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DIAGNOSIS OF DIABETES MELLITUS USING ACETONE AS BIOMARKER IN HUMAN BREATH

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ABSTRACT

This project is to design and develop a non-invasive method to diagnose diabetes mellitus which is commonly known as Diabetes. It is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period of time. It is essential to monitor the blood glucose levels of a diabetic patient frequently. As of 2019, an estimated 463 million people had diabetes worldwide and it causes approximately 4.2 million deaths. It is the 7th leading causation of death globally. Hence it is necessary to diagnose the disease earlier, so that we can prevent the patient from suffering. It can be done using a technique called breath analysis. Breath analysis is a technique in which the diseases in human beings can be diagnosed using human breath. Human breath naturally consists of over 3500 Volatile Organic Compounds (VOC) other than of major gases like oxygen, nitrogen and carbon dioxide. Each VOC is a biomarker to various diseases and metabolism of our body. Likewise, acetone is one of the 3500 VOCs and it is a biomarker to diabetes mellitus. Hence the measurement of acetone gas in our breath leads to the detection of diabetes mellitus. The normal range of acetone gas in our breath is less than 0.8 ppm. If the value exceeds the normal range, the person is affected with diabetes. The acetone level in human breath is detected using a Grove HCHO – VOC gas sensor. The sensor is connected to the microcontroller which will control the entire operation. The data collected from the sensor will be analyzed for the disease. If an abnormal change is detected in the level of acetone, it will alert the person such that the person requires immediate medication. The main advantage of this project is the non-invasive way of detecting diabetes which does not involve any pain staking invasive laboratory methods.

Keywords: Diabetes Mellitus, Biomarker, Diagnose, Acetone, Breath Analysis.

1. INTRODUCTION

Diabetes mellitus (DM) is a disease of imperfect control of blood levels of glucose. In diabetes mellitus, human body has trouble moving glucose, which is a type of sugar, from blood into cells. This leads to the glucose level high in blood and not enough of it in cells, and the cells need glucose as a source of energy. In general, the human body controls how much glucose is in the blood relative to how much gets into the cells with the help of two hormones: insulin and glucagon. Insulin is used to reduce blood glucose levels, and glucagon is used to increase blood glucose.

Insulin is secreted by beta cells in the center of the islets, and glucagon is secreted by alpha cells in the periphery of the islets. Insulin decreases the amount of glucose in the blood and glucagon does exactly the opposite, it increases the blood glucose level in blood. Diabetes mellitus is diagnosed when the blood glucose levels get too high, and this is seen among 10% of the world population. There are two dominant types of diabetes - Type 1 and Type 2 and has subclassifications – gestational diabetes, drug-induced diabetes and diabetic ketoacidosis (DKA). About 10% of people with diabetes have Type 1, and the remaining 90% of people with diabetes have Type 2.

The Type 1 diabetes results from failure of the pancreas to produce enough insulin due to loss of beta cells. It appears as childhood or adolescence; it can also develop in adults. In diabetes Type 1, destruction of beta cells usually starts early in life, but sometimes up to 90% of the beta cells are destroyed before symptoms crop up. Four clinical

symptoms of uncontrolled diabetes, that all sound similar, are polyphagia (poly - a lot; phaga - eating), glycosuria (glucose - glucose; uria – urine), polyuria (poly – a lot; uria – urine), and polydipsia (poly – a lot; dipsia – thirst).

Type 2 diabetes begins with insulin resistance, a condition in which cells fail to respond to insulin properly. It appears commonly among adults.

Gestational diabetes occurs when pregnant women without a previous history of diabetes develop high blood sugar levels. It returns to normal soon after delivery.

One really serious complication with diabetes type 1 is called diabetic ketoacidosis (DKA). Diabetic ketoacidosis (DKA) is a life-threatening problem of diabetes mellitus. Hence it is essential to detect the diabetes level and to undertake the necessary treatment in order to maintain it. Otherwise, it causes serious impact on patient's health and finally it leads to death. DKA impact from a shortage of insulin; in response, the body switches to burn fatty acids, which produces ketone bodies in acidic nature. That ketone bodies break down into acetone and escape as a gas while exhaled from the lungs, which gives a sweet fruity smell to a person's breath. DKA is diagnosed when testing finds low blood pH, high blood sugar, and ketoacids in either the urine or blood. In these type of diabetes produces ketone bodies in blood urine and breath (acetone – which produces fruity smell).

