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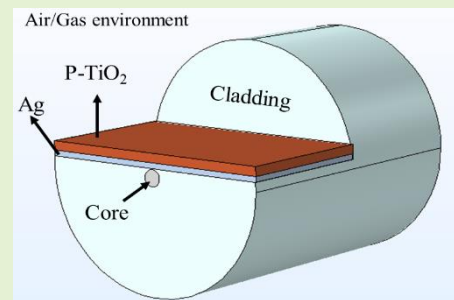
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VOC biomarker monitoring for diabetes through exhaled breath using Ag/P-TiO₂ composite plasmonic sensor

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Abstract— The detection of diabetes at an early stage is considered to be highly significant in the successful treatment of the disease. The patient has been reported to generate unique volatile organic compounds (VOCs) profiles in their exhaled breath which can be utilized as biomarkers to diagnosis the disease conditions. In this article, we theoretically report a simple breath sensor for the highly sensitive detection of isopropanol (IPA), which is the biomarker for both types of diabetes, in exhaled breath using a D-shaped composite plasmonic sensor (DSCPS). The sensing response of the sensor is characterized by using a full-vectorial finite element method (FEM) for the detailed analysis of DSCPS, where a porous TiO₂ (P-TiO₂) layer is used as low index sensing material on the top of thin Ag film. The design of the proposed sensor is based on the wavelength modulation technique. A maximum sensitivity of 0.25, 0.35, 0.45, and 1.35 nm/% can be achieved for 20%, 40%, 60%, and 80% volume fraction of IPA, respectively, with a 30% porosity of TiO₂, which is the maximum filled porous voids that provides the highest sensitivity.



Index Terms— Diabetes, Volatile Organic Compounds, Optical Sensor, Finite Element Method, Biomarkers

I. Introduction

SINCE past decades the breath analysis has been considered as a potentially powerful tool for the diagnosis and analysis of various medical diseases [1], [2]. Even in ancient times, many physicians found certain odors in exhaled breath associated with specific disease and their stage e.g., the renal failure associated with some ‘fishy’ smell and similarly diabetic patient has a ‘fruity’ odor [3]. Hence, the monitoring and analysis of volatile organic compounds (VOCs) biomarkers from the exhaled breath is recognized as a new frontier in health inspections and diabetes diagnostics owing to its potential in developing noninvasive, rapid, and inexpensive screening and measurement tools. Real-time monitoring of VOCs has attracted a huge interest towards their detection, monitoring and analysis. In general, diabetic patient has some specific VOCs in

their exhaled breath such as acetone, ethanol, isopropanol, 2-propanol, etc. depending on the type of diabetes [4].

To diagnose and monitor the stage of diabetes, various techniques have been applied to detect these VOCs in exhaled breath including gas chromatography (GC), liquid chromatography (LC), gas chromatography coupled with mass spectrometry (GCMS), and liquid chromatography coupled with mass spectrometry (LCMS) [5]. These techniques utilize an ion-pair extraction method and quantification by mass spectrometry (MS) which can detect various biomarkers in the breath sample. However, these techniques are very time-consuming, expensive, and complicated which require skilled technicians. To overcome these limitations many researchers, bring new technology for the development of VOC sensors such as electrochemical sensor [6], optical sensors [7], etc., among of which the optical-based VOC sensor get more attention in order to achieve high sensitivity and real time monitoring.

In the twentieth century, there has been a huge development of optical fiber in the sensing technology because of its several advantages such as electromagnetic immunity, remote sensing, on-line monitoring, low weight, and small size, etc. Nowadays, multiple sensors based on various configurations such as D-shape, uncladded, tapered, etc., are in practice for numerous sensing applications [8-12]. One of the application areas where these properties of optical fiber make a great competitor is for the detection and real-time monitoring of VOCs [13, 14]. In this article, we explore the role of optical fiber in the biomedical

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application of early detection of diabetes from the VOCs in exhaled breath based on a D-shaped composite plasmonic sensor (DSCPS). Acetone is one of the most common VOCs that is found in many diseases. However, this article more focuses on Isopropanol (IPA) as it is a common VOC presenting in both types of diabetes [15], [16]. Isopropanol has specific physical and chemical properties such as colorless, alcoholic odor, and bitter taste. It has been considered as a highly volatile compound. Its inhalation leads to irritation to the nose, eyes and throat. It can also be a cause of drowsiness, dizziness, and nausea. The consumption of its huge amount may lead to the coma [17].

