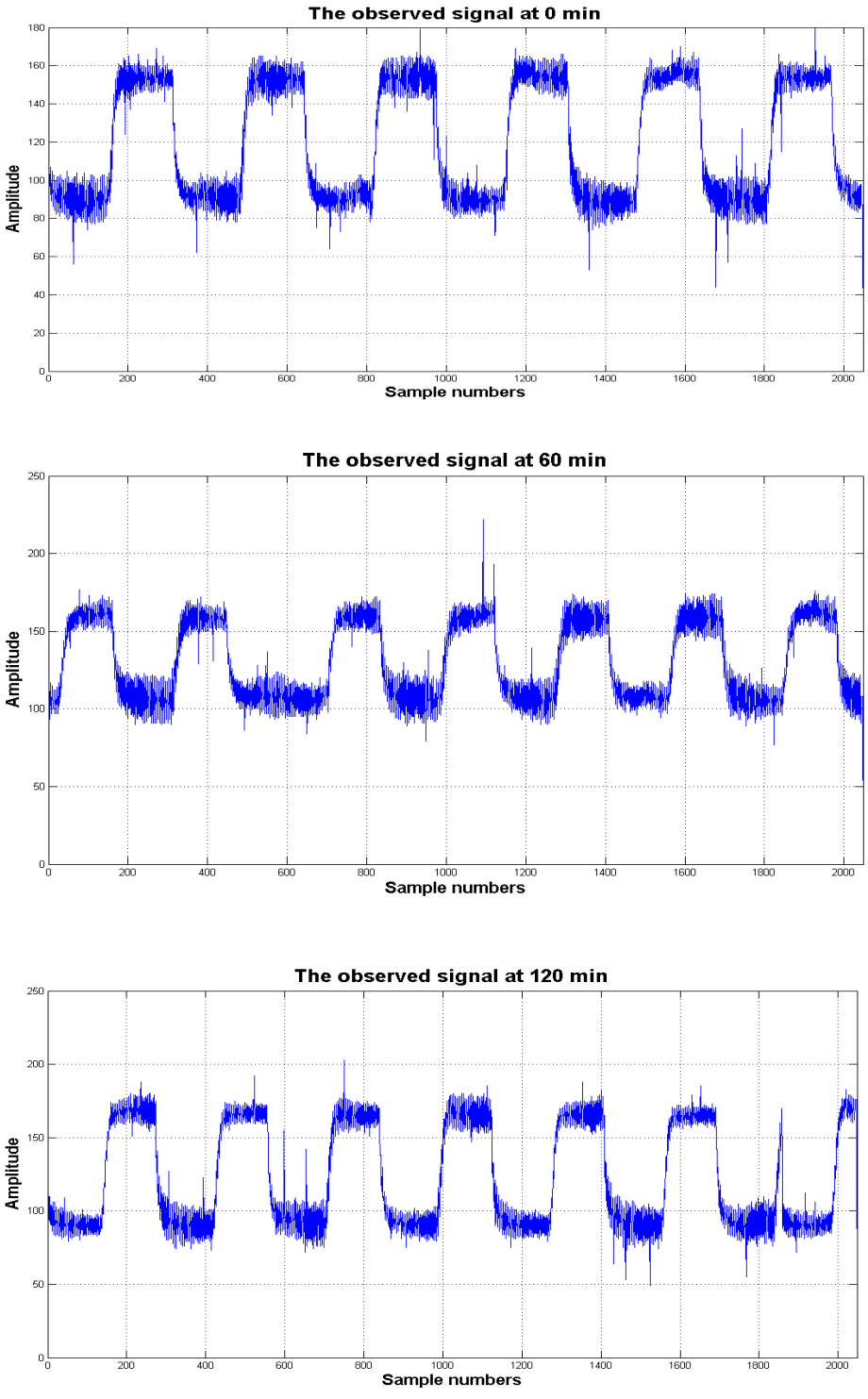

Fig. 5: Depicts the observed signal of a volunteer at 0 min, 60min and 120min

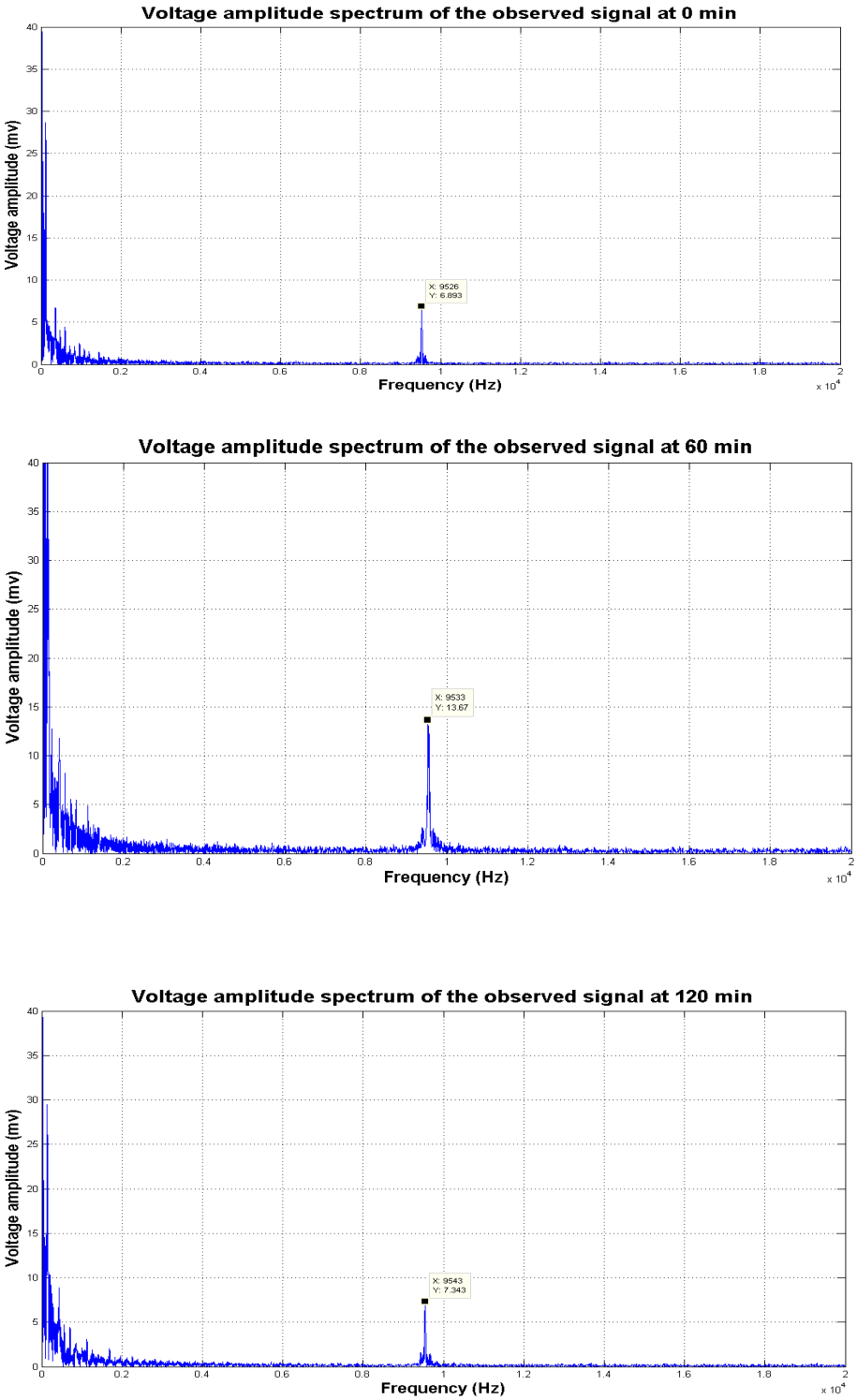

Fig. 6: Depicts the voltage amplitude spectrum of the observed