

Research Article

The Influence of Blood Glucose Meter Resistance Variation on the Performance of a Biosensor with a Gold-Coated Circuit Board

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Received 22 August 2018; Accepted 13 December 2018; Published 11 February 2019

Academic Editor: Javier Reina-Tosina

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In this study, a novel gold-coated test strip for blood glucose measurement has been designed. Such gold-coated test strip is feasible for mass production to achieve economies of scale. Cyclic voltammetry was applied to test strips to undergo electrochemical reaction under a potential range of ± 0.4 V. Glucose oxidase (GOD) was added into $K_3[Fe(CN)_6]$. When glucose oxidase undergoes electrochemical reaction, the medium, $K_3[Fe(CN)_6]$, will act as an electron acceptor, causing the electrodes on the test strip to generate a pair of clear anodic and reductive peaks. The maximum of the anodic and reductive peaks can be used as reference to adjust the resistance of the blood glucose meter. The experimental results show that by adjusting the resistance of the blood glucose meter, the accuracy of blood glucose meter reading can be tuned and blood glucose reading can be stabilized. Therefore, when the resistance of the blood glucose meter is at $2.4\text{ K}\Omega$, the standard deviation (STD) and coefficient of variation (CV) of the test strip are lower than those of the test strips measured at resistances of $2.2\text{ K}\Omega$ and $2.6\text{ K}\Omega$. It has been proved in this study that adjusting the resistance of the blood glucose meter can optimize the chemical reaction on gold-coated test strips as well as its reading. This method can also be applied to tune the accuracy of readings for test strips coated with other materials.

1. Introduction

A blood glucose meter uses blood glucose test strips to measure the blood glucose level of a diabetic patient. The measurement is quick and only requires a small amount of blood. The measured value is recorded in a blood glucose meter which also contains blood glucose data from previous measurements [1–4]. The reaction zone on the electrode of the blood glucose test strip is covered with glucose oxidase, which allows electrons formed in-between the oxidase and electrode surfaces to be transported to the biochemical sensor [5, 6]. The electrode-sensing circuit of the biochemical sensor typically is made from screen-printed carbon paste which acts as the base material for the test strip. Such carbon paste-coated test strip has been widely used in clinical tests for measuring the blood glucose level of diabetic patients [7]. Besides carbon paste, the electrode of test strip can also be made from other base materials such as graphene and gold [8–13]. A gold-coated test strip has the merits of excellent conductivity and a reliable fabrication process. Through

electrochemical reaction of glucose oxidase (GOD), oxidase is catalyzed by electrodes to give the best performance [14]. The working potential of electrodes causes oxidase to undergo electrochemical reaction, creating a set of clear anodic and reductive peaks, which suggests that the reaction between electrodes and oxidase on the test strip is stable [15]. Other types of electrochemical biosensors for the determination of blood glucose levels based on gold structures and glucose oxidase have also been investigated [16]. Therefore, in this study, an effective method was proposed to create an excellent oxidase-based sensing test strip. In this test strip, gold-coated electrode was adopted as the base material since gold has good conductivity and is quite stable. The working principle of the blood glucose meter is based on the electrochemical reaction induced by cyclic voltammetry. By varying the resistance, different electrochemical reactions on the electrode of the test strip will occur. Due to different currents, the oxidase in the reaction zone containing $K_3[Fe(CN)_6]$ will undergo different electrochemical reactions. Such difference in electrochemical reaction will generate different readings

for the test strip. The readings for the test strip were collected, and the accuracy of the readings was determined according to the ISO 15197:2013 standard [17]. Therefore, the aim of this study is to demonstrate the reading accuracy of gold-coated test strips and to investigate the influence of electrochemical resistance on the stability and performance of gold-coated electrodes.

2. Experimental

2.1. GOD Reagent Preparation. 256 U/mg GOD was purchased from Amano Enzyme Inc. (Nagoya, Japan). $K_3[Fe(CN)_6]$ and GOD were well mixed to prepare different solutions. The deionized water used for preparing the solution was purified by various filters to remove impurities. The purpose of using deionized water (18 M Ω -cm resistivity) is to minimize the influence of impurity on the prepared solution.

2.2. Preparation of Test Strips. During the preparation of test strips, the negative film of the desired circuit was laminated on the dry photoresist film which was coated on the copper layer under appropriate temperature and pressure. The substrate with the negative film and dry photoresist was delivered into the UV (ultraviolet) exposure machine to undergo exposure process. After the photoresist under the transparent region of the negative film was exposed to UV light, it underwent polymerization (such region after the developing process will become the protecting material for the etching process) to transform the image of the desired circuit on the dry photoresist. After the etching process of the copper layer, the desired circuit for the working and the reference which was protected by the polymerized photoresist remained. The substrate of the test strip is made of FR4 FRP (glass fiber-reinforced plastic) printed circuit board. The circuit layout of the blood glucose test strip is shown in Figure 1, which clearly shows the copper wire on the test strip substrate. The circuit board containing copper wire was immersed into electroplating solution to coat a layer of nickel with thickness of 120~160 μ m, followed by the immersion plating of gold layer with thickness of 1~2 μ m. The reaction zone on the test strip contains working electrode and reference electrode. The overall area of the reaction zone is 2 \times 2 mm as shown in Figure 2. An ASYMTEK Nordson X-1020 Axiom Semiconductor Jetting Dispenser [18] with an ASYMTEK Nordson DJ-9000 jet dispensing valve [19] was used to carry out the dispensing operation of glucose oxidase (GOD). A droplet of glucose oxidase (GOD) with the volume of 0.45 mg was dispensed onto the reaction zone (2 mm \times 2 mm) of each test strip. When the GOD droplet on the reaction zone of the test strip was dried, a hydrophilic layer was added onto the test strip surface.

