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ORIGINAL ARTICLE

Prospective Utilization of Modulated Ultrasound with Infrared Unit to Predict Three Different Ranges of Blood Glucose Concentration Levels in Various Human Whole Blood Mixed Intralipid Phantom Samples and Its Performance Evaluation by Clarke and Parkes Error Grid Analysis

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ABSTRACT
This research article represents the outcome of blood glucose determination tests performed over various human whole blood mixed intralipid samples. In this methodology, the amplitude-modulated ultrasonic standing waves has been applied to the various human whole blood mixed intralipid samples. These ultrasonic standing waves excite molecules present in that prepared phantom samples. Accordingly, the phantom constituent molecules start oscillating depending upon their physical and chemical characteristics. These unique and typically frequency specific oscillations are molecular specific in nature. The sensitive IR LED and its Detector Assembly captures those oscillations corresponding to the glucose molecule concentrations. The output signals has been processed through the specially designed algorithms to extract the embedded glucose concentration related information in various human whole blood mixed intralipid samples. Here, the indigenously developed instrumental result about the three different ranges of blood glucose concentration in the phantom samples has been cross checked with the established methodology. Moreover, its performance evaluations have been validated through Clarke and Parkes Error Grid Analysis. The Error Grid analysis shows that all the readings occupy the clinically significant A and B zones. Consequently, this technique presents a new methodology for noninvasive glucometer design and development.
Key words: Blood glucose, Intralipid phantom, Amplitude modulated ultrasound, Infrared unit, Error grid analysis, Noninvasive glucometer.

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INTRODUCTION

The diabetic subject daily needs to crosscheck his/her blood glucose levels for tight vigilance over it. Moreover, this procedure has been useful to avoid serious medical emergencies in near future [1-3]. Current technology offers several invasive procedures to monitor blood glucose levels on daily basis [3, 4]. Invasive blood glucose determining technology invites skin related infection hazards, patient mental agony, patient incompliance along with it [1-5]. For better alternative, scientist from all over the world provides several new concepts for noninvasive blood glucose determining technology [5]. Many of the noninvasive technologies had shown promising and produce reliable results [5]. Those new prominent technologies comprises infrared absorption spectroscopy [5,6], near infrared scattering spectroscopy [5,7], Raman spectroscopy [5,8], fluorescent spectroscopy [5,9], thermal gradient spectroscopy [5,10], polarimetry technologies [5,11], polarization heterodyning approaches [5,12], photonic crystal techniques [5,13], photoacoustic Technologies [14], photo thermal technologies [5,15], optical coherence tomography (OCT) techniques [5,16] , ultrasound-modulated optical techniques [16], Occlusion

spectroscopy [18]. All these approaches had shown their promising qualities for noninvasive blood glucose measurements [5, 19, and 20]. However, until today, successful along with medically significant noninvasive technology does not exist [5, 19, and 20].

Glucose induced weak signals, overlapping of spectral properties, inadequate SNR ratios, background noise hindrances, etc, all this aspects constitutes the complication factor towards the advent of successful noninvasive blood glucose determining technology [19, 20]. More research oriented experimental studies were needed for evaluating the glucose-induced characteristics of skin tissue and light interactions with it [19, 20]. Various phantom based experiments have been performed nowadays for such evaluations [21-23]. Similarly, we had exploited intralipid phantom based experiments with our new methodology for resembling tissue-optical characteristics [21-23]. Here, we had studied the effect of modulated ultrasound and infrared techniques for determining three different ranges of blood glucose concentration levels in various human whole blood mixed intralipid phantom samples. Rest of this research article has been categorized as follows. Section II constitutes the materials and methodology portions for determining blood glucose in noninvasive way. Section III includes experimental results and discussion portion of the research article. Section IV represents the conclusion portion of the research article.

MATERIALS AND METHODOLOGY

Intralipid Tissue Phantom Preparation

Intralipid phantom possess the optical properties, which mimics the living biological tissues optical properties. Intralipid phantoms can be utilized for experimentation validations, optimizing purposes, quality control measures [21-24]. Therefore, phantoms of good quality and property have been utilized for lab experimental purposes [21-24]. The compositions of the Intralipid emulsion phantom as synthesized in our lab are as follows:

Table No. 1. Intralipid Composition [22, 23]

Soybean oil	100 g	107.88 ml
Lecithin	12 g	11.64 ml
Glycerin	22.50 g	17.84 ml
Water	861 g	862.66 ml
Total	995.5 g	1000 ml

The optical property of intralipid phantom varies from one preparation to the other. Consequently, standardization and validations of each intralipid samples were needed prior to the experimental works [22-23].

