<u>**Original Article**</u>

A Feasibility Study of Non-invasive Blood Glucose Level Detection Using Near-Infrared Optical Spectroscopy

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Abstract

Diabetes mellitus, a common disease of the modern era, is a glucose level disorder in the human body that affects the vital organs of the body and damages them gradually if left untreated. Regular blood glucose monitoring is one of the prescribed routines to control the complications of diabetes. Unfortunately, most available methods of blood glucose level measurement involve invasive ways. Invasive techniques are painful, make the finger skin calloused and the patients suffer from the risk of infectious diseases. Hence, there lies a need to develop an effective non-invasive blood sugar measurement technique to relieve the patients from the nuisance. In order to address the issue, a non-invasive technique has been designed and implemented using 940 nm near-infrared (NIR) LED and a corresponding photodiode. Initially, the in-vitro test was performed over the glucose solution of various concentrations to check the sensitivity of the device. After that pilot experiments were carried out on diabetic patients. The obtained results conformed the theory of near infra-red spectroscopic optical theory. The results also showed that the developed technique can be comparable with the conventional invasive glucometer based method. Furthermore, the implemented prototype is economically viable, especially for the low-income population. This promising results thus pledge the potentials, feasibility, and reliability of the NIR based non-invasive blood glucose detection devices.

Keywords: Diabetes mellitus, blood glucose, near-infrared spectroscopy, glucometer.

Introduction

In the year 2017, around 451 million people had been suffering from diabetes mellitus with an estimated increase of up to 693 million by the year 2045 globally [1]. Despite spending $850 billion for the healthcare of diabetic people, 5 million amongst the diabetic patients died around the world in that year [1]. Alarmingly, half of the diabetic patients did not go through any diagnosis of the disease and the case is severe in low-income countries like Bangladesh [1]. It is a case of

concern that approximately 82 million people suffer from diabetes in the Southeast Asia region alone [2].

Diabetes mellitus (or diabetes) occurs when the blood glucose level is always higher than the normal range. It is a chronic, life-long condition that affects the ability to use the energy found from food. Usually, all kinds of carbohydrates are converted into a simple sugar named glucose. Glucose works as the fuel for the cells in the body. A hormone named insulin produced by the pancreas is needed in the bloodstream to absorb the glucose and use it for the accumulation of energy. In the case of diabetic patients, either pancreas does not produce enough insulin, and/or the body cells cannot utilize the produced insulin properly. As a result, the glucose cannot be absorbed in cells and gets accumulated in the blood. Consequently, the sugar level becomes higher than the normal level and gradually damages the blood vessels in the kidney, heart, eyes, and other organs [3]. If diabetes remains untreated, it often causes heart diseases, stroke, blindness, and nerve damage in the feet.

Diabetes is highly prevalent in developing and under-developed countries [3]. It is impossible until now to cure diabetes entirely by the available methods. To minimize the complications associated with diabetes, a patient has to keep his blood sugar level in the standard range. Regular blood glucose monitoring, exercise, a healthy diet plan, oral medication, and insulin shots play a vital role in the medication of diabetes. The available methods for monitoring blood sugar levels are mostly invasive. A patient's finger is pricked to collect a blood sample and the glucose level is measured. People having a higher level of diabetes need to check their sugar levels frequently. This repetitive finger puncturing causes irritation, discomfort, and pain. The skin of the finger becomes very rough and scratched. There always lies a risk of infection in this invasive method. Moreover, the most common strip-based invasive method is costly for the poor patients suffering from high diabetes because they have to check their sugar level two or three times a day and pay for each strip every time. So, an effective and reliable non-invasive method for measuring the blood sugar level will definitely be a boon to this case.