In the present work, a D-shaped optical fiber sensor coated with a layer of thin silver (Ag)/porous TiO₂ (P-TiO₂) composite for the detection of isopropanol (IPA) has been proposed. This proposed sensor is performed on wavelength interrogation technique that utilizes the modal loss analysis for the optimization of structural parameters and investigates its sensing response with various volume fractions of IPA in air void. The numerically simulated results exhibit that the proposed idea achieves a high sensitivity of 1.35 nm/% at the highest volume fraction of IPA.

II. STRUCTURAL DESIGN AND NUMERICAL ANALYSIS

The sensor is designed on a standard single mode fiber with a core/cladding diameter of 9/125 μm . The cladding material is made of fused silica and the core of the fiber is made of germanium doped silica. The optical fiber is designed to have a D-shaped with Ag/P-TiO₂ composite coated on the top of the D-shaped surface as shown in Figure 1. Here the thin layer of Ag has been considered because of its high detection accuracy and sharp resonance peak [18]. Figure 1(a) exhibits a detailed schematic diagram of the designed IPA sensor for breath monitoring and figure 1(b) illustrates the meshing and mode of interest that takes place for the designed sensor. The refractive index of the fiber materials is evaluated by Sellmeier relation as shown in equation 1 [19]:

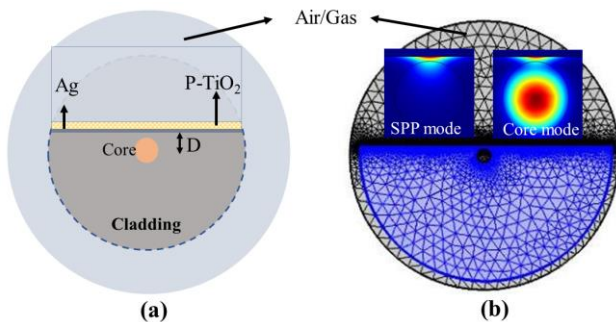


Fig. 1. (a) Schematic cross-sectional view of the proposed sensor and (b) corresponding field distribution.

$$n^2(\lambda^2) = 1 + \frac{B_1\lambda^2}{\lambda^2 - C_1} + \frac{B_2\lambda^2}{\lambda^2 - C_2} + \frac{B_3\lambda^2}{\lambda^2 - C_3} \quad (1)$$

where $B_{1,2,3}$ and $C_{1,2,3}$, represent Sellmeier's coefficients whose values are taken from the previous article [19]. The dielectric constant of thin Ag film is calculated by using the Lorentz-Drude model relation [20]:

$$\epsilon_m = 1 - \frac{\Omega_p^2}{\omega(\omega - j\Gamma_0)} - \sum_{j=1}^k \frac{f_j \omega_p^2}{(\omega_j^2 - \omega^2) + j\omega\Gamma_j} \quad (2)$$

where, ϵ_m , ω , Ω_p and Γ_0 represent the dielectric constant, angular frequency, plasma frequency, and damping frequency, respectively, whose values are considered from the reported article [20]. The RI value calculated from the Lorentz-Drude model always falls near to the experimentally obtained RI [21].

The design of sensors based on pure or composite plasmonic materials requires an accurate calculation of real and complex modal effective index (n_{eff}) values. On the other hand, a rigorous analysis is needed to calculate the modal loss along with the modal effective index change with the presence of measurand for optical fiber-based sensor. All aforementioned parameters such as modal loss and n_{eff} can be calculated by solving Maxwell's equations for the cylindrical waveguide. Thus, a full vectorial numerically efficient finite element method (FV-FEM) based on COMSOL Multiphysics [22] have been used as a numerical tool to determine the accurate modes propagated through the proposed optical fiber sensor. To propose a highly sensitive configuration we have optimized all possible structural parameters before to characterize the device as sensor, such as the thickness of Ag (t_{Ag}), thickness of P-TiO₂ ($t_{\text{P-TiO}_2}$), and the percent of porosity.