Instrument Experimental Setup

The pilot study were performed with this instrument experimental setup as given in Figure No.1 to determine the significance of the amplitude modulated ultrasound with infrared techniques in determining different ranges of blood glucose concentration levels in various human whole blood mixed intralipid phantom samples.

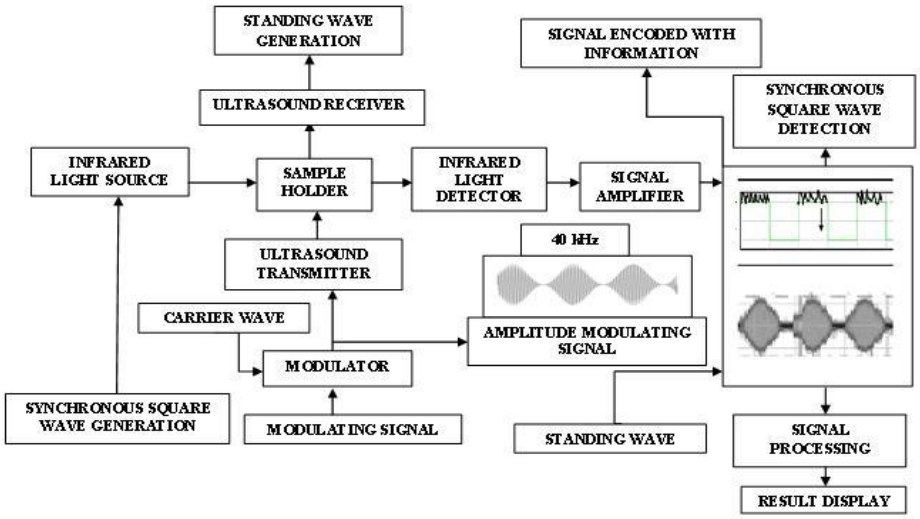


Figure No.1: Schematic Block Diagram of the instrument experimental setup.

The instrument experimental setup mainly composed of amplitude modulated ultrasound and infrared unit. The ultrasound transmitter unit provides amplitude modulated standing ultrasonic waves to the sample holder as shown in Figure No.2 respectively.

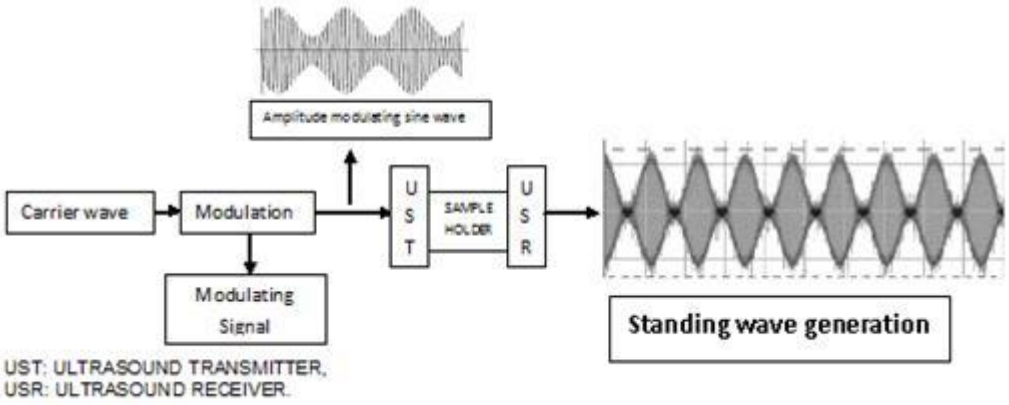
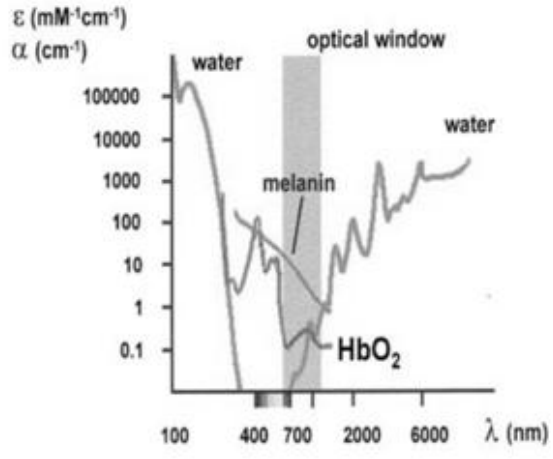