Several research works have been performed for non-invasive blood glucose measurement based on near-infrared (NIR) photoacoustic spectroscopy, Raman spectroscopy [4], polarization technique, and light scattering technique [5, 6]. As a non-invasive method, the transilluminated laser beam has been used to measure glucose concentration [7]. Tang *et al.* demonstrated that the

metabolic heat conformation technique could be used for blood sugar level identification [8]. In near-infrared (NIR) spectroscopy, glucose cells produce the weakest NIR absorption signals in the human body [9]. NIR spectroscopy causes a penetration depth of 1 to 100 millimeters and the penetration depth is inversely proportional to the signal wavelength [10, 11]. Heise *et al.*, one of the pioneers of the non-invasive method, has several publications on the NIR method [12-14]. Maruo *et al.* reported the efficiency of this approach using an in-vivo method. Their work is associated with the NIR diffuse reflectance spectroscopy through fiber optics on the forearms of diabetes patients [11], and the results showed that there is a positive sign of the correlation between anticipated values and the reference glucose levels.

There are some advantages associated with NIR spectroscopy. Photoconductive detectors are highly sensitive in NIR spectroscopy. In the signal bandwidth of NIR, water becomes reasonably transparent. So, this makes it possible to use the NIR signal for blood glucose monitoring. In addition, the measured signal of NIR has more energy than that of mid-infrared (MIR) spectroscopy. Furthermore, non-invasive blood glucose measurement using NIR is less expensive than MIR. Moreover, NIR based methods are small, compact, less costly, and less harmful to the body compared to the laser-based non-invasive method. These advantages have made NIR quite popular in the measurement of blood sugar level.

In this context, the aim of this research was to design and develop a non-invasive method of blood sugar level detection based on the NIR signal. A simple, compact, and cost-effective prototype was developed using a NIR light-emitting diode LED and a detector. With the prototype, in-vitro and in-vivo experiments were carried out. The main research focus was to explore the feasibility of NIR based blood glucose level detection.

Principle of Glucose Measurement

When a light beam interacts with the human body tissue, scattering, and absorption by body tissue cause attenuation of the light beam. There lies a mismatch between the refraction index of extracellular fluid and the cell membrane. As a result, light scattering occurs in tissues. The cellular membrane index is assumed to be relatively constant, whereas the extracellular fluid's refractive index changes with glucose concentration [15].

Beer-Lambert Law that plays a prime role in this absorbance measurement states that the absorbance of light through any solution is proportional to the concentration of the solution and the path length traveled by that light rays [16]. If the glucose concentration is low, it causes more scattering, longer path length, and less absorption. On the contrary, if the glucose concentration is high, it causes less scattering, smaller path length, and more absorption by the tissue. When the tissue has high glucose concentration, the reflected light has lower intensity compared to the tissue with low glucose content because more absorption occurs in tissue with high glucose concentration. According to the light transport theory, the attenuation of light can be written as [17]-

$$I = I_O\, e^{\mu_{eff} L} \qquad (1)$$

Where, I is the reflected light intensity, I_O is the incident light intensity, and L is the optical path length inside the tissue. Attenuation of light inside the tissue depends on the coefficient known as the effective attenuation coefficient (μ_{eff}), which is written as

$$\mu_{eff} = \sqrt{3\mu_a(\mu_a + \mu_s')} \qquad (2)$$

Where, the absorption coefficient (μ_a) is described as the probability of absorption of photons inside the tissue per unit path length and is given by,

$$\mu_a = 2.303\varepsilon C \qquad (3)$$

Where, ε is the molar extinction coefficient, and C is the tissue chromophore concentration.

The reduced scattering coefficient (μ_s') is defined by [15],

$$\mu_s' = \mu_s(1 - g) \qquad (4)$$

Where, g is the average of the cosine of the scattering angles having a representative value of 0.9 and μ_s is the scattering coefficient [17].

Path length decreases with an increase in glucose concentration. The refractive index of blood cells is assumed constant having an approximate value of 1.350-1.460 [16]. After an analysis of equations 1 to 4, it can be inferred that μ_a depends on blood glucose concentration. When the blood glucose concentration rises, the value of μ_a rises. As a result, μ_{eff} also increases and causes

a rise in attenuation level. From equation. 1, it can be said that when attenuation increases, the intensity of reflected light decreases. Hence, it can be deduced that the intensity of reflected light is inversely proportional to the blood sugar concentration.