Currently, diabetes mellitus is diagnosed by both invasive (finger pricking -blood test) and non-invasive (urine test) methods. Here this is one of the non-invasive methods of diagnosing using breath. Human breath analysis is one of the earlier methods to diagnose disease. There are about over 3500 Volatile Organic Compounds present in our exhaled breath, one of such VOC is acetone. The VOC's contained in exhaled human breath are detected with the help of the sensors. It is found that acetone acts as the biomarker for diabetes mellitus. By detecting and mapping the concentration of acetone present in the exhaled human breath we can observe the prior stages of the disease. This can be done with the help of breath analysis technique. By mapping the concentration of acetone and diagnosing with the standard values we can ensure that the patient is affected with diabetes or not. Detection of acetone can be done with the help of GROVE – HCHO VOC gas sensor. The normal acetone level in exhaled breath of healthy person is less than **(0.1 PPM – 0.8 PPM)**. The patients who are affected from diabetes will have acetone concentration more than (**1.8 PPM – 5.0 PPM)**. The detected concentration is displayed in the display so that they know their state of health.

Through this method, we can ensure a person's safety by continuously monitoring the concentration of ammonia in exhaled breath at a particular time interval. It is one of the cost-efficient ways to detect the disease such that the poor people can afford it easily. One of the main advantages of this method that it does not involve risk factors like finger pricking and pain stacking methods involved in laboratory methods.

2. LITERATURE REVIEW

Fahad Usman., et al. [1] identified acetone as a non-invasive biomarker for diagnosing diabetes from exhaled human breath. They studied and discussed about diabetes, death rate, biomarker and biosensors, and concentration of acetone for normal (0.1 ppm - 0.8 ppm) and diabetes (1.8 ppm - 5.0 ppm) persons. They gathered standard concentration from WHO.

Claire Turner., [2] investigates the potential for monitoring compounds in breath and emitted through skin for inferring blood glucose concentration. Potential markers and an assessment of their suitability for non-invasive monitoring are discussed. The varying technologies developed for monitoring VOCs (volatile organic compounds) in breath and from skin of diabetics using acetone as a biomarker. They discussed about breath analysis and concentration of acetone in diabetics and non-diabetics person.

Valentine Saasa., et al. [3] describe the methods used in the field of breath analysis to monitor and diagnose diabetes mellitus. Currently the diagnosis and monitoring of blood glucose and ketone bodies that are used in clinical studies involve the use of blood tests. This method entails pricking fingers for a drop of blood and placing a drop on a sensitive area of a strip which is pre-inserted into an electronic reading instrument. Furthermore, it is painful, invasive and expensive, and can be unsafe if proper handling is not undertaken. Human breath analysis provides a non-invasive and rapid method for detecting various VOCs (volatile organic compounds) that are indicators for different diseases. In patients with diabetes mellitus, the body produces excess amounts of ketones such as beta-hydroxybutyrate, acetoacetate, and acetone. Acetone is exhaled during respiration.

Dixit K., et al. [4] research on non-invasive blood glucose monitoring has led to the development of various devices, easing diabetes management through comfortable, minimally invasive/non-invasive continuous blood-glucose monitoring. Nevertheless, they still suffer from issues such as lag time and the requirement of frequent calibration. Breath analysis is newly budding domain for diagnosing and monitoring the disease using non-invasive method. It is painless, safe, and allows repetitive sampling. However, the intricacies of breath analysis need to be well-studied to enable accurate, reliable, and reproducible monitoring.

Righettoni M., et al. [5] proposed about Si-doped WO3 chemo-resistive gas sensors have been fabricated by flame spray pyrolysis. These nanoparticles had excellent acetone sensing properties with a great potential for application in non-invasive medical diagnostic by breath analysis. In fact, theWO3 ε-phase thermal stability was enhanced greatly by Si-doping (up to 500 °C) allowing detection in the ppb range of acetone in ideal (dry air) and realistic (90%) breath conditions. However, gas sensing performances such as the sensor response and the response time are also dependent on the measurement system and conditions.

Maureen I. Harris., et al. [6] proposed that most of the US people do not check their blood glucose level because of cost and income. So, they proposed about the importance of blood glucose control in the prevention of diabetes complications and the role of self-monitoring in achieving blood glucose control, it may be prudent for physicians and their patients to make greater use of this technique.