2.3. Analysis of Electrochemical Measurements. In this study, CHI1221 electrochemical analyzer was used to carry out the electrochemical cyclic voltammetry experiment. The analyzer was equipped with two electrodes: one acting as the working electrode and the other one as the reference electrode. During measurement, potential was applied in-between the working

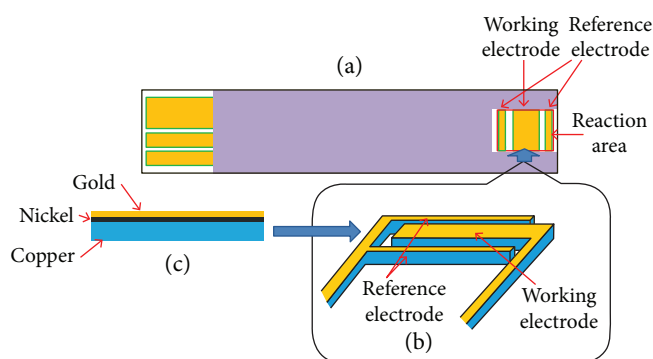


FIGURE 1: Schematic diagram of the gold-coated blood glucose test strip: (a) reaction zone electrode of the blood glucose test strip, (b) circuit layout of the reaction zone electrode, and (c) layer structure of the conducting material. The purpose of electroplating is to deposit a thin gold film on the copper layer. However, when gold contacts the copper layer directly, the physical phenomenon of electron diffusion will occur (due to difference in potential). Therefore, a layer of nickel must be coated in-between gold and copper, acting as the buffer layer. Such process is called the nickel-gold electroplating process.

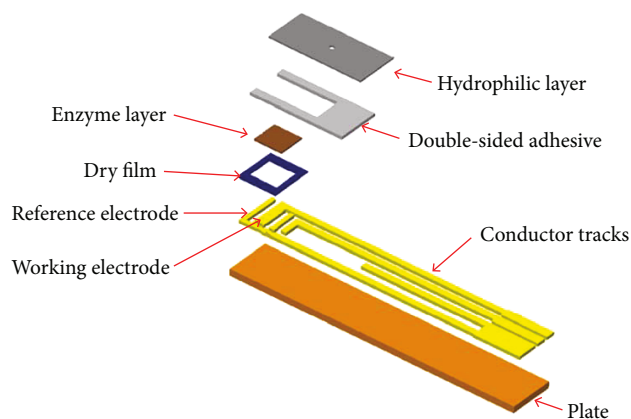


FIGURE 2: Schematic diagram showing the design of the gold-coated test strip.

electrode and the reference electrode. The experiment was carried out under the temperature of $25 \pm 2^\circ\text{C}$ in the laboratory. The test strip used in the experiment underwent cyclic voltammetry electrochemical reaction with potential fixed at ± 0.4 V. The electrochemical measurement system used different concentrations of standard solutions to measure the blood glucose test strip through the medium, $K_3[Fe(CN)_6]$, serving as the electron acceptor. The test strip utilized a PET hydrophilic layer on the surface to absorb standard solution. The cyclic voltammetry electrochemical reactions that occurred in the reaction zone of the gold-coated test strip were observed as shown in Figure 3. The glucose oxidase in the reaction zone of the test strip was combined with standard solutions of different concentrations. The medium, $K_3[Fe(CN)_6]$, acting as electron acceptor, in glucose oxidase then triggered the chemical reaction of glucose oxidase to occur in the reaction zone. After the occurrence of

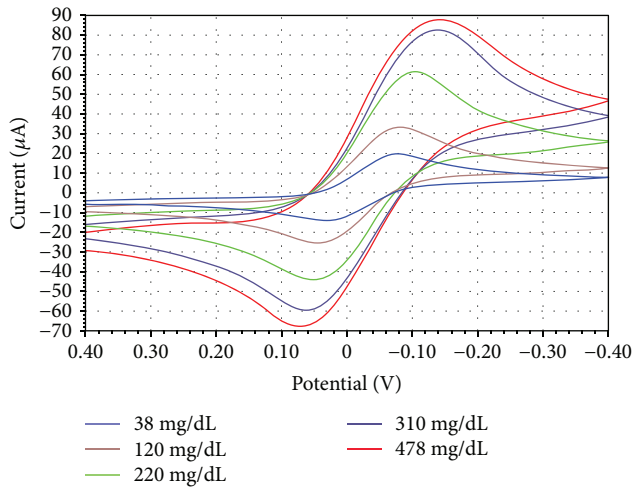


FIGURE 3: The potential for electrochemical reaction was set at the range of ± 0.4 V. The result of electrochemical reaction of the test strip containing standard solution of different concentrations was analyzed. The results show that the higher the concentration of standard solution, the greater the current as indicated by the anodic and reductive peaks.

electrochemical reaction in the reaction zone of the test strip, different currents were generated for standard solutions with different concentrations, namely, 38 mg/dL, 119 mg/dL, 220 mg/dL, 310 mg/dL, and 478 mg/dL.

