1.Mohd Hafiz Jali[1*], 2.Ahmad Nur Azeim Ahmad Zamzuri[1], 3.Hazli Rafis Abdul Rahim[2], 4.Md. Ashadi Md Johari[3], 5.Aminah Ahmad[3], 6.Mohamad Faizal Baharom[1], 7.Huda Adnan Zain[4], 8.Sulaiman Wadi Harun[4]

[1*]Faculty of Electrical Engineering, Universiti Teknikal Malaysia Melaka, 76100 Durian Tunggal, Melaka, Malaysia
[2]Faculty of Electronics and Computer Engineering, Universiti Teknikal Malaysia Melaka, 76100 Durian Tunggal, Melaka, Malaysia
[3]Faculty of Electrical and Electronic Engineering Technology, Universiti Teknikal Malaysia Melaka, 76100 Durian Tunggal, Melaka, Malaysia
[4]Department of Electrical Engineering, University of Malaya, 50603 Kuala Lumpur, Malaysia
ORCID: 1. 0000-0002-2894-7285; 3. 0000-0002-6001-0230; 5. 0000-0002-1393-6663; 6. 0000-0003-2887-3922

Detection of acetone as a potential non-invasive diagnosis tool for diabetes patients

Abstract. This work investigated the demonstration of acetone detection device as a potential tool to diagnose diabetes patients. It offers simple and low cost approach based on glass substrate platform. The glass substrate was coated with agarose gel as a sensitive material to increase the sensing response. It has superiority in term of high porosity and capable to absorb molecule around it. The sensing mechanism is based on the change in refractive index (RI) of the agarose gel coating layer when exposed to variation acetone concentration level. This is due to the intensity of the light weakening by absorption and scattering when light propagated through the sensing material. The proposed sensor produces a significant response towards acetone concentrations with the output voltage reduced linearly from 1.6V to 1.2V. The sensitivity and resolution of the agarose coated glass substrate improves by a factor of 1.08 and 1.14 respectively as compared to uncoated glass substrate. It also performed better in term of linearity, stability, response time and hysteresis. The non-involvement of costly laser source based instruments make the proposed sensor become more practical for large production while maintaining a good sensing performances. Based on the experiment results, the proposed acetone sensor has a persuasive potential as an early biomarker for diabetes diagnosis tool.

*Streszczenie. W ramach tej pracy zbadano demonstrację urządzenia do wykrywania acetonu jako potencjalnego narzędzia do diagnozowania pacjentów z cukrzycą. Oferuje proste i tanie podejście oparte na platformie z podłożem szklanym. Szklane podłoże pokryto żelem agarozowym jako wrażliwym materiałem w celu zwiększenia odpowiedzi wykrywania. Ma przewagę pod względem wysokiej porowatości i zdolności do wchłaniania otaczających ją cząsteczek. Mechanizm wykrywania opiera się na zmianie współczynnika załamania światła (RI) warstwy powłoki żelu agarozowego pod wpływem zmian poziomu stężenia acetonu. Wynika to z intensywności osłabienia światła przez absorpcję i rozpraszanie podczas propagacji światła przez materiał czujnika. Proponowany czujnik daje znaczną odpowiedź na stężenia acetonu przy napięciu wyjściowym obniżonym liniowo z 1,6V do 1,2V. Czułość i rozdzielczość podłoża szklanego pokrytego agarozą poprawia się odpowiednio o współczynnik 1,08 i 1,14 w porównaniu z podłożem szklanym niepowlekanym. Działał również lepiej pod względem liniowości, stabilności, czasu odpowiedzi i histerezy. Rezygnacja z kosztownych instrumentów opartych na źródle laserowym sprawia, że proponowany czujnik staje się bardziej praktyczny w przypadku dużych produkcji, przy jednoczesnym zachowaniu dobrych parametrów wykrywania. W oparciu o wyniki eksperymentu, proponowany czujnik acetonu ma potencjał przekonujący jako wczesny biomarker narzędzia diagnostycznego cukrzycy. (**Wykrywanie acetonu jako potencjalnego nieinwazyjnego narzędzia diagnostycznego dla pacjentów z cukrzycą**)*

Keywords: acetone, agarose gel, glass substrate, diabetes
Słowa kluczowe: aceton, żel agarozowy, podłoże szklane, cukrzyca

Introduction

Diabetes melitus is a manageable disorder due to insufficient insulin action in blood [1]. The lack of insulin hormone would cause the conversion of starches, sugar and other nutrient into energy stunted [2]. Currently, diabetes is basically monitored by the blood glucose detector and are not particularly adequate in their exactness and sensitivity. The existing technology for the detection of blood glucose in the market comprises of professional blood test equipment and the handheld domestic blood glucose detector. Both are invasive testing devices, which require constant needle detection, expensive, painful, less comfortable and can be unsafe if it is not handling properly [3].