Figure No.2: Represents the standing wave generation pattern.

Ultrasonic receiver unit has been utilized here for observing pattern of ultrasonic standing wave as this phenomenon plays the significant role in glucose concentration determinations. Both the ultrasound transmitter and receiver of 40 kHz operating frequency has been utilized here. This ultrasonic wave produces series of oscillation in phantom samples. The infrared assembly (IR light and detector) detected these molecular specific series of oscillations. Specially designed signal processing unit picks up the glucose concentration related information and displays the glucose concentration levels.

Principle Involved in Detecting Glucose Concentration in Whole Blood Mixed Intralipid Phantom Samples through Amplitude Modulated Ultrasound and Infrared Unit

In the indigenously developed technique we had, utilized piezo crystal based ultrasonic transmitter and receiver with central operating frequency of 40 kHz. These types of piezo crystal based ultrasonic unit within this operating frequency were safe for human use [25, 26].Similarly, Infrared LED (Light Emitting Diode) of 940nm spectral band and its respective detector assembly had been utilized here. The 940nm spectral band exists within the tissue optical window range, which extends from 700nm to1100nm range [27-30]. Within this range the optical hindrance form other molecular entities like oxyhemoglobin, deoxyhemeglobin and water were sufficiently less to facilitate the observation of glucose molecules more significantly [27-30]. Moreover these facts can be proved from Figure No.3, 4 and 5 respectively.



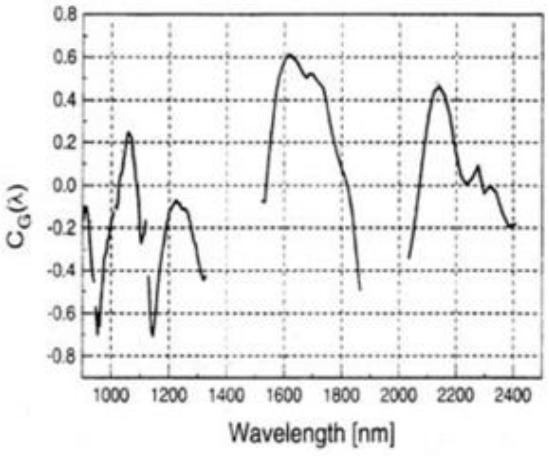


Figure No. 3. **Figure No. 4.**

Figure No.3: Represents the tissue optical window range from 700nm to 1100nm respectively [4, 27].

Figure No.4: Represents the glucose absorption pattern in the Infrared spectral band [4, 28].

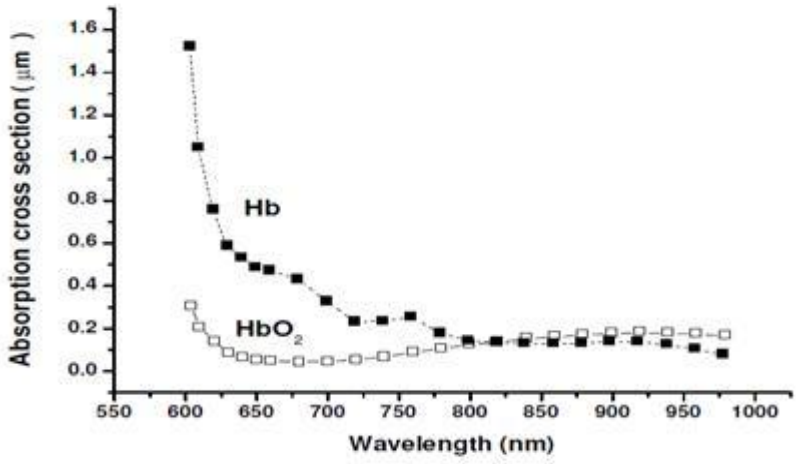


Figure No.5: Represents the absorption pattern of oxyhemoglobin and hemoglobin within the spectral range of 550nm to 1000nm respectively [4, 29, 30].