2.4. Blood Glucose Meter Circuit and Measurement. In this study, the internal circuit of the blood glucose meter used for the experiment was adjusted. The blood glucose meter used is a Joinsoon EON L blood glucose meter which has been certified by FDA. The blood glucose meter offered a measurement voltage source, VDD. The voltage source VDD was split by resistors R_1 and R_2 to give V_{th} (equation 1). The V_{th} working voltage was then adjusted by resistor R_3 . The effect of R_3 on current change is depicted in Figure 4. Based on the current range of the anodic and reductive peaks from the electrochemical reaction, the output current of R_3 was adjusted (equation 2). Four standard solutions with different concentrations were used to carry out test strip measurement. In addition, benchmarking measurements were carried out by YSI-2300 instrument. The standard solution measured by YSI-2300 instrument had a concentration of 38 mg/dL, 120 mg/dL, 220 mg/dL, 310 mg/dL, and 478 mg/dL. The measurement results of the test strip were referred to the requirements of ISO 15197:2013 [16]; when the glucose concentration is lower than 100 mg/dL, STD should be within the range of ± 15 mg/dL; when the glucose concentration is higher than 100 mg/dL, CV should be in the range of $\pm 15\%$. In addition, the error of bias analysis should also be in the range of $\pm 15\%$. Moreover, linear regression analysis was conducted for data analysis; the closer the correlation coefficient (R^2) is to 1, the more accurate the test strip measurement is. Clarke Error Grid analysis was adopted to assess the significance of test strip measurement on clinical usage. A: clinical accuracy; B: clinically irrelevant deviation ($>15\%$); C: unnecessary

overcorrection possible; D: dangerous failure to detect and treat; E: erroneous treatment.

3. Results and Discussion

3.1. STD (Standard Deviation) and CV (Coefficient of Variation). Blood glucose meter adjusted the resistance of R_3 according to the current change from cyclic voltammetry electrochemical reaction. Blood glucose test strips containing standard solution with concentrations of 38 mg/dL, 120 mg/dL, 220 mg/dL, 310 mg/dL, and 478 mg/dL were measured, and the result was shown in Tables 1 and 2. Table 1 shows the measurement result under different resistance conditions. It is clear that when the resistance is at 2.2 K Ω , the average blood glucose reading is lower. However, when the resistance is at 2.4 K Ω , the average blood glucose reading is closest to that of standard solution. The average blood glucose reading at a resistance of 2.6 K Ω is higher than that of standard solution.

From the above results, it is known that the reading obtained by the blood glucose meter under a resistance of 2.4 K Ω is closer to the reading of standard solution as compared to the readings measured under resistances of 2.2 K Ω and 2.6 K Ω . According to the requirement of ISO 15197:2013 [16], when the glucose concentration is lower than 100 mg/dL, STD should be within the range of ± 15 mg/dL and when the glucose concentration is higher than 100 mg/dL, CV should be in the range of $\pm 15\%$. Therefore, when the glucose concentration of standard solution is lower than 100 mg/dL (i.e., 38 mg/dL), only the STD value is used for reference. On the other hand, when the glucose concentration of standard solution is higher than 100 mg/dL (i.e., 120 mg/dL, 220 mg/dL, 310 mg/dL, and 478 mg/dL), only the CV value is used for reference. This explains why in Table 2, some results only have STD values while others only have CV values.

As shown in Table 2, when the concentration of standard solution is 38 mg/dL, a resistance of 2.4 K Ω gives the lowest STD comparing with resistances of 2.2 K Ω and 2.6 K Ω . CV values are compared for standard solutions with concentrations of 120 mg/dL, 220 mg/dL, 310 mg/dL, and 478 mg/dL. Among them, a resistance of 2.4 K Ω gives the lowest CV values while resistances of 2.2 K Ω and 2.6 K Ω show relatively higher CV values. However, comparing the average reading in Table 2 with STD/CV values in Table 2, the average reading at a resistance of 2.4 K Ω is closest to the standard value of YSI. The STD/CV values at a resistance of 2.4 K Ω are within the scope of ISO 15197:2013.

3.2. Test for the Accuracy of the Control Solution. A total of 250 data were tested for the measurement of test strips under resistances of 2.2 K Ω , 2.4 K Ω , and 2.6 K Ω . The measurement results were summarized in Tables 3 and 4 for standard solutions with glucose concentrations of <100 mg/dL and ≥ 100 mg/dL, respectively.