Prototype Design and Implementation

Wavelength Selection

The near-infrared light window lies between 600 nm to 1300 nm [15]. When the light comes across a tissue, they interact with low energy radiation. In the near-infrared window, the light gets its maximum penetration depth in tissue. Glucose provides light absorption peaks at wavelengths of 940 nm, 970 nm, 1197 nm, 1408nm, 1536nm, 1688nm, 1925 nm, 2100nm, 2261nm, and 2326nm [17]. Besides glucose, there are several other components in blood such as water, platelets, red blood cells, etc. At 940 nm wavelength, the attenuation of the optical signal by other constituents of blood becomes minimum [15]. As a result, the desired penetration depth is found, and the actual glucose concentration can be identified.

*Structure and Working Principle of the Device*

The proposed device was developed using a NIR LED and corresponding NIR detector, both having a wavelength of 940 nm as glucose has light absorption peaks in this wavelength. A block diagram of the complete system can be observed in Figure 1.
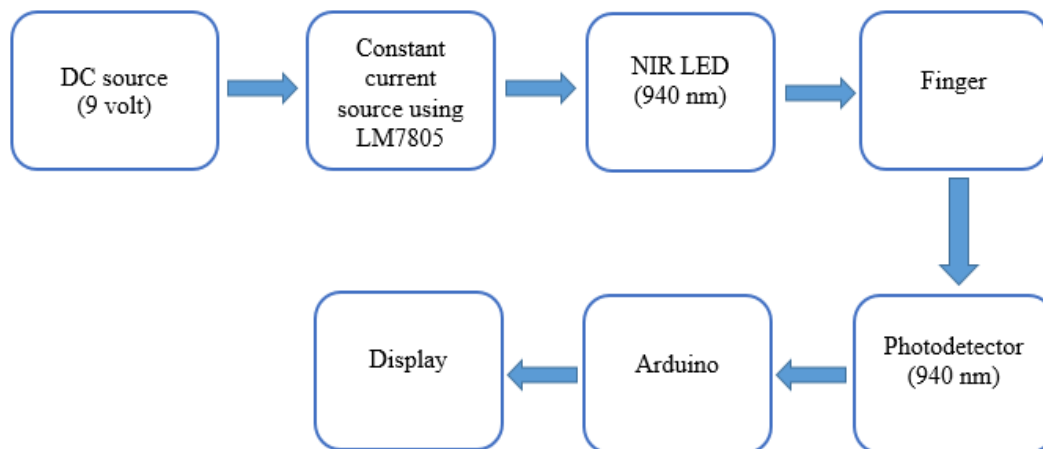
**Figure 1.** Block Diagram of the NIR based Blood Glucose Detection Device.

The experiments were performed in a black box so that light from the environment could not contaminate it. When the reflected light falls on the photodetector, it starts conducting. Then using