Marco Righettoni et al. was among the first researchers that developed a non-invasive breathing control detector that is capable to quickly measure extremely low acetone concentrations under ideal settings in real time conditions. The signal-to-noise ratio is likewise high [4]. It indicates that a portable, cost-effective device for the substitution of the burdensome invasive diabetes sensors that can detect diabetes through breath analysis can be provided rather than detection based on blood glucose. Recent trend in accessing the traces of glucose using human serums such as sweat, saliva, urine and breath offer persuasive alternatives for blood measurements. These non-invasive glucose detection rapidly emerge with the advent of nanotechnology-based sensors which enhanced the sensitivity, selectivity and compatibility with electronic circuit [5]. The portable and convenient feature of the acetone

recognition detector is more useful to assist the diagnosis, monitoring and evaluation of diabetes, compared with the traditional intrusive and standardised approach for blood sugar detection using expensive and large devices.

Various platforms such as plastic optic fiber [6], silica microfiber [7], PEN substrates [8], paper substrates [9], ITO/PET substrates [10], liquid crystal cell [11] and polyimide substrates [12] has been utilized to develop optical sensing device . However, these platforms required complex fabrication and manufacturing process as well as costly design. In order to develop a cost effective sensing device, a glass substrate could be used as a platform. It is widely available in market and easy to handle. Nevertheless, the uncoated glass substrate without any sensitive material coated on it is less sensitive. It exhibits a low sensing performance because it has small refractive index contrast between the surround analyte. Thus, a higher refractive index coating material is essential to increase the sensing response. One of the sensitive material is agarose gel. It is a hydrophilic material that exhibit high porosity which absorb molecule around it. The porosity decreases as the concentrations increase [13]. It is cause by the swelling phenomenon which cause the refractive index of the gel change as the concentrations of the surrounding molecules change [14]. Besides that, it has advantages of being a stable, low-cost, and widely used material due to its porous character and strong water absorption capabilities. The optical characteristics of the composite coating alter in response to variations of its surroundings analyte. [15]. The detection towards the

surround medium is based on the intensity modulation that influence the output intensity or voltage of transmitted light based on variations in acetone concentrations level.

At present, existing optical sensor mostly working with expensive laser source, optical spectrum analyser and photodetector which are less feasible for mass production. Therefore, a more practical approach that has low manufacturing cost is crucially important for large scale production [16]. This paper reported the development of acetone sensing device based on agarose gel coated glass substrate which has been demonstrated for the first time to our knowledge. It has been demonstrated as a sensing tool by combining the glass substrate with sensing circuit contains of simple light source, photodetector, conditioning amplifier and data acquisition (DAQ) unit. The light source using LED is transmitted through the glass substrate and receive by photodetector to convert to voltage signal. Green LED was chosen for the light source based on previous study conducted by [6]. It is then connected to conditioning amplifier circuit to appropriate signal to the DAQ unit for signal processing of the transmitted light to compute data for output voltage analysis. The proposed sensor fully utilizes the unique characteristic of changeable refractive index agarose gel coating material which react well with the acetone concentrations level applied.

Sensing mechanism

According to the Lambert-Beer law, scattering coefficient of the coating material and the total fraction power carried in the sensing region have a significant impact on light travel through the glass substrate. The light attenuation via the sensing medium is describes in equation (1) [17]:

$$(1) \qquad I = I_o e^{-\alpha L}$$

where I is the intensity of light leaving the sensing region, I_o is the intensity of the light entering the sensing region, α is the scattering coefficient and L is the length of the sensing region. It also influenced by the absorbing material's bulk absorption coefficient, concentration, and effective fraction of total directed power [18]. When light propagates through the sensing material, as shown in Figure 1, the intensity of the light may be weakened by absorption and scattering. When light collides with an atom, scattering occurs. The atom is stimulated to a higher energy level, then returns to its previous level, emitting a photon with the same frequency as the one it received. When there are refractive index mismatches at borders, this happens.