Oscillations has been produced in the human whole blood mixed intralipid phantom samples when ultrasonic standing sound waves propagates through it [31-38]. Practically when two anti directional moving waves merges, the standing wave generation occurs [31-38]. Standing waves possess both the higher and lower values just twofold over a distance of a solitary wavelength [31-38]. Placement based acoustic potential energy were generated within the molecules in the propagating segment [31-38]. Similarly, the molecule tends to cloud near minimum acoustic potential energy localizations [31-38]. Those clouding points were very close to pressure nodes, which are spaced from each other by a distance of half a wavelength [31-38]. Consequently, when ultrasonic wavelengths are higher than the molecular diameters, the radiation force ($\mathbf{F_r}$) acting over the volume of molecules ($\mathbf{V_c}$) positioned by a length of ($\mathbf{z}$) from the node of pressure had been expressed from the gradient of the molecular acoustic potential energy and described in equation No.1 as follows:

$$\mathbf{F_r} = -\left[\frac{\pi \mathbf{p_0^2 V_c \beta_w}}{(2\lambda)}\right].\boldsymbol{\phi}(\boldsymbol{\beta},\boldsymbol{\rho}).\mathbf{sin}(4\pi \mathbf{z}/\boldsymbol{\lambda}) \quad \textbf{(1)}$$

Here,
$\mathbf{F_r}$ = Force of Radiation
$\mathbf{V_c}$ = Volume of the molecules present in that human whole blood mixed intralipid phantom samples
$\mathbf{z}$ = dimension of the distance.
$\mathbf{P_o}$ = peak amplitude of the modulated ultrasonic standing waves under application.
$\boldsymbol{\lambda}$ = wavelength of amplitude modulated ultrasonic standing waves.
When the conceptions of compressibility factors ($\boldsymbol{\beta_w}$) were measured [31-38], the mathematical equation has been represented as follows:

$$\boldsymbol{\phi}(\boldsymbol{\beta},\boldsymbol{\rho}) = [\frac{\mathbf{5_{\rho_c} - 2_{\rho_w}}}{\mathbf{2_{\rho_c} + \rho_w}} - (\frac{\boldsymbol{\beta_c}}{\boldsymbol{\beta_w}})] \quad \textbf{(2)}$$

Here,
$\boldsymbol{\beta_c}$ = molecular compressibility of those molecules present in that human whole blood mixed intralipid phantom samples.
$\boldsymbol{\rho_c}$ = densities of molecules present in that human whole blood mixed intralipid phantom samples
$\boldsymbol{\rho_w}$ = densities of medium present in that human whole blood mixed intralipid phantom samples

When a beam from Infrared LED were introduced to measure the glucose molecule based specific oscillating signatures pattern for its particular concentration determination, the Lambert-Beer law fundamentals were measured to illustrate the observable fact as follows [31-38]:

$$\mathbf{A(v)} = -\mathbf{log\, I(v)/I_0(v)} \quad \textbf{(3)}$$

Here,
A= Absorption profile.
v= relevant wave number.
I= light intensity of the adjoining medium.

I_0= light intensity after propagating through the human whole blood mixed intralipid phantom samples.

Study Volunteers

The group of 30 adult volunteers (25 males and 05 females of height 171±6.3 cm, weight 78±5.1 kg) has been chosen for this pilot study. Out of which 10 adults volunteers has been selected with Random BGL (Blood Glucose Level) ranging between (70-140) mg/dl. Furthermore, next 10 adults has been selected with Random BGL (Blood Glucose Level) ranging between (141-199) mg/dl. Similarly, remaining 10 adults has been selected with Random BGL (Blood Glucose Level) ranging between (200-260) mg/dl. Objective of this pilot study has been explained to them and their written consent were obtained for the pilot experiments. The Institute Ethical Committee had approved the pilot study.