For the measurement results with a glucose concentration of <100 mg/dL as shown in Table 3, the measurements under the resistance of 2.4 K Ω with a concentration of 5 mg/dL all (100%) fall within the scope. Comparing to the

$$V_{th} = \frac{R_2}{R_1 + R_2} V_{DD} \quad (1)$$

$$I_{R3} = \frac{V_{th}}{R_3} \quad (2)$$

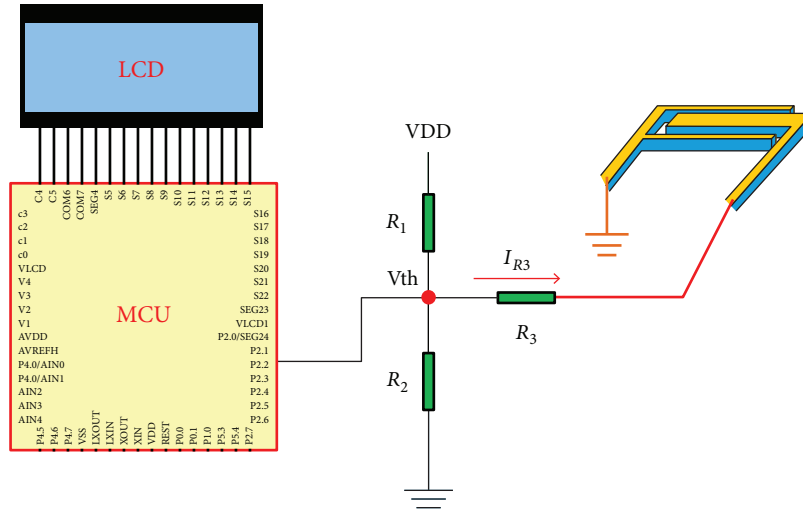


FIGURE 4: Circuit diagram of the blood glucose meter—working electrode is connected to R3 while reference electrode is connected to cathode (negative electrode). MCU P2.2 receives the data resulted from electrochemical reaction and the data is shown on LCD display.

TABLE 1: Average reading of test strips measured by a blood glucose meter under different resistance conditions.

YSI reading	R_3 2.2 K Ω (mg/dL)	R_3 2.4 K Ω (mg/dL)	R_3 2.6 K Ω (mg/dL)
38 mg/dL	28.1	38.6	57.8
120 mg/dL	91.9	119.7	155.9
220 mg/dL	187.6	220.0	258.5
310 mg/dL	281.5	315.1	338.5
478 mg/dL	442	472.8	526.8

TABLE 2: Reading of test strips with different concentrations of standard solution obtained by a blood glucose meter under different resistance conditions, showing the influence of resistance on STD and CV.

YSI reading	R_3 2.2 K Ω STD/CV	R_3 2.4 K Ω STD/CV	R_3 2.6 K Ω STD/CV
38 mg/dL	3.7/—	3.0/—	5.8/—
120 mg/dL	—/5.1	—/3.7	—/6.0
220 mg/dL	—/5.3	—/3.7	—/5.0
310 mg/dL	—/5.2	—/3.5	—/5.1
478 mg/dL	—/4.9	—/3.6	—/5.1

results for the resistances of 2.2 K Ω and 2.6 K Ω , 12% of the measurements under the resistance of 2.2 K Ω with a concentration of 5 mg/dL fall within the scope, 64% of the measurements under the resistance of 2.2 K Ω with a concentration of

TABLE 3: The range of test strip measurements under the resistances of 2.2 K Ω , 2.4 K Ω , and 2.6 K Ω for standard solutions with glucose concentrations of <100 mg/dL.

Resistance	Within 15 mg/dL	Within 10 mg/dL	Within 5 mg/dL
2.2 K Ω	46/50 (92%)	32/50 (64%)	6/50 (12%)
2.4 K Ω	50/50 (100%)	50/50 (100%)	50/50 (100%)
2.6 K Ω	19/50 (38%)	0/50 (0%)	0/50 (0%)

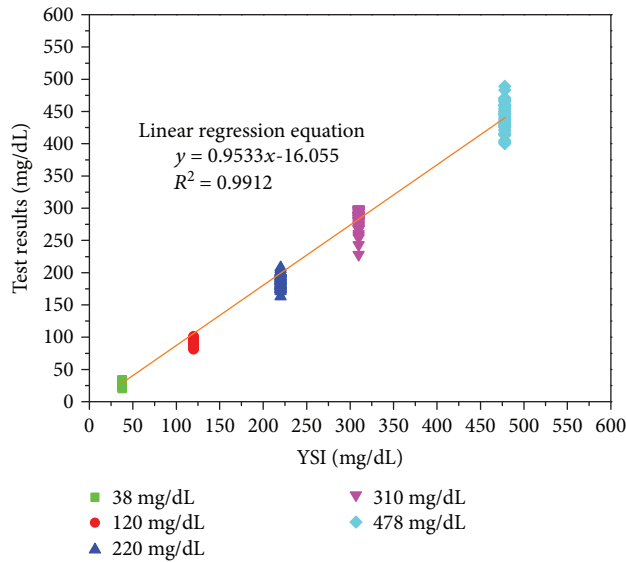
TABLE 4: The range of test strip measurements under the resistances of 2.2 K Ω , 2.4 K Ω , and 2.6 K Ω for standard solutions with glucose concentrations of ≥ 100 mg/dL.