Chen, X., et al. [7] proposed an innovative method of lung cancer pathologic analysis and early diagnosis at the cellular level was introduced. An optimum HS-SPME-GC method was used to detect the odors of some cells in human breath, including squamous cell carcinoma cells, adenocarcinoma cells, bronchioloalveolar carcinoma cells, non-small cell carcinoma cells, bronchial epithelial cells, tastebud cells, osteogenic cells, and lipocytes, and we were able to obtain an odor chromatogram of these cells.

3. METHODOLOGY

In this chapter we are going to discuss about the proposed methodology or working of our project. In this project we proposed Human Breath Analysis technique to identify the diabetes mellitus in a human. It is a technique in which various diseases in humans can be identified easily through exhaled human breath. In this technique, human breath is analyzed for the normal concentration of ammonia in order to identify the liver cirrhosis. One of the biggest advantages of this technique is the early detection of diseases in human beings in a non- invasive way.

Figure 2.1 HUMAN BREATH ANALYSIS TECHNIQUE

It is done with the help of gas sensing technology. For sensing the acetone gas presented in our human breath as one of the 3500 VOCs, we have used a type of acetone gas sensor called Grove HCHO VOC gas sensor. It is a general-purpose sensor that it can be used for various purposes. The sensor is powered with the microcontroller which has a power source pin of 3.3V. The microcontroller used here is PIC16F877A which is the brain of this entire system.

The sensor will sense the input acetone gas as soon as it is powered. At the same time, the microcontroller was programmed in such a way to read the input signal. Here the analog output pin of the sensor is used to sense the gas since it gives the raw values continuously. The analog output from the sensor is not in a readable form. Hence it is

converted into readable digital form with the help of 10-bit Analog to Digital Converter which is already present in the microcontroller.

The output which is sensed by the sensor is analyzed and compared with the normal standard concentration of the acetone gas which is also programmed in the microcontroller. The normal standard concentration of acetone in exhaled human breath is found out by performing the literature survey. The corresponding output will be displayed in the displaying unit. Hence the person can be verified with their corresponding present health status. If the output value is confirmed with diabetes mellitus, person have to get medication at right time. If the output is normal, the entire process can be repeated in case of any critical situation occurs in future.

It will greatly pave the way for detecting diseases using this breath analysis technique in these modern days as it possesses many advantages over other invasive laboratory methods. The test can also be done in a short period of time.

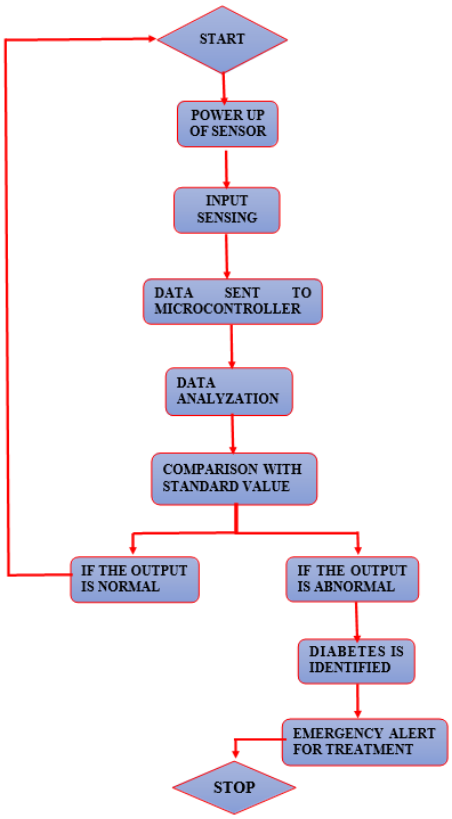

Figure 2.2 WORK FLOW PROCESS

2.1 SENSOR CALIBRATION

The calibration of sensor is very important in doing any project work. It is very important before using any sensors in project. It is a process of rectifying the undesired outputs to desired outputs. Sensors are made up of electronic and electrical components. Since those components are sensitive to various factors like temperature, humidity, external shocks and vibration etc., it will lead to the undesired output results. The sudden change in the working environment also leads to the deviation of output results such that the measured outputs differ from the expected outputs. Hence calibration plays a significant role in increases the chance of getting desired output results. It will improve the performance and accuracy of the sensor by removing errors in measurements.