Error Grid Analysis

Clarke Error Grid Analysis has been applied here to importantly verify the performance of our indigenously developed instrumental setup with the established medical device (Accu-chek Active blood glucose monitoring device).

Clarke Error Grid utilizes the Cartesian plot based diagrammatic approaches to compute the predicted blood glucose values against the real blood glucose values [39-43]. It consists of 5 zones usually named as: Zone A, Zone B, Zone C, Zone D and Zone E respectively [39-43]. The values obtained within the Zones A and B is clinically significant [39-43]. The values in the Zone C to Zone E are clinically not acceptable [39-43].

The Parkes Error Grid introduces a newly constructed error grid sets based on the consensus report of 100 medical experts of diabetics [39, 44, 45]. It can provide a clear distinction between Type I and Type II diabetics. It consists of 5 zones usually named as: Zone A, Zone B, Zone C, Zone D and Zone E respectively [39, 44, 45]. Zone A signifies medically accurate blood glucose value determinations, with nothing effect towards the therapeutic management [39, 44, 45]. Zone B signifies altered medical action, small or less effect towards the therapeutic goal [39, 44, 45]. Zone C signifies altered medical action, liable to provide modest effect towards the therapeutic goal [39, 44, 45]. Zone D signifies altered medical action, liable to provide considerable effect towards the therapeutic goal [39, 44, 45]. Zone E signifies altered medical action, liable to provide hazardous effect towards the therapeutic goal [39, 44, 45].

At present scenario in the domain of endocrinology, generalized consensus error grid for determining errors in blood glucose level predictions does not exist. Therefore, we had utilized both the critical approaches (Clarke and Parkes) for verifying our results.

EXPERIMENTAL PROCEDURES

During the lab experimental works, the following steps were followed.

1. The whole blood samples of all the adult volunteers were collected in vacuum-based blood collecting vessels where K_2 EDTA is present as an anticlotting agent.
2. Change in the hematocrit and oxygen concentration level varies the glucose-induced signals [18]. Therefore, Nitrogen bubbling has been applied to induce de-oxygenation in the whole blood samples for 45mins.
3. The pH level of the blood samples were maintained by the Phosphate Buffer Solution (PBS).
4. 1ml of whole blood content obtained from every adult volunteer had been mixed with 1ml of intralipid phantom samples separately as test preparation for the experimental purposes.
5. This whole blood mixed intralipid samples were placed in the indigenously developed instrumental setup for its respective glucose concentration measurements.
6. The blood glucose concentration obtained from the indigenously developed instrumental setup had been crosschecked for its accuracy with the results obtained from the standard Accu-chek Active blood glucose monitoring device. Accu-chek Active medical device of Roche Diagnostics GmbH make had been utilized here [46-47].
7. Moreover, both the readings were processed through Clarke and Parkes Error Grid analytical tools for indigenously developed instrumental setup performance evaluations.

RESULTS AND DISCUSSION

Intralipid phantom samples have been used widely for mimicking light tissue interaction phenomenon in optical experiments and techniques [21-24]. Large and increasing number of diabetic population, demand for noninvasive glucometer had influence us for designing and developing an experimental technique for determination of glucose levels in human whole blood mixed intralipid phantoms [21-24]. We had obtained blood samples from the respective volunteers with Random BGL levels ranging for 70mg/dl to 260mg/dl for our experimental purposes. Consequently we had divided those samples into three categories depending upon their Random blood glucose levels.

Category I- includes samples with Random blood glucose levels ranging from 70mg/dl to 140mg/dl.
Category II- includes samples with Random blood glucose levels ranging from 141mg/dl to 199mg/dl.
Category III- includes samples with Random blood glucose levels ranging from 200mg/dl to 260mg/dl.
The samples from each category (I, II, III) have been prepared by adding 1ml of blood samples from each category to the 1 ml of intralipid phantom solution respectively. This procedure has been followed for preparing all the human whole blood mixed intralipid phantom samples. The final prepared samples have been placed inside the sample holder section of the instrumental setup for its glucose content determinations. All final readings acquired have been compared with the readings obtained from the established medical device (Accu-chek Active blood glucose monitoring devices). Consequently its performance evaluation had been done with help of Error Grid Analysis for all three categories of Random blood glucose level mixed intralipid phantom samples respectively.