As the refractive index of the surround analyte increases, optical transmittance (T) reduces. This lead to more light leakage, which enhances the sensitivity towards acetone levels [19]. During exposure to varying concentrations of acetone, the output intensity surrounding the sensing region varies [20]. Under varying concentration levels, the intensity of light throughout the absorbing medium changes. It corresponded to analyte concentration variations in the detecting area [17]. Equation (2) is used to calculate optical transmittance (T) at the sensor's output [19]:

$$(2) \qquad T = \frac{I}{I_o} = e^{-\alpha L}$$

Moreover, the proposed sensor work by supplying a light source at one edge of the glass substrate. During the light transmission through the glass substrate, the scattering effect from the coated materials upon exposure to varying amounts of acetone occurred. This lead to the decrement of light intensity with respect to the concentrations level of the analyte. By referring to Figure 1,

the output light intensity of the proposed sensor reduced when expose to the increasing concentrations level of the acetone. Due to the increase refractive index contrast between the coating layer and the surrounding medium, lossy waveguide scenario occurred which lead to greater light leakage when concentrations increase. Hence, less light reach to photodetector as the concentrations level increase. In addition, more light scattering occur which lead to higher leakage and lower output voltage value [21]. Other factors contributed to this phenomenon is the variation of electrical conductivity due to adsorption process when analyte applied to the coating layer. The voltage reduction pattern would eventually contribute to improve the sensing performance of the proposed sensor.
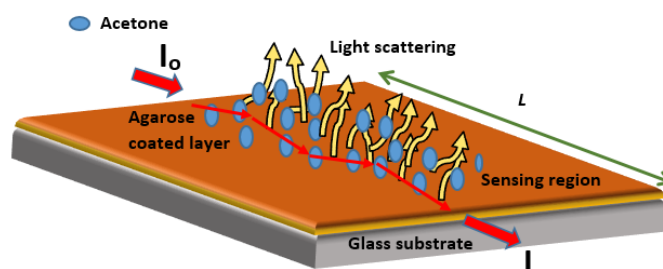

Fig.1. Sensing mechanism of the proposed sensor

Experiment details

Before the coating procedure, the glass substrates need to be prepared according to the following procedure. Microscope glass substrates (Heathrow Scientific LLC, USA) were first immersed in a container of soapy water, clear water and acetone [CH_3COCH_3] (Bendosen Laboratory Chemical, Germany) for 15 minutes in a sequence for the ultrasonic cleaning process. It was then located in an oven at $90^\circ C$ for 1 hour to remove organic material [22]. Subsequently, the agarose gel was prepared by dissolving the agarose gel (Sigma Aldrich) into water. Then the mixture was heated to $50^\circ C$. Then, small aliquot of the mixture was deposited on the glass substrate and was left in normal room temperature for 24 hours. The agarose gel coated glass substrate is shown in Figure 2.

The configuration of the proposed sensor is depicted in Figure 3. It comprise of light source which utilize green LED with wavelength between 495 nm to 570 nm based on report in [23]. The glass substrate was placed between the light source and photodetector. Photodetector was used to convert the light intensity into voltage signal. They were positioned as closed as possible at both edges of the glass substrates. The angle of the LED was set at 50° at the edge of the glass substrate to ensure 60° of incident angle in order to ensure total internal reflection. The photodetector is then connected to the conditioning amplifier to amplify the voltage signal for signal processing in Data Acquisition (DAQ) unit [21]. The simple and low cost Arduino microcontroller was employed as the DAQ unit. It is then connected to the personal computer (PC) to analyse the output signal and investigate the sensing performance. The sensing experiment was conducted in room temperature to emulate the real environment situation. It was conducted for acetone concentration level from 0% to 15% in which the results were investigated with refer to 0% as a reference value (pure water). The experiment was conducted in room temperature to emulate the real environment scenario [24]. The behaviour of the output voltage was then analysed according to the performance sensing parameters such as sensitivity, linearity, repeatability, hysteresis, stability and response time.
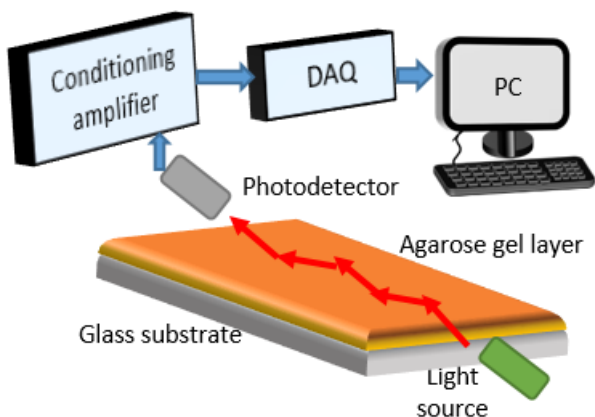
Fig.2. Agarose gel coated glass substrate