III. EQUIVALENT INDEX OF P-TiO₂ DUE TO IPA CONDENSATION

TiO₂ has been already found as selective material for alcohol sensing among which it has been observed to be more selective for IPA [23-25]. Here, we proposed a novel idea to utilize an DSCPS for the efficient detection of IPA. The proposed design consists of a thick film of P-TiO₂ on the top of a thin Ag film ($n = 0.19509$). The P-TiO₂ has a comparatively lower refractive index than a bulk TiO₂ ($n = 2.4995$). As it contains multiple air voids ($n = 1$) throughout the film. The equivalent refractive index of P-TiO₂ has an inverse relationship with the porosity as shown in Fig.2. The high surface ratio of porous structure allows the film to have higher IPA absorption and capillary condensation of IPA in the air voids. The porous TiO₂ exhibits more advantages compared to bulk TiO₂ in this work due to higher specific surface area [26], [27]. As the TiO₂ can be selectively absorb the IPA, the air voids of P-TiO₂ on the top surface of D-shaped optical fiber can be replaced by the condensed IPA. Based on various volume fractions of absorbed and condensed IPA, the dielectric constant of P-TiO₂ as well as its n_{eff} changes.

Various quantitative models are proposed in order to evaluate the permittivity of any heterogeneous media, e.g., Bruggeman model, Maxwell-Garnet theory, and Lorentz-Lorenz model. In the present work, the Lorentz-Lorenz model is used to calculate the equivalent refractive index (n_e) and effective refractive index (n_{eff}) of P-TiO₂, using the following relation [28], [29].

$$\frac{n_e^2 - 1}{n_e^2 + 2} = (1 - P) \left(\frac{n_c^2 - 1}{n_c^2 + 2} \right) + (P - V) \left(\frac{n_a^2 - 1}{n_a^2 + 2} \right) + V \left(\frac{n_d^2 - 1}{n_d^2 + 2} \right) \quad (3)$$

where n_c , n_a , and n_d represent refractive index of bulk TiO₂ [30], air, and dispersed media (condensed IPA [31]),

respectively. P and V are the porosity and volume fraction of the IPA. The refractive index value obtained from the Lorentz-Lorenz modal are closer to the RI obtained from experimental data. Variation of the corresponding refractive index of P-TiO₂ and equivalent refractive index of P-TiO₂ in the presence of various volume fractions of IPA is shown in Fig. 2. The equivalent refractive index (n_e) state the combine refractive index of P-TiO₂ and IPA in presence of condensed IPA. It can be clearly seen from Fig. 2 that the refractive index of P-TiO₂ decreases exponentially with increasing in porosity as shown

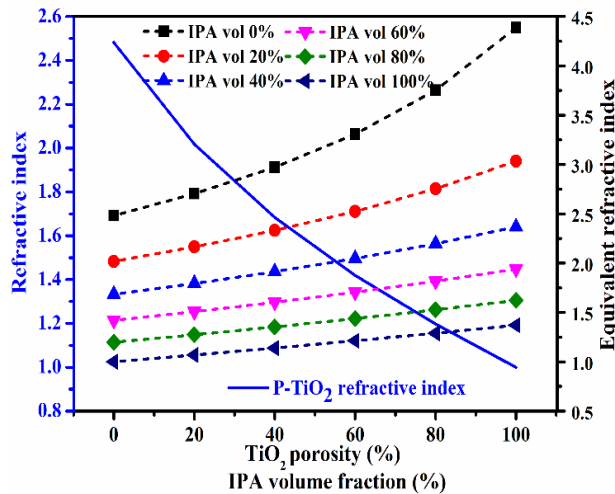


Fig. 2. Variation in refractive index with porosity and change of equivalent refractive index of P-TiO₂ with various volume fraction of condensed IPA.

by solid blue line. However, in the presence of condensed IPA, the equivalent refractive index increases with the TiO₂ porosity percentage as shown by dotted line for each IPA volume fraction.

IV. RESULT AND DISCUSSION

The excitation of surface plasmon resonance (SPR) can be characterized by calculating the confinement loss of the fundamental mode, which is a main detection factor for every SPR based fiber sensors. The modal loss of the proposed IPA sensor is evaluated by using imaginary part of effective refractive index ($Im(n_{eff})$). The $Im(n_{eff})$ is directly proportional to the confinement loss as shown by following relation [32].

$$\alpha \left(\frac{dB}{m} \right) = 8.686 \cdot k_0 \cdot Im(n_{eff}) \quad (4)$$

where the wavenumber (k_0) is defined as $2\pi/\lambda$.