the voltage across the detector, the blood glucose concentration is calculated by the Arduino, which was programmed with the mathematical relationship obtained after analyzing the data from the invasive and non-invasive method. Then the result is shown on the LCD display. Figure 2 presents the schematic representation of the NIR based glucose level detector. 9V DC battery was used as a power source. Additionally, an LM7805 voltage regulator was used to ensure a constant voltage supply of 5V to both the LED and to the Arduino board. With a series resistor in the LED loop, this provides a constant current to the LED, giving light of constant intensity.
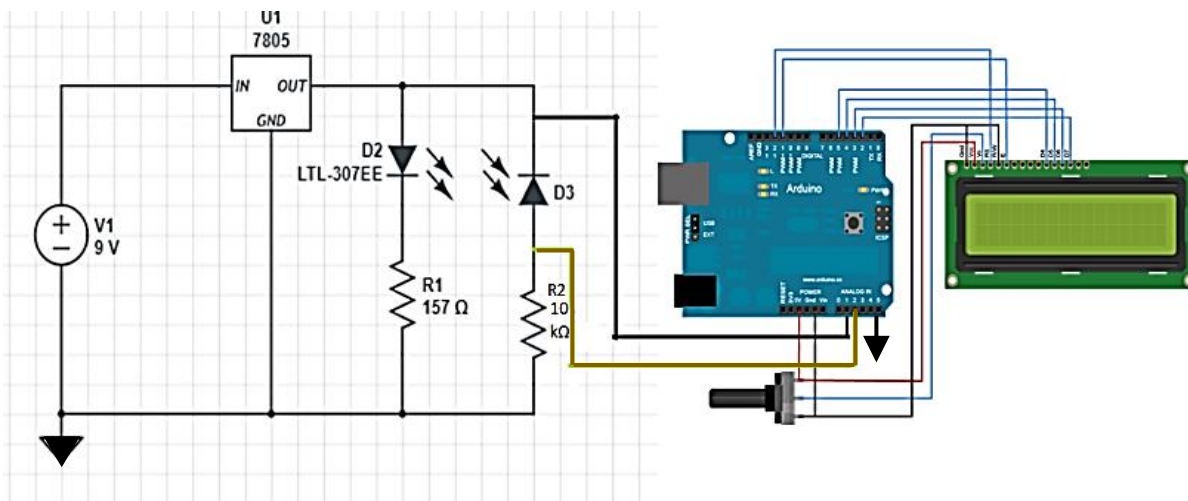
Figure 2. Schematic Diagram of the NIR Blood Glucose Detector.

A person taking the test has to place his/her thumb on the sensor patch, as presented in Figure 3. The infra-red light falls on the finger, and a portion of light gets reflected. The NIR LED, and detector are placed in a small compact black colored acrylic box with a partition between them. So, it is not possible for the infra-red light to fall on the detector directly. Only the light that gets reflected from the finger falls on the detector. For identifying the reflected signals correctly, the emitter and detector are placed on the same side of the finger. As a result, the transmitted and reflected signals have a 180° phase shift between them.
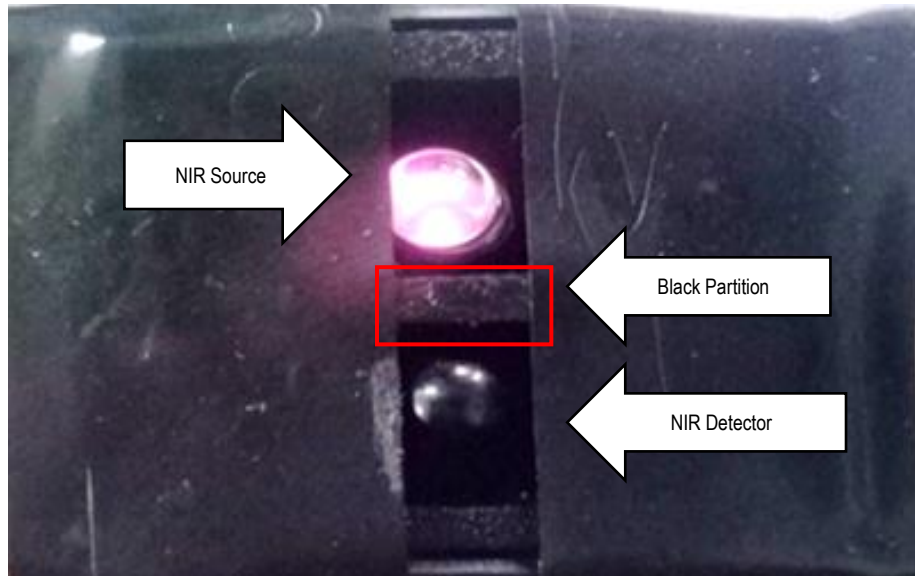
Figure 3. Sensor Patch of the NIR Blood Glucose Detector.