Fig. 3 Experimental setup of the proposed sensor

Result and discussion

Repeatability test was conducted for at least three times to determine the standard deviation of the output voltage. Based on Figure 4(a), the repeatability readings for uncoated glass is not distributed precisely. The differences between the readings ranging around 0.4V. Whereas for agarose coated glass in Figure 4(b), the precision of the readings for each concentration is better compared to uncoated glass. The different between one reading to another is less than 0.2V which is adequate for sensing device. Hysteresis analysis was conducted by recording the output voltage during forward and reverse measurement. Based on Figure 5(a), the differences between forward and reverse values are quite obvious especially on 9% and 12% concentration level for uncoated glass. The differences between forward and reverse measurement for uncoated glass approximately around 0.5V. While for agarose coated glass in Figure 5(b), most of the experimental values between forward and reverse has only slight deviation for all the readings.
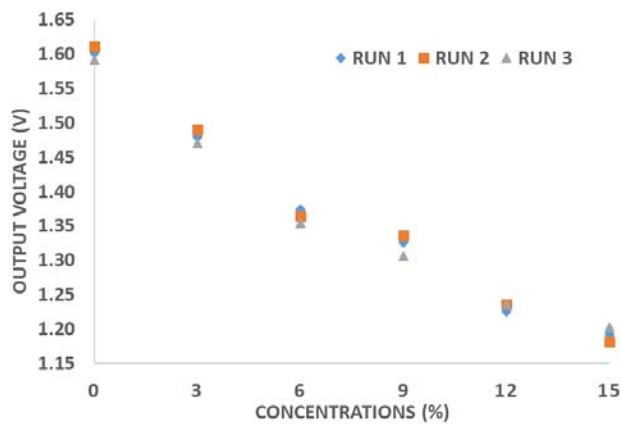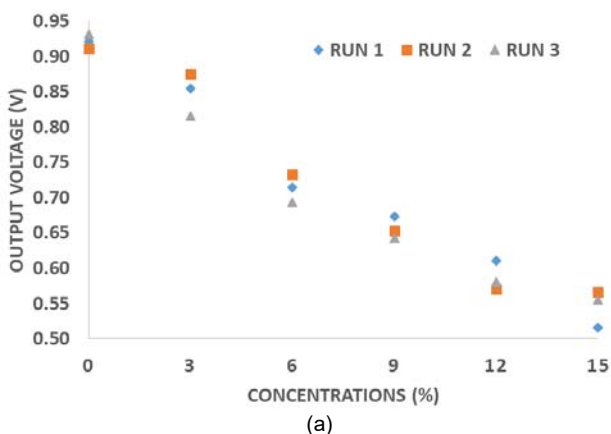

(b)