Error Grid Analysis (Clarke and Parkes) of Category I blood samples mixed intralipid phantom sample preparations

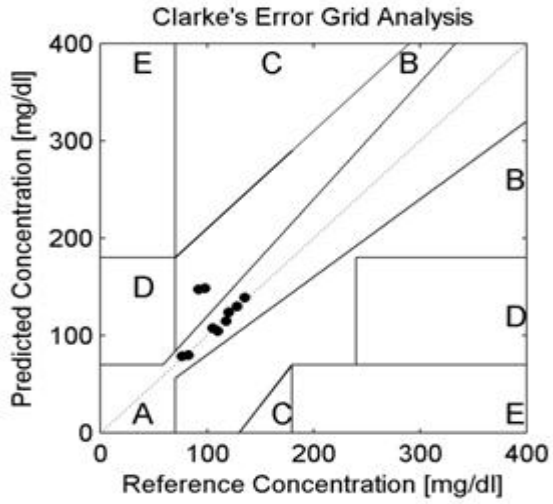


Figure No.6

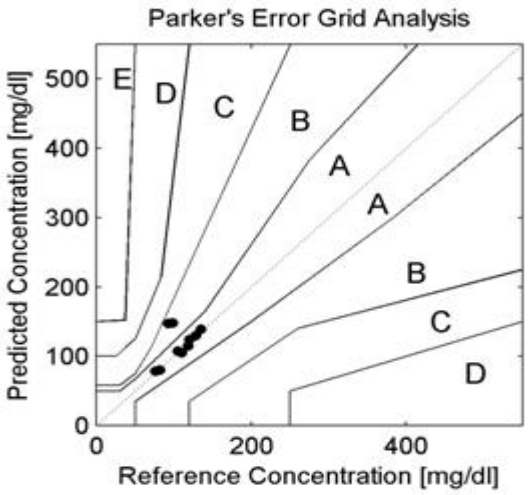


Figure No.7

The Clarke and Parkes Error Grid Analysis of Category I blood samples mixed intralipid phantom sample preparations had been shown in Figure No. 6 and 7 respectively. The results acquired from the Clarke Error Grid analysis had been expressed as A zone=80.00%, B zone=20.00%, C zone=00.00%, D zone=00.00%, E zone=00.00% respectively.
Similarly, the results acquired from the Parkes Error Grid analysis had been expressed as A zone=80.00%, B zone=20.00%, C zone=00.00%, D zone=00.00%, E zone=00.00% respectively.

Error Grid Analysis (Clarke and Parkes) of Category II blood samples mixed intralipid phantom sample preparations

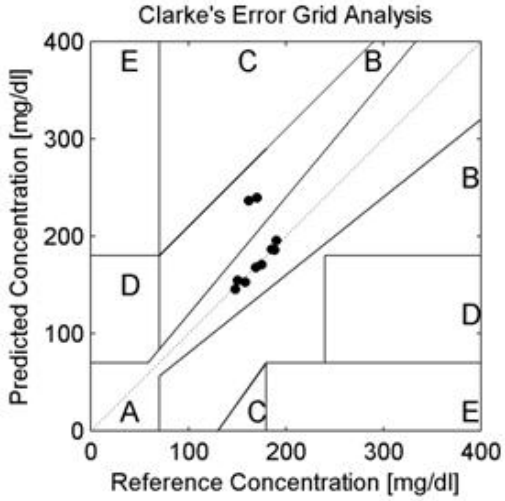


Figure No.8

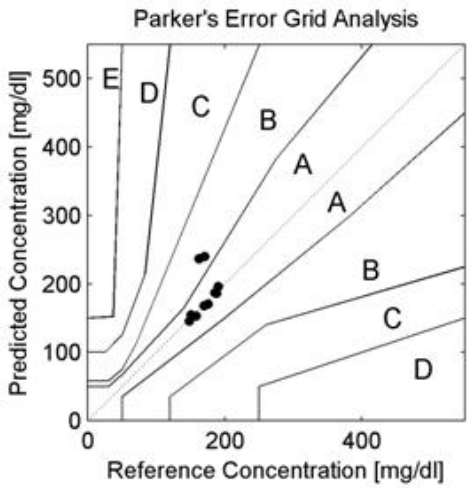


Figure No.9

The Clarke and Parkes Error Grid Analysis of Category II blood samples mixed intralipid phantom sample preparations had been shown in Figure No. 8 and 9 respectively. The results acquired from the Clarke Error Grid analysis had been expressed as A zone=80.00%, B zone=20.00%, C zone=00.00%, D zone=00.00%, E zone=00.00% respectively.
Similarly, the results acquired from the Parkes Error Grid analysis had been expressed as A zone=80.00%, B zone=20.00%, C zone=00.00%, D zone=00.00%, E zone=00.00% respectively.