Resistance	Within 15%	Within 10%	Within 5%
2.2 K Ω	84/200 (42%)	80/200 (40%)	24/200 (12%)
2.4 K Ω	200/200 (100%)	200/200 (100%)	169/200 (85%)
2.6 K Ω	102/200 (51%)	54/200 (27%)	24/200 (12%)

10 mg/dL fall within the scope, and 92% of the measurements under the resistance of 2.2 K Ω with a concentration of 5 mg/dL fall within the scope. On the other hand, the measurements under the resistance of 2.6 K Ω with concentrations of 5 mg/dL and 10 mg/dL all fall out of the scope, while 38% of the measurements under the resistance of 2.6 K Ω with a concentration of 15 mg/dL all fall within the scope. The above results suggest that the measurement of the test strip under the resistance of 2.4 K Ω with concentrations < 100 mg/dL will give more accurate reading.

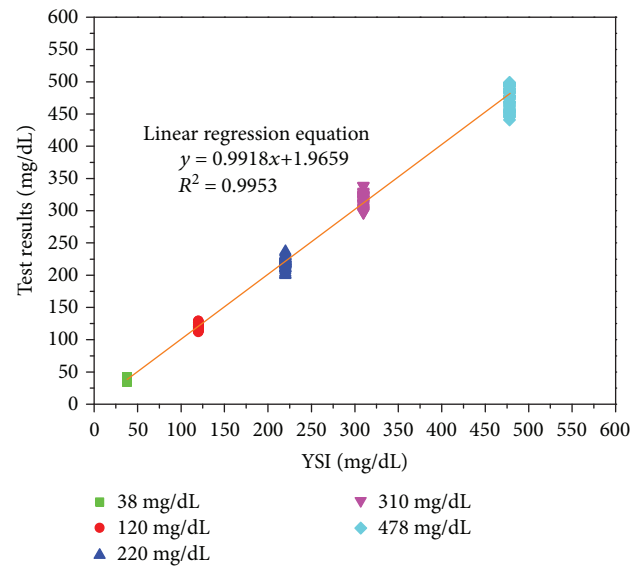
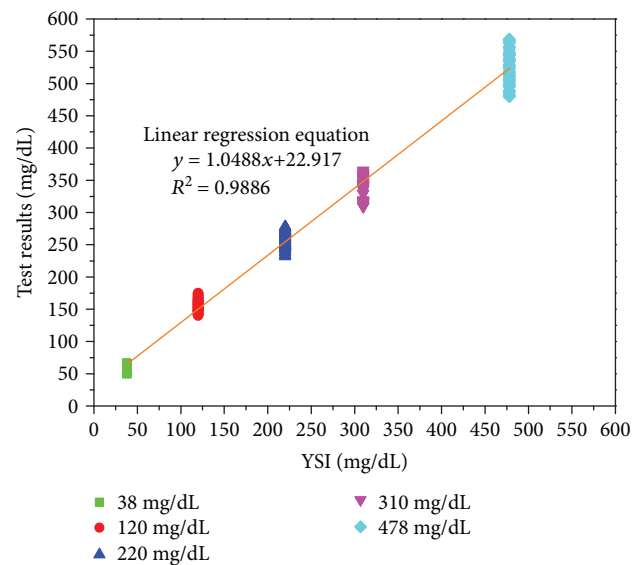
TABLE 5: Linear regression.

Resistance	N	Slope	Y intercept	Correlation coefficient (R^2)
2.2 K Ω	250	0.9533	-16.055	0.9912
2.4 K Ω	250	0.9918	1.9659	0.9953
2.6 K Ω	250	1.0488	22.917	0.9886

FIGURE 5: Correlation graph between test strip readings measured by the blood glucose meter at a resistance of 2.2 K Ω and measurements of standard solution from YSI.

When the test strip measurements were carried out with concentrations ≥ 100 mg/dL, 200 data were analyzed for each resistance condition, namely, 2.2 K Ω , 2.4 K Ω , and 2.6 K Ω , as shown in Table 4. For the resistance of 2.2 K Ω , 12% of the test strip measurements fall within the 5% range, 40% of the test strip measurements fall within the 10% range, and 42% of the test strip measurements fall within the 15% range. On the other hand, for the resistance of 2.4 K Ω , 85% of the test strip measurements fall within the 5% range and 100% of the test strip measurements fall within the 10% and 15% range. For the resistance of 2.6 K Ω , 12% of the test strip measurements fall within the 5% range, 27% of the test strip measurements fall within the 10% range, and 51% of the test strip measurements fall within the 15% range. From the above results, it is noted that the measurement of the test strip under the resistance of 2.4 K Ω with concentrations ≥ 100 mg/dL will give more stable reading.