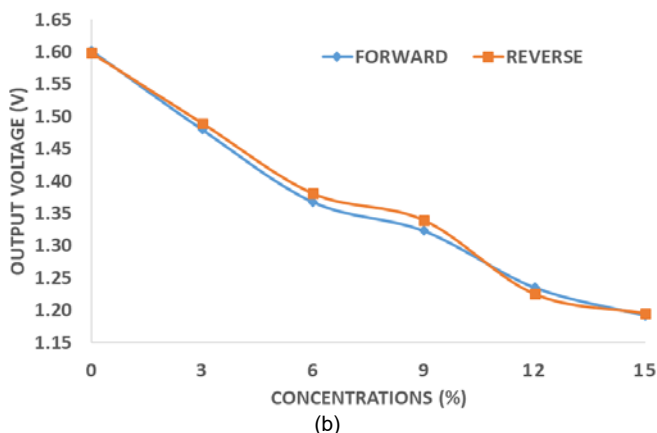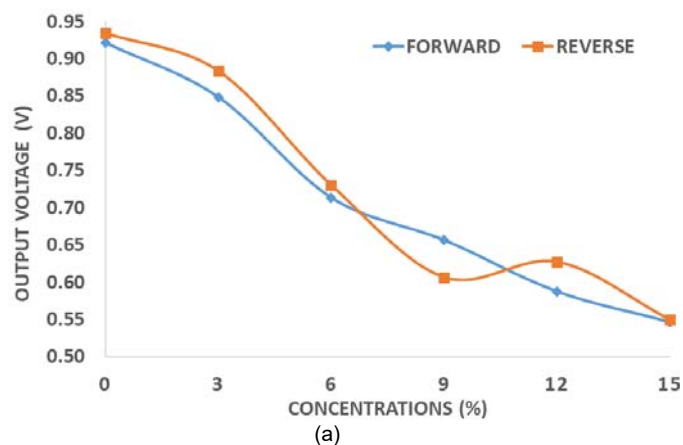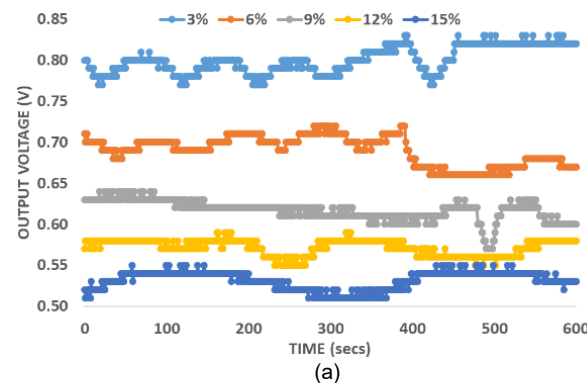Fig.4. The repeatability of; a) Uncoated glass and b) Agarose coated glass

(a)

(b)

Fig. 5. The hysteresis graph of; a) Uncoated glass and b) Agarose coated glass
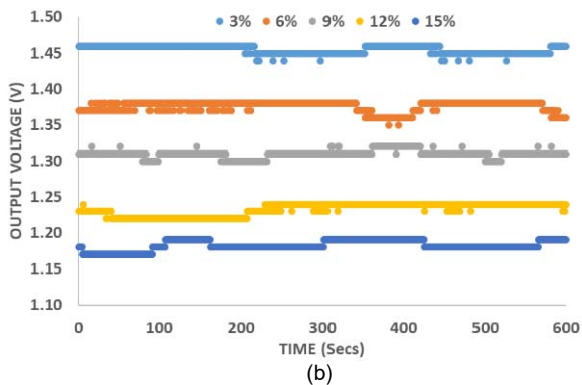

(a)

(a)

(b)

Fig. 6. The stability of; a) Uncoated glass and b) Agarose coated glass

The stability of the sensors is depicted in Figure 6. It was conducted by acquiring the output voltages continually for 10 minutes (600 seconds) in every second. Based in Figure 6(a), it is obvious that the readings for the uncoated glass produce a less stable output voltage throughout the test duration. This is due to the uncoated glass has the low refractive index contrast between the surrounding medium. This cause greater resistance on the fabricated sensor and thus making it less stable. As compared to agarose coated glass in Figure 6(b), the output readings on each concentration has less attenuation and better stability due to higher refractive index contrast between the surrounding environment.

Subsequently, time response analysis was performed to both sensors. Response time was conducted by applying acetone from minimum concentration value directly to maximum concentration value while recovery time was performed by applying acetone from maximum concentration value directly to minimum concentration [24]. The time taken for the test is 480 seconds or 8 minutes in total. For every 120 seconds or 2 minutes, the concentration of Acetone need to be change from lowest concentration to highest concentration and vice versa until it accomplished for 2 cycles. Response time for the uncoated glass to react from lowest concentration highest concentration is 1.0 second while for agarose coated glass is 0.7 second as shown in Figure 7(a). While Figure 7(b) shows the recovery time required for both samples. The recovery time to react from highest concentration to lowest concentration is 1.0 second for uncoated glass while for agarose coated glass is 0.7 second. This show the proposed sensor response faster as compared to uncoated glass.

The sensing response for both sensors towards the concentrations level from 0% to 15% is illustrated in Figure 8. The agarose gel coated glass has better sensitivity with 0.0269 V/% as compared to uncoated glass with 0.025 V/%. The linearity of the proposed sensor also improved with 96.91% which is better than uncoated glass with 95.41%. This is due to detection of the acetone is based on the change in refractive index of the coating material. The RI change of the coating materials will modulate the output light intensity [14]. Thus the coating layer produce higher RI value as compare to the glass substrate that cause a lossy waveguide which lead to the decrement of the output voltage.