In our project, we use GROVE HCHO – VOC gas sensor for detecting acetone gas in human breath. Hence it is necessary to calibrate the sensor for accurate output. The operation of this sensor is based on the changing resistance of

the heated coil thus measuring the concentration of the particular gas. Two parameters are involved while calibrating the sensor. They are as follows:

- R0 – Sensor resistance of instantaneous concentration of measuring gas
- Rs – Internal resistance of the sensor changing in clean air or environment

The concentration measurement of a particular gas is also depending on the ratio of Rs and R0. Hence it is found out as a primary stage of calibrating the sensor. The sensor will show some random values as output when it is connected to microcontroller. It is necessary to calibrate it to zero. For that purpose, we are going to take average of that random values as a secondary step of calibration. Hence, we coded the microcontroller in such a way to calculate the average value using looping controls. The loop will run for 500 times and the average of the values was taken.

The calculated average was converted into equivalent sensor voltage since this conversion calibrate the sensor to zero in an effective manner. The Rs value of the sensor is also calculated every time by converting the values into equivalent sensor voltage. The obtained R0 value will be used to find the ratio for changing Rs value at every step.

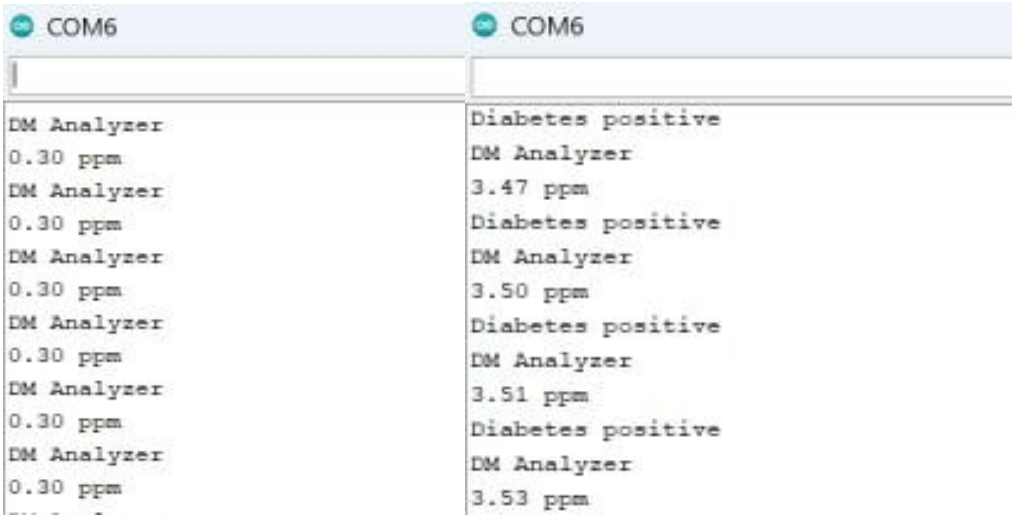

Figure 2.3 SENSOR OUTPUT BEFORE AND AFTER CALIBRATION

4. MODELING AND ANALYSIS

In this project we are using a GROVE HCHO VOC gas sensor to analyze the concentration of acetone in human breath. Hence this experiment plays a very important role to analyze the characteristics of the sensor and to determine the applicability of this particular type sensor in real time monitoring. It is conducted to verify that the above used sensor meets the above characteristics for the efficient measurement of acetone in human breath in real time application.

3.1 ANALYSIS I

The analysis is carried out with the detection of acetone gas which is to be measured in human breath. But human breath has minute level of acetone and it is volatile. So, acetone solution from laboratory is taken as sample for this analysis. The general calibration of the sensor is carried out and made the sensor ready to detect the acetone. To generate the acetone odor or gas, we have used acetone solution in same concentrations and in different environment.

The acetone solution (10ml) was taken in a beaker to conduct the experiment. Before commencing of the experiment, the sensor was preheated by supplying the power for about thirty minutes for obtaining the best results. This analysis was carried out in an **open environment** such that the gas sensor is placed near to the beaker containing acetone solution. Then the sensor detected the acetone gas which is evolved from the solution. The data obtained from the sensor is viewed in the monitor and it is recorded for further analysis. The data was collected for every second and the collected data was tabulated for further analysis.

TABLE 3.1 READINGS OF ACETONE DATA 1

TIME (IN S)	CONCENTRATION OF ACETONE (IN PPM)
1	0.30
5	0.39
10	0.60
15	0.83
20	1.11
25	1.43
30	1.80
35	2.21
40	2.48
45	2.62
55	2.82
60	2.92

The data which is tabulated are used to plot the graph against time in seconds for analyzing the response of sensor in detecting the concentration of acetone gas which is released from the acetone solution. From the graph, we inferred the characteristics of sensor in determining the acetone concentration in solution clearly.