3.3. Test Strip Measurement Results Analyzed by Linear Regression. Table 5 shows the linear regression analysis of experimental results for resistances of 2.2 K Ω , 2.4 K Ω , and 2.6 K Ω . A total of 250 reading data were used to perform the analysis for each resistance condition and compared with the results of standard solution from YSI. The correlation graph obtained for resistances of 2.2 K Ω , 2.4 K Ω , and 2.6 K Ω is shown in Figures 5, 6, and 7, respectively. As shown

FIGURE 6: Correlation graph between test strip readings measured by the blood glucose meter at a resistance of 2.4 K Ω and measurements of standard solution from YSI.FIGURE 7: Correlation graph between test strip readings measured by the blood glucose meter at a resistance of 2.6 K Ω and measurements of standard solution from YSI.

in Figure 5, when the resistance is at 2.2 K Ω , the distribution of measured readings for standard solution with concentrations of 220 mg/dL and 310 mg/dL is more scattered. The resulting correlation graph has a slope of 0.9533, an Y intercept of -16.055, and a correlation coefficient (R^2) of 0.9912. As shown in Figure 6, when the resistance is at 2.4 K Ω , the distribution of measured readings for glucose standard solution with concentration ranging from low to high is more focused. The resulting correlation graph has a slope of 0.9918, a Y intercept of 1.9659, and a correlation coefficient

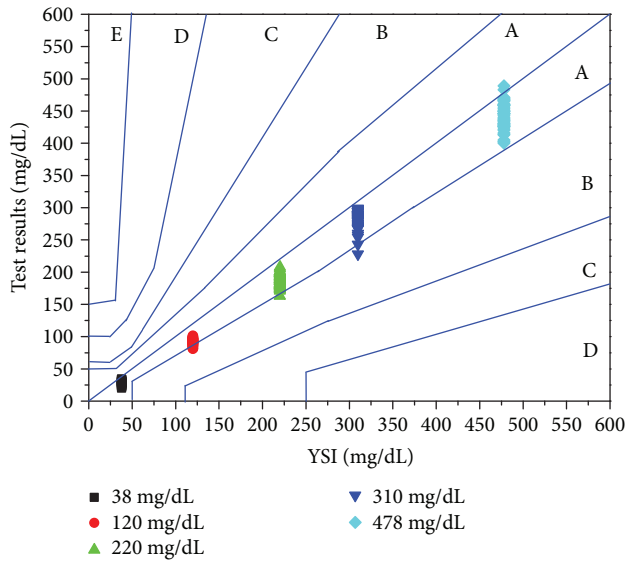


FIGURE 8: Clarke Error Grid analysis for the distribution of test strip readings measured by the blood glucose meter at a resistance of 2.2 K Ω as compared with the measurements of standard solution from YSI; some readings fall in zone B.

(R^2) of 0.9953. As shown in Figure 7, when the resistance is at 2.6 K Ω , the distribution of measured readings for glucose standard solution with concentration ranging from low to high is more scattered. The resulting correlation graph has a slope of 1.0488, a Y intercept of 22.917, and a correlation coefficient (R^2) of 0.9886. The correlation graph for a resistance of 2.4 K Ω has the smallest Y intercept comparing with that for resistances of 2.2 K Ω and 2.6 K Ω . This suggests that the actual readings for test strips at resistances of 2.2 K Ω and 2.6 K Ω show larger deviation comparing with the standard values of YSI. Therefore, the actual readings for test strips at a resistance of 2.4 K Ω are closer to the standard values of YSI.

3.4. Test Strip Measurement Results Illustrated by the Clarke Error Grid. Figures 8, 9, and 10 show the Clarke Error Grid analysis result for test strip readings as compared with the measurements of standard solution from YSI for resistances of 2.2 K Ω , 2.4 K Ω , and 2.6 K Ω , respectively. As shown in Figure 8, comparing with YSI measurement results, the distribution of readings from 250 measurements at a resistance of 2.2 K Ω is deviated from zone A and moving towards lower zone B. As shown in Figure 9, comparing with YSI measurement results, the distribution of readings from 250 measurements at a resistance of 2.4 K Ω is located in zone A. As shown in Figure 10, comparing with YSI measurement results, the distribution of readings from 250 measurements at a resistance of 2.6 K Ω is deviated from zone A and moving towards upper zone B. The distribution of readings measured for test strips at a resistance of 2.4 K Ω is more crowded together, especially for the readings of standard solution with a concentration of 38 mg/dL. This suggests that the readings for low-concentration standard solution are closer to the readings of YSI, meaning more accurate test strip reading. On the other hand, the distribution of readings measured at a