Table 1 summarize all the sensing performances of the both sensors. In short, the agarose coated glass produced better results in all criterion as compared to the uncoated glass. The standard deviation of the proposed sensor is smaller as compared to the uncoated glass which resulting in better resolution with 0.5353.
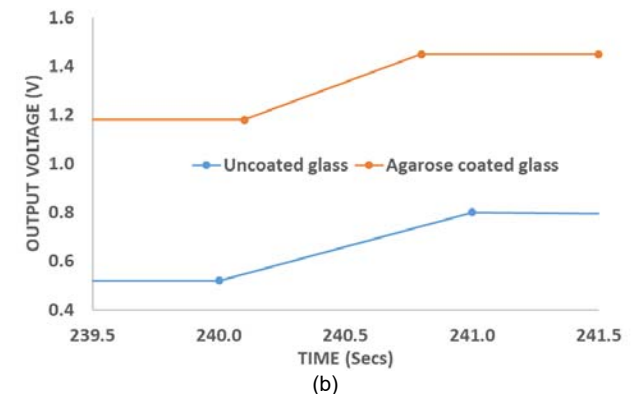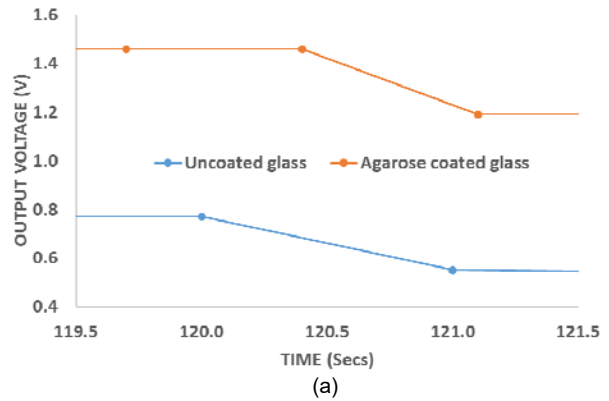

(a)

(b)

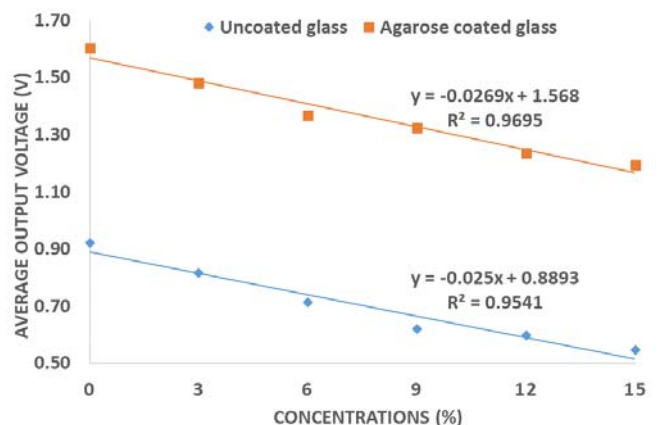Fig. 7. Time response; a) Response time and b) Recovery time

Fig. 8. Trendline of both sensors

Table 1. Summary of the sensing performances

Parameters	Uncoated glass	Agarose coated glass
Sensitivity (V/%)	0.025	0.0269
Linearity (%)	95.41	96.91
Std. deviation (V)	0.0153	0.0144
Resolution (%)	0.612	0.5353
Time response (Secs)	1.0	0.7

Conclusion

This work has successfully demonstrated an acetone sensor for diagnosis tool of diabetes patients. The detection is based on agarose coated glass substrates which has superiority in term of evading the used of expensive laser source based equipment which is less viable for large scale production. By employing components that are widely available in the market, the proposed sensor become more practical sensing devices for mass usage. Overall the proposed sensor has shown better sensing performances results in term of sensitivity, linearity, response time, repeatability, stability and

hysteresis as compared to its counterpart. This is based on the fact that the agarose coating material act as changeable RI layer when different concentrations level of acetone was applied. It improved the light interaction towards the surround analyte as well as the sensing response. Hence, this low cost and simple acetone detection device has a bright potential to become a viable early biomarker for diabetes diagnosis tool.