Cost Estimation

The costs of different components of the prototype can be found in Table I. The total cost is approximately $14 or BDT 1,190 which is on the reasonably economic side. The total cost will eventually come down for the final output due to mass production benefits.

Table 1. The Costs of Different Components.

Item Name	Cost (USD/ BDT)
Sensor patch	0.6/51
LM7805	0.4/34
Arduino Uno	5/425
Battery and jumper wires	1/85
LCD Display	6/510
Miscellaneous	1/85
The total cost of the prototype	**14/1190**

Experimental Paradigm

1. In-vitro Test

Ten solutions of different concentrations between 20 to 350 mg/dL were used. The sensor patch was placed against the test tube wall, and then the corresponding output voltage was measured using a multimeter. The problem of stabilizing the photodiode was mitigated after doing the experiment in a closed black box. This in-vitro experiment was performed to examine the relationship between change in glucose concentration and NIR light.
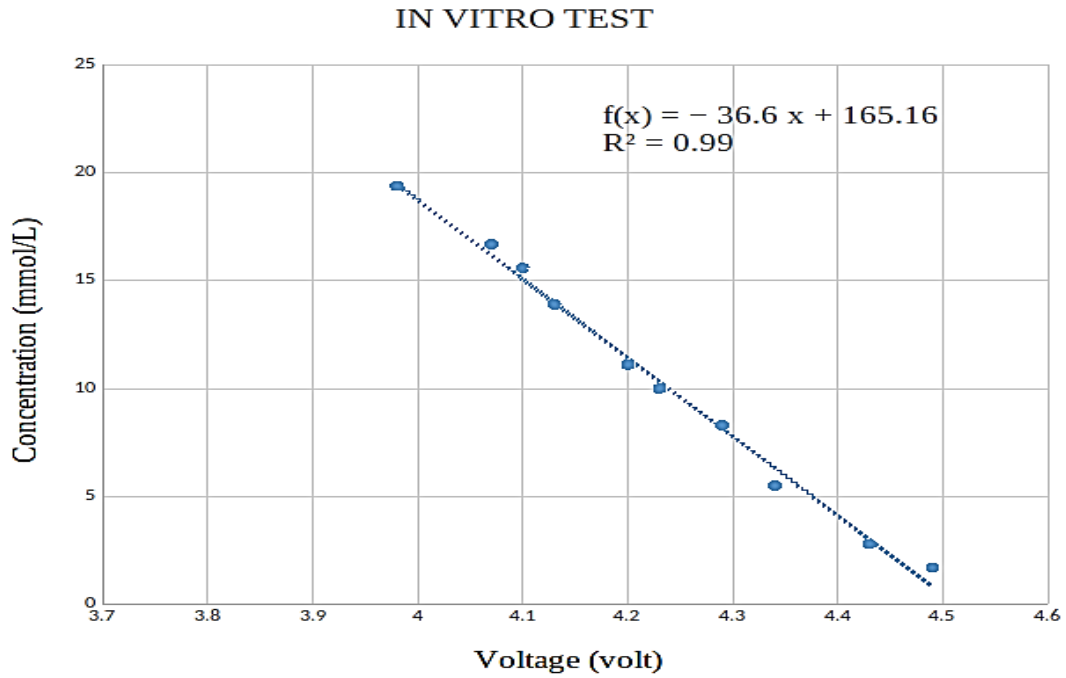
2. In-vivo Test