signal of a volunteer at 0 min, 60min and 120min

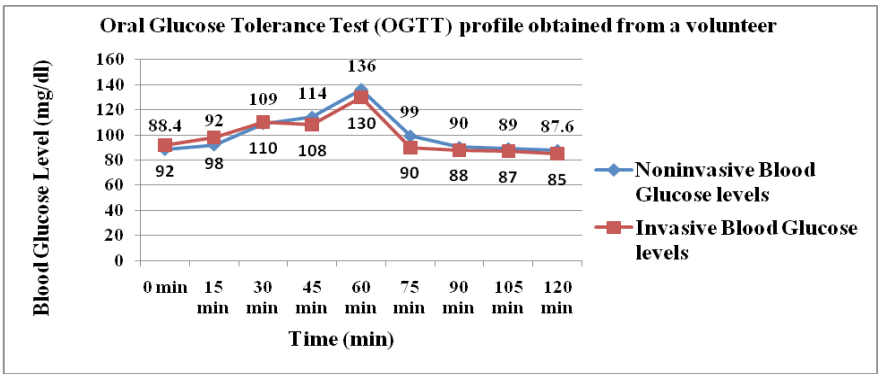

Fig. 7: Sequential variations in the blood glucose level; noninvasive and invasive blood glucose levels. Volunteer: Male adult, age 27