Authors: Dr. Mohd Hafiz Jali is a senior lecturer at Faculty of Electrical Engineering. Universiti Teknikal Malaysia Melaka, Hang Tuah Jaya, 76100 Durian Tunggal, Melaka, Malaysia. E-mail: mohd.hafiz@utem.edu.my. Ahmad Nur Azeim Ahmad Zamzuri Is a undergraduate student at Faculty of Electrical Engineering, Universiti Teknikal Malaysia Melaka, Hang Tuah Jaya, 76100 Durian Tunggal, Melaka, Malaysia. E-mail: b011710106@student.utem.edu.my. Dr. Hazli Rafis Abdul Rahim Is a senior lecturer at Faculty of Electronic and Computer Engineering, Universiti Teknikal Malaysia Melaka, Hang Tuah Jaya, 76100 Durian Tunggal, Melaka, Malaysia. E-mail: hazli.rafis@utem.edu.my. Dr. Md .Ashadi Md. Johari Is a lecturer at Faculty of Electrical and Electronic Engineering Technology, Universiti Teknikal Malaysia Melaka, Hang Tuah Jaya, 76100 Durian Tunggal, Melaka, Malaysia. E-mail: ashadi@utem.edu.my.. Dr. Aminah Ahmad Is a lecturer at Faculty of Electrical and Electronic Engineering Technology, Universiti Teknikal Malaysia Melaka, Hang Tuah Jaya, 76100 Durian Tunggal, Melaka, Malaysia. E-mail: aminah@utem.edu.my. Dr. Mohamad Faizal Baharom is a senior lecturer at Faculty of Electrical Engineering. Universiti Teknikal Malaysia Melaka, Hang Tuah Jaya, 76100 Durian Tunggal, Melaka, Malaysia. E-mail: mohamad.faizal@utem.edu.my. Huda Adnan Zain is PhD student at Department of Electrical Engineering, University of Malaya, Kuala Lumpur 50603, Malaysia. E-mail: had3457@gmail.com. Sulaiman Wadi Harun is a professor at Department of Electrical Engineering, University of Malaya, Kuala Lumpur 50603, Malaysia. E-mail: swharun@um.edu.my.

REFERENCES

[1] J. Karalliedde and L. Gnudi, "Diabetes mellitus, a complex and heterogeneous disease, and the role of insulin resistance as a determinant of diabetic kidney disease," *Nephrology dialysis transplantation,* vol. 31, pp. 206-213, 2016.

[2] C. Deng, J. Zhang, X. Yu, W. Zhang, and X. Zhang, "Determination of acetone in human breath by gas chromatography–mass spectrometry and solid-phase microextraction with on-fiber derivatization," *Journal of Chromatography B,* vol. 810, pp. 269-275, 2004.

[3] V. Saasa, T. Malwela, M. Beukes, M. Mokgotho, C.-P. Liu, and B. Mwakikunga, "Sensing technologies for detection of acetone in human breath for diabetes diagnosis and monitoring," *Diagnostics,* vol. 8, p. 12, 2018.

[4] M. Righettoni, A. Tricoli, and S. E. Pratsinis, "Si: WO3 sensors for highly selective detection of acetone for easy diagnosis of diabetes by breath analysis," *Analytical chemistry,* vol. 82, pp. 3581-3587, 2010.

[5] P. Makaram, D. Owens, and J. Aceros, "Trends in nanomaterial-based non-invasive diabetes sensing technologies," *Diagnostics,* vol. 4, pp. 27-46, 2014.

[6] H. R. B. A. Rahim, S. Manjunath, H. Fallah, S. Thokchom, S. W. Harun, W. S. Mohammed, *et al.*, "Side coupling of multiple optical channels by spiral patterned zinc oxide coatings on large core plastic optical fibers," *Micro & Nano Letters,* vol. 11, pp. 122-126, 2016.

[7] M. H. Jali, H. R. A. Rahim, S. S. Hamid, M. A. M. Johari, H. H. M. Yusof, S. Thokchom, *et al.*, "Microfiber loop resonator for formaldehyde liquid sensing," *Optik,* vol. 196, p. 163174, 2019.

[8] K. Tian, B. Tudu, and A. Tiwari, "Growth and characterization of zinc oxide thin films on flexible substrates at low temperature using pulsed laser deposition," *Vacuum,* vol. 146, pp. 483-491, 2017.

[9] A. Araújo, A. Pimentel, M. J. Oliveira, M. J. Mendes, R. Franco, E. Fortunato, *et al.*, "Direct growth of plasmonic nanorod forests on paper substrates for low-cost flexible 3D SERS platforms," *Flexible and Printed Electronics,* vol. 2, p. 014001, 2017.