The in-vivo test was performed through a pilot study over 20 diabetic patients at the Shaheed Suhrawardy Medical College Hospital, Dhaka, Bangladesh, under medical supervision from the medicine unit with consents from the participants. To carry out the in-vivo test, at first, the blood glucose concentration was measured using a glucometer (Easy Touch GCHb), and then output voltage was detected by our developed device for each person. Subjects were requested to sit down in a relaxed position and place the finger gently over the sensor patch. After placing the finger over the sensor, the data was calculated by our device.
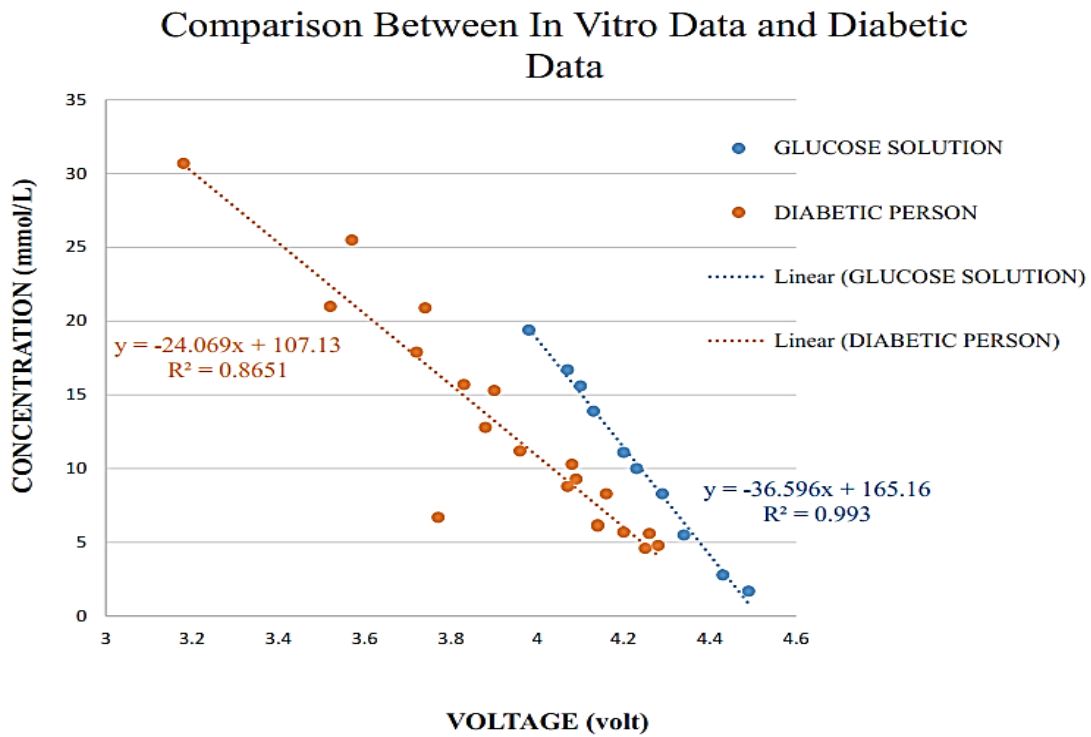
Results and Discussions

In-vitro tests were performed using the glucose solution of various concentrations, and the corresponding voltage was measured using the developed device. In-vitro results are shown in Figure 4. The output voltage decreases with an increase in glucose concentration that supports our initial theoretical modeling. In-vivo data were collected from diabetic patients with the help of the developed noninvasive device as well as with the Easy Touch GCHb glucometer. In-vivo and in-vitro data are plotted, and a comparison is shown in Figure 5. The glucose solution used in the in-vitro test was taken in a test tube. A test tube has a higher reflectance capacity than a human finger because there are so many different organelles, blood components, and several layers of skin on the finger. Thus the amount of absorbance is higher and reflected light's intensity becomes lower in the finger. Hence, if the test tube's solution and the patient have the same glucose concentration, the voltage found from the patient will be lower than the voltage found from the test tube. This phenomenon can be seen in Figure 5.

IN VITRO TEST

$$f(x) = -36.6\,x + 165.16$$
$$R^2 = 0.99$$

Figure 4. Glucose Concentration vs. Voltage Graph for In-Vitro Test

Comparison Between In Vitro Data and Diabetic Data

GLUCOSE SOLUTION

DIABETIC PERSON

.... Linear (GLUCOSE SOLUTION)

.... Linear (DIABETIC PERSON)

$$y = -24.069x + 107.13$$
$$R^2 = 0.8651$$

$$y = -36.596x + 165.16$$
$$R^2 = 0.993$$

Figure 5. Comparison between in-vitro and in-vivo data.