A relation between fundamental and surface plasmon polariton (SPP) modes including spectral loss and effective index at various wavelengths (varying from $\lambda = 0.93 \mu m$ to $1.06 \mu m$), at their optimized structural parameters with 0% of IPA is shown in Figure 3. It can be clearly seen that the real effective refractive index ($Re(n_{eff})$) of fundamental mode decreases slowly (shown by black dots) with increasing the operating wavelength. On the other hand, the $Re(n_{eff})$ of SPP mode decreases sharply (shown by red dots) with the wavelength. At

the wavelength of $1.006 \mu m$, the $Re(n_{eff})$ of both fundamental mode and SPP mode match each other and the complete energy transfer from the fundamental core mode to the SPP mode is occurred resulting in the resonance condition in which the wavelength is known as resonance wavelength (λ_R). The confinement loss spectra presented with the solid blue line in

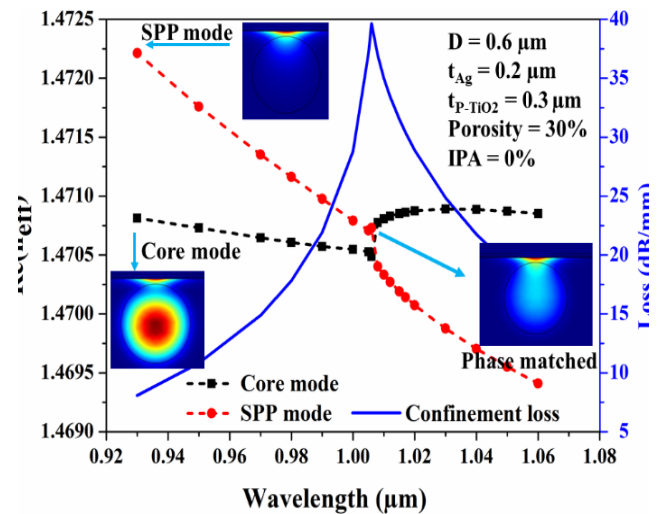


Fig. 3. Dispersion affinity curve of the sensor for fundamental core and SPP modes at 0% volume fraction of IPA.

Fig. 3, increases exponentially and reaches the maximum energy transfer from the fundamental core mode to SPP mode at the λ_R . After reaching the maximum loss, the optical loss starts decreasing exponentially. The inset images in Fig. 3 show the optical field of the fundamental core mode, SPP mode, and the phase-matched mode at λ_R with 0% volume of IPA.

A. Optimization of Polishing Depth (D)

The polishing depth (D) of the sensor plays an important role for coupling the light from the core mode to SPP mode. To obtain maximum coupling of light, the polishing depth of the sensor needs to be optimized before the characterization. To optimize and investigate the influence of polishing depth

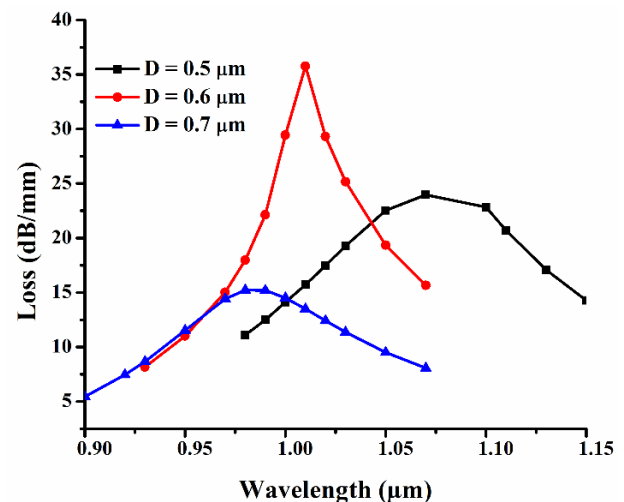


Fig. 4. Confinement loss spectra corresponding to various polishing depths (D).

various polishing depths of $D = 0.5, 0.6$, and $0.7 \mu\text{m}$ are considered with fixed t_{Ag} , $t_{\text{P-TiO}_2}$, percent of porosity, and IPA volume fraction. The variation of confinement loss with various polishing depths is illustrated in Fig. 4. As the value of D in increased from 0.5 to $0.7 \mu\text{m}$, the loss reached the maximum of 35.78 dB/mm at $D = 0.6 \mu\text{m}$. At $D = 0.5 \mu\text{m}$ and $0.7 \mu\text{m}$, a comparatively lower loss value of 23.96 and 15.22 dB/mm are obtained, respectively. Therefore, the analysis of the sensor for the maximum possible sensitivity is fixed with $D = 0.6 \mu\text{m}$ as optimized depth for the device. As we can see from Fig.4, the variation of polishing depth leads to the variation in loss spectra. This is because the interaction region of electric field of fundamental mode at the metal dielectric interface is more prominent at the optimized depth. With increasing of D , the metal-dielectric interface reaches further from the core of optical fiber and hence the strength of electric field becomes smaller resulting in the reduction of the modal loss.