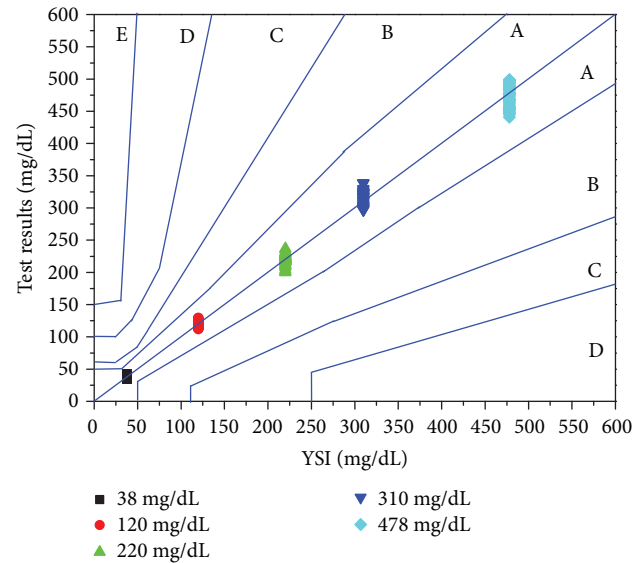


FIGURE 9: Clarke Error Grid analysis for the distribution of test strip readings measured by the blood glucose meter at a resistance of 2.4 K Ω as compared with the measurements of standard solution from YSI; readings are concentrated in zone A; therefore, measurements at resistance of 2.4 K Ω have clinical value.

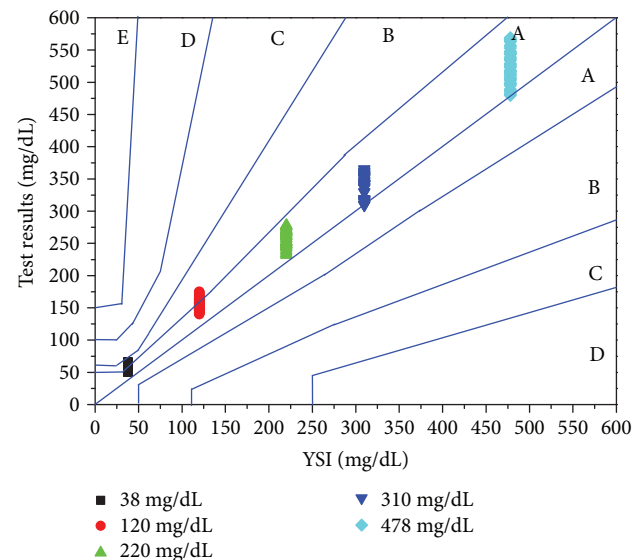


FIGURE 10: Clarke Error Grid analysis for the distribution of test strip readings measured by the blood glucose meter at a resistance of 2.6 K Ω as compared with the measurements of standard solution from YSI; some readings fall in zone B.

resistance of 2.2 K Ω is located towards lower zone B while the distribution of readings measured at a resistance of 2.6 K Ω is located towards upper zone B, implying that readings of the test strip are deviated from YSI readings.

3.5. Bias Analysis of Test Strip Measurement Results. Figures 11, 12, and 13 show the bias analysis result for test strip readings as compared with the measurements of

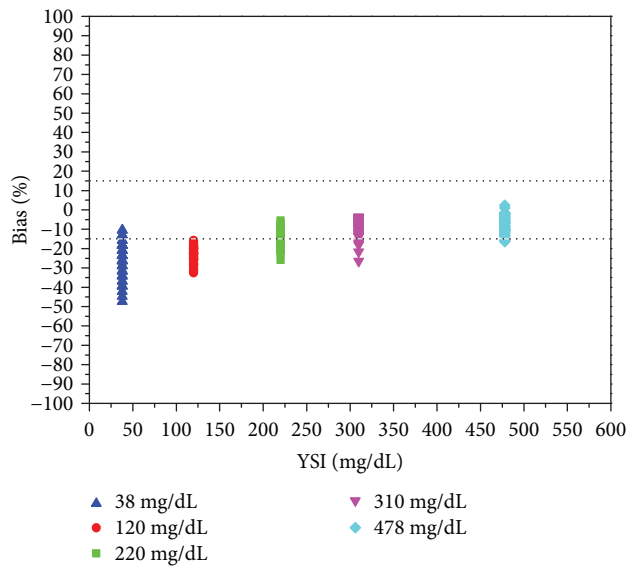


FIGURE 11: Bias analysis result for the distribution of test strip readings measured at a resistance of 2.2 KΩ; the distribution of readings exceeds the $\pm 15\%$ range.