The device was programmed using the equation associated with the diabetic patients' data under our experiment. The equation associated with diabetic patients' data is y = -24.069x + 107.13. Here, x is the output voltage of the device, and y is the corresponding blood sugar level of that subject. The equation has a correlation coefficient of 0.93, which is promising. A comparison between blood glucose concentrations measured by the invasive and non-invasive method is shown in Table 2, where error calculation has been performed considering the available invasive method as the standard.

Table 2. Blood glucose level comparison between the invasive and non-invasive method

Blood Glucose concentration by Glucometer (mmol/L)	Measured voltage by the non-invasive device (volt)	Blood Glucose concentration by Non-invasive device (mmol/L)	Percentage of Error $\frac{IR-NR}{IR}\times100\%$
4.6	4.25	4.8	-4.35%
4.8	4.28	4.1	14.58%
5.6	4.26	4.6	17.85%
5.7	4.2	6.0	-5.26%
6.1	4.14	7.5	-22.95%
6.2	4.14	7.5	-20.96%
8.3	4.16	7.0	15.66%
8.8	4.07	9.2	-4.54%
9.3	4.09	8.7	6.45%
10.3	4.08	8.9	13.59%
11.2	3.96	11.8	-5.36%
12.8	3.88	13.7	-7.03%
15.3	3.9	13.3	13.07%
15.7	3.83	14.9	5.09%
17.9	3.72	17.6	1.68%
20.9	3.74	17.1	18.20%
21	3.52	22.4	-6.67%
25.5	3.57	21.2	16.86%
IR= Invasive device's reading and NR = non-invasive device's reading.			*Average error = 2.43%*

From Table 2, some of the readings seem too erroneous. One reason could be that some of the participants were admitted to the hospital with multiple complications and were too ill to follow the procedures appropriately. Taking into this, an average error of 2.43% was obtained in general. Hence, it can be deduced that the developed prototype can reasonably detect blood glucose levels

and this NIR based non-invasive technique has promising potentials. For optimized performance, it would be better to repeat the measurement multiple times for a single blood glucose concentration.

Humanitarian Impact

Till now most of the diabetes patients identify their blood glucose level with an outmoded, age-old procedure. They prick their finger, put a drop of blood on a test strip, and place the test strip in a glucometer which detects the blood sugar level. On the contrary, patients need to place their finger over our sensor patch. There is no need for any finger pricking anymore. The existing non-invasive blood glucose monitor's price ranges from 25$ to 1000$ and more. Most of them are unavailable in the low and medium income countries like Bangladesh. Diabetic patients of poverty-stricken areas of the world cannot access those machines because of their relatively high price, low availability, and strip dependency. The cost of our designed model is $14 or BDT 1,190, which is cheaper in comparison with the available models. In addition, the device has a time cost occurrence as there is no need for an additional strip like regular cost occurring parts. The proposed technique is swift, painless, and budget-friendly and, therefore, economically viable especially for people in impoverished countries.

Conclusion

In summary, a non-invasive device with a 940 nm NIR LED and a photodetector for blood glucose measurement was designed, implemented, and tested. Both in-vitro and in-vivo experiments were performed. Results obtained in both cases follow the optical theory of near infra-red spectroscopy. The calculated correlation coefficient of the designed device is quite satisfactory. A comparison between the invasive and non-invasive devices' data ensures the feasibility, efficiency, and reliability of the developed method. This method is simple, inexpensive, user-friendly, and portable. It helps the user get rid of those pain, irritation, risk, and discomfort associated with the invasive technique. With all the mentioned features, we hope that this technique has the potential to become a blessing in the field of blood glucose level detection. Further studies are planned with a higher number of people in community-based clinics and hospitals in order to improve the correlation coefficient of the device. Moreover, a smartphone-based platform is in development stage so that the patients can check their blood glucose level on the phone's display and can have the data saved for multiple other benefits.

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