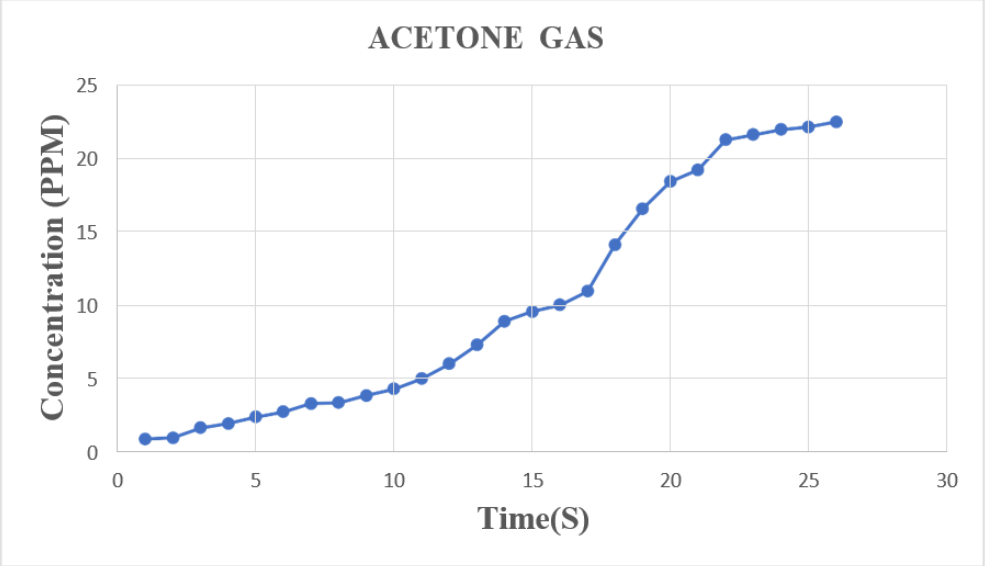

Figure 3.1 GRAPHICAL REPRESENTATION OF ACETONE DATA 1

3.2 ANALYSIS II

Another experiment analysis using the different concentration of acetone solution (10ml) was carried out to analyze the performance of sensor in detecting the gas. In this analysis, the experiment was done in a **closed environment**. Then the sensor detected the acetone gas which is evolved from the solution. The data obtained from the sensor is viewed in the monitor and it is recorded for further analysis. The data was collected for every second and the collected data was tabulated for further analysis.

Table 3.2 READINGS OF ACETONE DATA 2

TIME (IN S)	CONCENTRATION OF ACETONE (IN PPM)
1	0.40
5	0.53
10	0.70
15	0.95
20	1.20
25	1.45
30	1.70
35	1.95
40	2.20
45	2.45
50	2.70
55	2.95
60	3.30

The data which is tabulated are used to plot the graph against time in seconds for analyzing the response of sensor in detecting the concentration of acetone gas which is released from the acetone solution. From the graph, we inferred the characteristics of sensor in determining the acetone concentration in solution clearly.

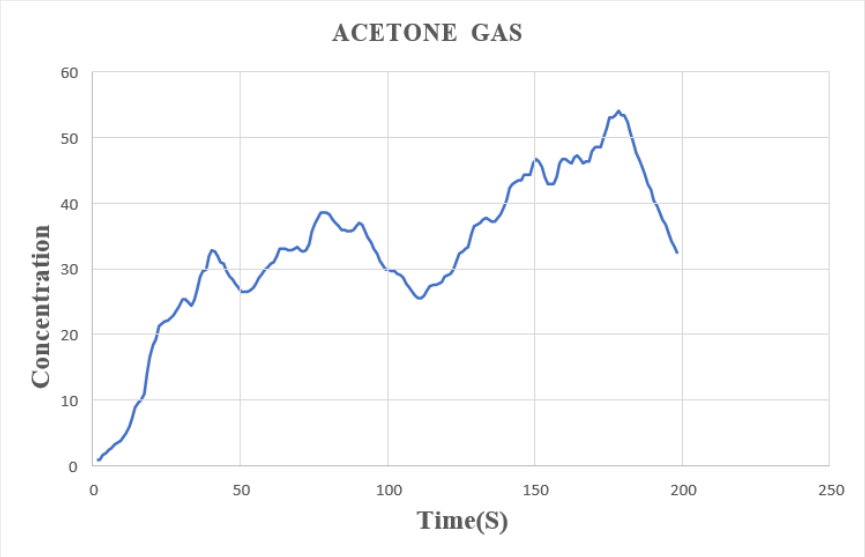

Figure 3.2 GRAPHICAL REPRESENTATION OF ACETONE DATA 2

5. RESULTS AND DISCUSSION

Experiment analysis was carried out regarding the performance characteristics of the sensor and its behavior. The analysis was done in different concentrations of acetone solution. In this chapter we will discuss about the results obtained from each concentration.