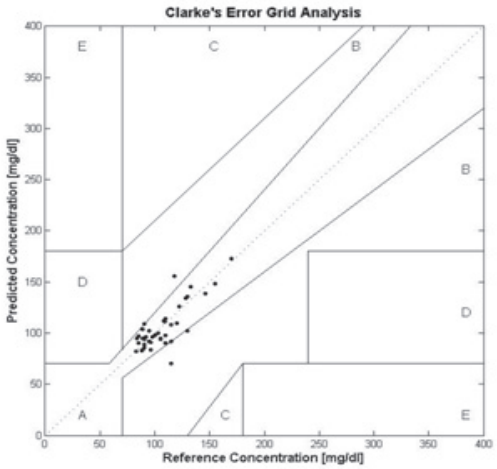

Fig. 8: The Clarke error grid delivers a plot of reference blood glucose concentration and predicted blood glucose concentration into a five regions: A, B, C, D, E. The proportion of the total data falling in the regions of A, B, C, D, E are 91.11%, 08.88%, 0%,0% and 0% respectively. Where Region A indicates that noninvasive blood glucose values which compliances within 20% of the reference glucose sensor (invasive glucometer), Region B indicates those dots which are outside 20% of the reference glucose sensor but would not provide wrong medical interpretations. Region C indicates those dots which provide the irreverent medical considerations. Region D indicates those dots which causes severe misinterpretation in determining the higher or lower blood glucose levels. Region E indicates those dots that would confuse the therapeutic management for higher or lower blood glucose levels and vice-versa.

excellent relationship in between the FFT signal voltage variations and the real time invasive blood glucose levels. The outcome of these studies resembles our earlier experimental readings[30, 31]. The main key factors which plays the major role in our technique as compared with the earlier techniques are; (a) standing wave utilization for result elevations (b) rational and consistent determinations of the transmitted light signals which is embedded with blood glucose level information. These hybrid technology merged together allows the measurement with high precision, greater sensitiveness etc. The blood glucose orientated output signals produced in our pilot study were due to; (a) the potentiality of the amplitude modulated ultrasound with infrared technique to monitor glucose induced variation of blood-tissue optical properties devoid of surrounding noises. (b) Low refractive index disparity on account of minimum absorption pattern of oxyhaemoglobulin, haemoglobulin, water, etc. at the tissue optical window range from 700nm to 1100nm. Our study demonstrates the potentiality of noninvasive blood glucose measurements using amplitude modulated ultrasound with infrared technique. It also indicates that the technology based upon infrared technique and modulated ultrasound can be developed to meet the blood glucose level related clinical accuracy requirements. Few error based signals are generated due to various factors like finger positioning, motion related artifacts, melanin based skin pigmentations, light interferences, time drift, machine drift, blood pressure and other physiological variations, etc. Various physiological and environmental influences cause the change in blood-tissue optical properties and therefore cause variation in voltage amplitude in the Fourier domain of the observed signals.

CONCLUSION

The usefulness of the combined method of the amplitude modulated ultrasound along with infrared technique for developing a noninvasive blood glucometer has been reported in this paper. The new concept for the blood glucose measurement using this hybridized idea was investigated and the investigation confirmed the assumption of the concept.

The infra-red LED operating in the wavelength region of 940nm and modulated ultrasound transmitter of 40 kHz has been used to conduct standard OGTT tests over 05 human subjects for noninvasive blood glucose measurement. Cross validation of the noninvasive results has been performed by the invasive blood glucose detection method.

Results of the conducted OGTT tests using this new method (amplitude modulated ultrasound with infrared technique) depicts that these new method is capable of non-invasive monitoring of the blood glucose level in human volunteers. Although at present these new method needs standardization with invasive glucose sensors. In near future, it will significantly decrease utilization of the various invasive techniques.

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Conflict of interest statement

Author's conflict of interest disclosure

The authors stated that there are no conflicts of interest regarding the publication of this article.

Author's Contribution

Md. Koushik Chowdhury Phd Research Scholar wrote the manuscript and also corresponding author of the manuscript. Md. Koushik Chowdhury and Anuj Srivastava performed experimentations and data collection during the studies. Dr.Neeraj Sharma (Associate. Professor) and Dr.Shiru Sharma (Assistant Professor) helped in overall supervision for the experimentations, final editing of the manuscript and getting necessary formal applications for the experimental purposes.

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