Error Grid Analysis (Clarke and Parkes) of Category III blood samples mixed intralipid phantom sample preparations

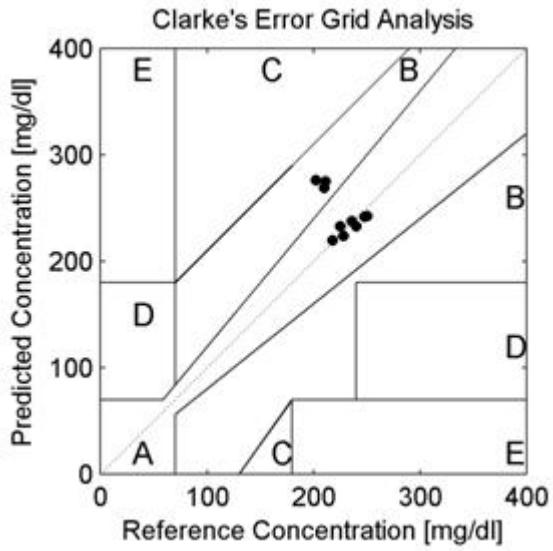


Figure No.10

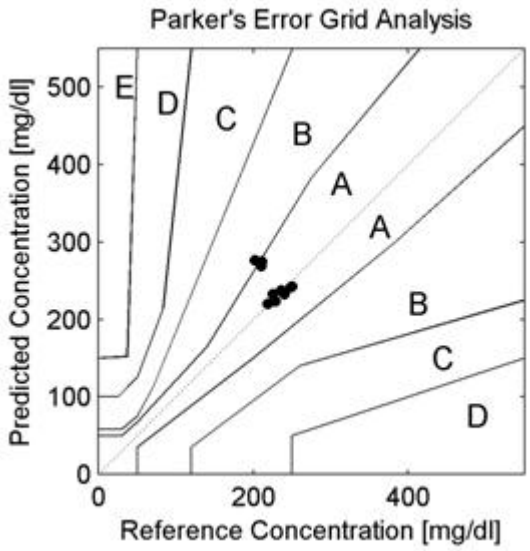


Figure No.11

The Clarke and Parkes Error Grid Analysis of Category III blood samples mixed intralipid phantom sample preparations had been shown in Figure No. 10 and 11 respectively. The results acquired from the Clarke Error Grid analysis had been expressed as A zone=70.00%, B zone=30.00%, C zone=00.00%, D zone=00.00%, E zone=00.00% respectively.
Similarly, the results acquired from the Parkes Error Grid analysis had been expressed as A zone=70.00%, B zone=30.00%, C zone=00.00%, D zone=00.00%, E zone=00.00% respectively.

All this results occupies the medical significant A and B Zones in Clarke and Parkes Error Grid Analysis. Consequently, it proves that our indigenously developed instrumental setup was successful in detecting different blood glucose levels in the range extending from 70mg/dl to 260mg/dl through human whole blood mixed intralipid phantom samples respectively.

CONCLUSION

Determination of blood glucose content in human whole blood mixed intralipid phantom samples has been conducted in this research article with the aid of amplitude modulated ultrasound and infrared unit respectively. Instrumental performances were critically verified through Error Grid Analysis. Outcome of Clarke and Parkes Error Grid Analysis depicts that all the experimental output readings occupy medically acceptable A and B zones respectively. These results direct towards the successful detection of respective blood glucose concentrations in sample preparations. In turn, it proves the potentiality of our indigenously developed MUS-IR instrumental setup for blood concentration determinations in phantom samples.

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CONFLICT OF INTEREST

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

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