In experiment analysis I, acetone solution (10ml) is used for generating acetone odor and the gas sensor is made to detect the gas in open environment. The data was collected and it is observed that the response of the sensor towards acetone gas is very high. The results obtained from the sensor was also identified as very high in detecting the acetone gas in open environment.

In the experiment analysis II, the same concentration of acetone solution (10 ml) is used and the data was collected from the sensor in closed environment. It is also observed from the results that the sensor is very sensitive in detecting the acetone gas. The output obtained from the sensor proved its high sensitivity again showing in its crystal-clear data and the same is verified in plotting the data in graph. Hence from both the analysis I and II, it is found that the sensor has high sensitivity towards acetone gas and proved that the usage of Grove HCHO VOC gas sensor in this project is correct. In this experiment, PIC16F877A and NodeMCU is used. PIC is user friendly and cost efficient. So, PIC is used for diagnose and analyze of acetone and the output is displayed in LCD (16X2). Here NodeMCU is used for the same purpose of analysis and the output is displayed in mobile application (Blynk application).

Figure 7.1 LCD OUTPUT

All the necessary characteristics of sensor was studied verified by conducting different experimental analysis. Hence the selection of Grove HCHO VOC gas sensor for this project is proved as a rightful choice to detect the abnormal detection of acetone which will be used in detecting diabetes mellitus. The sensor has a range of 10PPM – 1000PPM in detecting acetone but the concentration of acetone in breath actually falls under 0.8 – 5.0 PPM. Hence it requires a low range of sensors for detecting acetone in exhaled breath for that level. The sensor has to be specifically designed using MOS technologies to apply this project in real time. So, I have done this project as a prototype model suggesting that this can be done in future appropriately.

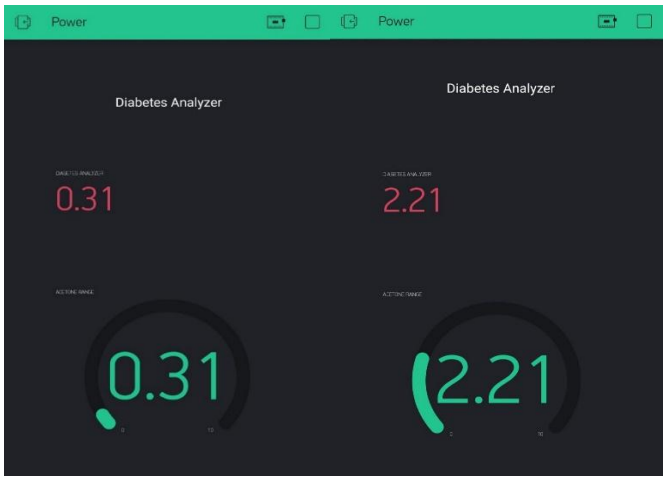

Figure 7.2 BLYNK APPLICATION OUTPUT.

6. CONCLUSION

Diagnosis of diabetes mellitus using human breath will play a major role in future. Research found that human breath analysis technique has a great potential to diagnose various other diseases like diabetes mellitus. The simple and cost-efficient means of diagnosing diabetes mellitus and is one of the future techniques. The time consumption of diagnosing the disease is also very less comparing to traditional laboratory diagnosing methods. An important highlight of this diagnosing technique is the non-invasive way such that it only uses the exhaled human breath for diagnosis. It does not involve any finger pricking method of diagnosis which leads to pain staking. It is very safe to undergo the diagnosis and it does not involve any hazardous procedures unlike in other X-rays or MRI scanning methods. This technique has many complexities like requirement of standard procedures, designing of appropriate gas sensors with low range and high accuracy but if it is are currently going for standards and procedures in incorporating this technique in today's world. Further enhancements can be done in future like

- Diagnosing through Image Processing Techniques
- Perform Machine Learning (ML) or AI algorithms
- Application of IoT techniques
- Data Collection using Cloud Technologies

It will be an additional advantage for this project if the above-mentioned technologies get added to this project. Then it will become as a very suitable method of diagnosing diseases in this modern world. It will also be very useful for the patients also for periodical analysis of their state of health.

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