[10] C. Zhang, Q. Luo, H. Wu, H. Li, J. Lai, G. Ji, *et al.*, "Roll-to-roll micro-gravure printed large-area zinc oxide thin film as the electron transport layer for solution-processed polymer solar cells," *Organic Electronics,* vol. 45, pp. 190-197, 2017.

[11] W. Wójcik, M. Vistak, Z. Mykytyuk, I. Diskovskyi, and R. Fafula, "Simulation of the light propagation in structured matrices with liquid crystal for optical sensor active medium designing," *Przegląd Elektrotechniczny,* vol. 96, 2020.

[12] C. Fung, J. Lloyd, S. Samavat, D. Deganello, and K. Teng, "Facile fabrication of electrochemical ZnO nanowire glucose biosensor using roll to roll printing technique," *Sensors and Actuators B: Chemical,* vol. 247, pp. 807-813, 2017.

[13] S. Hjertén and Y. Kunquan, "High-performance liquid chromatography of macromolecules on agarose and its derivatives," *Journal of Chromatography A,* vol. 215, pp. 317-322, 1981.

[14] M. Batumalay, S. W. Harun, N. Irawati, H. Ahmad, and H. Arof, "A study of relative humidity fiber-optic sensors," *IEEE Sensors Journal,* vol. 15, pp. 1945-1950, 2014.

[15] H. A. Zain, M. Batumalay, H. R. A. Rahim, M. Yasin, and S. W. Harun, "HEC/PVDF coated microbottle resonators for relative humidity detection," *Optik,* vol. 232, p. 166534, 2021.

[16] H. H. M. Yusof, S. W. Harun, K. Dimyati, T. Bora, K. Sterckx, W. S. Mohammed, *et al.*, "Low-cost integrated zinc oxide nanorod-based humidity sensors for arduino platform," *IEEE Sensors Journal,* vol. 19, pp. 2442-2449, 2018.

[17] P. C. Zieger, "Effects of relative humidity on aerosol light scattering," ETH Zurich, 2011.

[18] S. Azad, E. Sadeghi, R. Parvizi, A. Mazaheri, and M. Yousefi, "Sensitivity optimization of ZnO clad-modified optical fiber humidity sensor by means of tuning the optical fiber waist diameter," *Optics & Laser Technology,* vol. 90, pp. 96-101, 2017.

[19] H. H. M. Yusof, S. W. Harun, K. Dimyati, T. Bora, W. S. Mohammed, and J. Dutta, "Optical dynamic range maximization for humidity sensing by controlling growth of zinc oxide nanorods," *Photonics and Nanostructures-Fundamentals and Applications,* vol. 30, pp. 57-64, 2018.

[20] S. Azad, E. Sadeghi, R. Parvizi, and A. Mazaheri, "Fast response relative humidity clad-modified multimode optical fiber sensor with hydrothermally dimension controlled ZnO nanorods," *Materials Science in Semiconductor Processing,* vol. 66, pp. 200-206, 2017.

[21] H. H. M. Yusof, M. H. Jali, M. A. M. Johari, K. Dimyati, S. W. Harun, M. Khasanah, *et al.*, "Detection of formaldehyde vapor using glass substrate coated with zinc oxide nanorods," *IEEE Photonics Journal,* vol. 11, pp. 1-9, 2019.

[22] M. H. Jali, H. R. A. Rahim, M. A. M. Johari, H. H. M. Yusof, B. Rahman, S. W. Harun, *et al.*, "Formaldehyde sensing using ZnO nanorods coated glass integrated with microfiber," *Optics & Laser Technology,* vol. 120, p. 105750, 2019.

[23] H. R. B. A. Rahim, M. Q. B. Lokman, S. W. Harun, G. L. Hornyak, K. Sterckx, W. S. Mohammed, *et al.*, "Applied light-side coupling with optimized spiral-patterned zinc oxide nanorod coatings for multiple optical channel alcohol vapor sensing," *Journal of Nanophotonics,* vol. 10, p. 036009, 2016.

[24] M. H. Jali, H. R. A. Rahim, M. A. M. Johari, U. Ali, S. H. Johari, H. Mohamed, *et al.*, "Formaldehyde sensor with enhanced performance using microsphere resonator-coupled ZnO nanorods coated glass," *Optics & Laser Technology,* vol. 139, p. 106853, 2021.