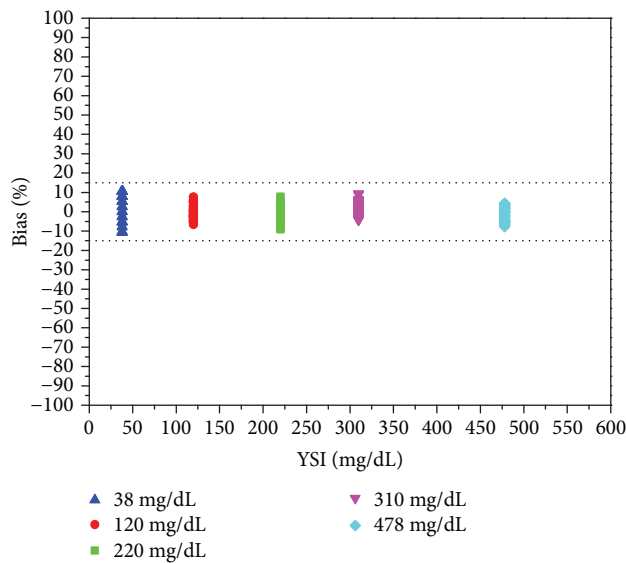


FIGURE 12: Bias analysis result for the distribution of test strip readings measured at a resistance of 2.4 KΩ; the distribution of readings is within the $\pm 15\%$ range, complying with the ISO 15197:2013 standard.

standard solution from YSI for resistances of 2.2 KΩ, 2.4 KΩ and 2.6 KΩ, respectively. As shown in Figure 11, when the resistance is at 2.2 KΩ, the distribution of readings from 250 measurements of the test strip in a bias analysis diagram clearly exceeds the $\pm 15\%$ range, especially for standard solution with a concentration of 38 mg/dL, which shows a bias range of -47.37%. As shown in Figure 12, when the resistance is at 2.4 KΩ, the distribution of readings from 250 measurements of the test strip in a bias analysis diagram is within the $\pm 15\%$ range, suggesting that the readings for all

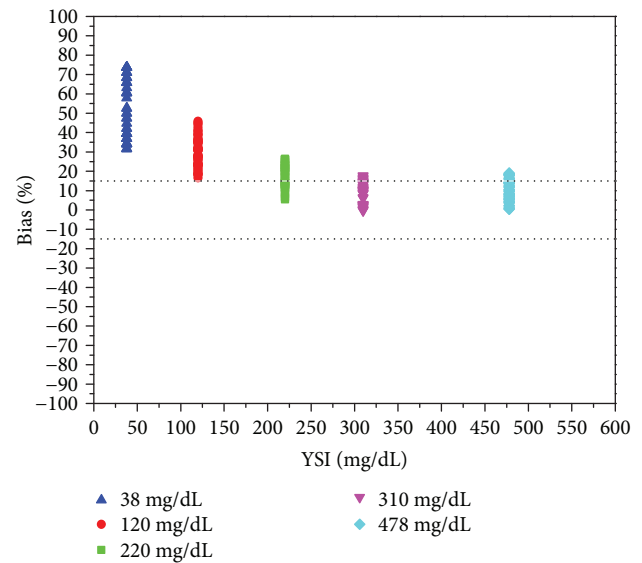


FIGURE 13: Bias analysis result for the distribution of test strip readings measured at a resistance of 2.6 KΩ; the distribution of readings exceeds the $\pm 15\%$ range.

concentrations of standard solutions are closer to the readings of from YSI, meaning more accurate test strip reading. As shown in Figure 13, when the resistance is at 2.6 KΩ, the distribution of readings from 250 measurements of the test strip in a bias analysis diagram clearly exceeds the $\pm 15\%$ range, especially for standard solutions with a concentration of 38 mg/dL, both of which have bias reaching as high as 73.68%.

3.6. Deviation Analysis of Test Strip Readings. For STD and CV analysis, the results of test strip measurement carried out under resistances of 2.2 KΩ, 2.4 KΩ, and 2.6 KΩ comply with the ISO 15197:2013 standard. However, this outcome does not apply for linear regression analysis, Clarke Error Grid, and bias analysis. Comparing test strip readings with the measurements of standard solutions from YSI, the readings of the test strip for a resistance of 2.2 KΩ mostly are low, while the readings of the test strip for a resistance of 2.6 KΩ are high. When the resistance of R_3 in the blood glucose meter increases, the current of I_{R3} will gradually decrease, making the reading of the test strip measured by the blood glucose meter to be deviated from the standard value. There are ways to compensate for the shifted blood glucose reading (higher or lower). However, these compensating methods cannot change STD and CV, since different resistances will change blood glucose meter's current supply, creating different electrochemical reactions. The resistance condition of 2.4 KΩ will optimize the electrochemical reaction of the gold-coated electrode test strip, giving lower test strip STD as well as CV and leading to higher accuracy for the gold-coated electrode test strip.

4. Conclusion

In this study, the characteristics of the gold-coated test strip for blood glucose measurement were investigated. The

glucose oxidase (GOD) in the reaction zone of the test strip covering the surface of the gold-coated electrode demonstrated the influence of the resistance of the blood glucose meter on the electrochemical reaction of the blood glucose test strip, which can be utilized to adjust test strip reading and accuracy. It has been proved in this study that by tuning the resistance of the blood glucose meter, the electrochemical reaction of the blood glucose test strip can be varied to improve the accuracy of reading. In this study, the resistance of electrochemical reaction was adjusted. It was found that by adjusting the resistance, the accuracy of test strip reading for blood glucose measurement can be improved. We hope that this finding can also be applied to other blood glucose test strips made from different materials, helping to improve the reading accuracy of these test strips.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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