B. Optimization of Thickness of Silver Layer (t_{Ag})

The next parameter needed to be optimised in this sensor is the thickness of the active plasmonic material as it leads to significant effects on the excitation of surface plasmon waves. Therefore, optimization of thickness of Ag for the excitation of enhanced plasmonic waves are studied with $D = 0.6 \mu\text{m}$. The effect of various Ag thickness on the optical loss is shown in Fig. 5. The thickness of Ag film was varied from $0.1 \mu\text{m}$ to $0.3 \mu\text{m}$ while the other parameters are fixed. It can be clearly seen from Fig. 5 that the $0.2 \mu\text{m}$ thick Ag film attains a maximum loss of 35.78 dB/mm . For $t_{\text{Ag}} = 0.2 \mu\text{m}$, and $0.3 \mu\text{m}$, lower losses of 11.01 and 10.1 dB/mm are obtained, respectively.

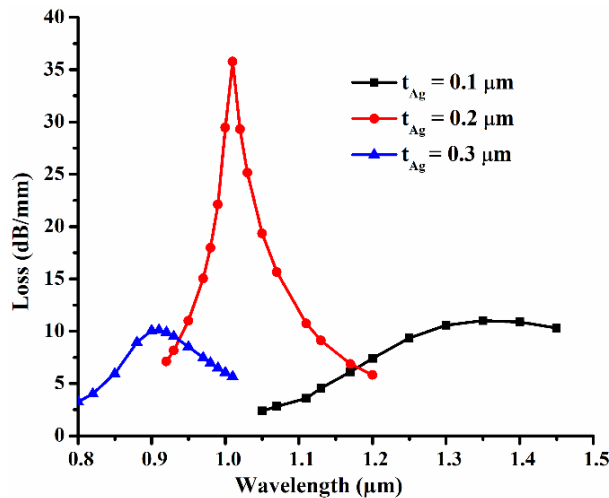


Fig. 5. Variation in confinement loss spectra with various thicknesses of Ag.

C. Optimization of Thickness of P-TiO₂ ($t_{\text{P-TiO}_2}$)

After optimizing the thickness of Ag film, the thickness of the P-TiO₂ layer is then considered as it is the layer for the condensed IPA to be absorbed. A variation of confinement loss spectra with respect to the thickness of various P-TiO₂ is shown in Fig. 6. The thickness of P-TiO₂ is varied from 0.2 to $0.4 \mu\text{m}$ in which maximum loss of 37.03 dB/mm is obtained at $0.3 \mu\text{m}$ thick P-TiO₂ layer. A lower confinement loss of 35.78 and 32.31 dB/mm for 0.2 and $0.4 \mu\text{m}$ layer are observed,

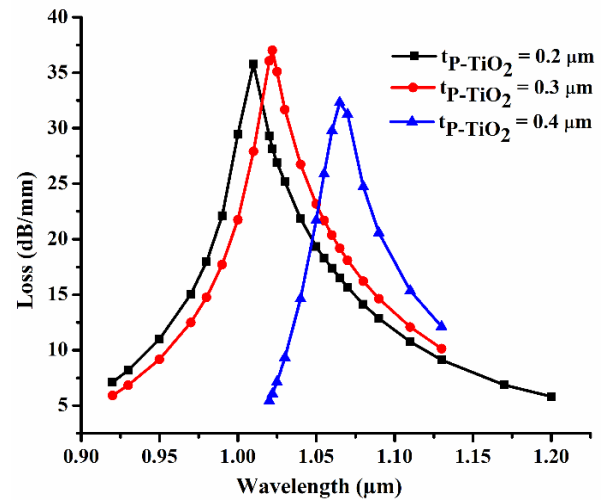


Fig. 6. Variation in confinement loss spectra with various thicknesses of P-TiO₂.

respectively. The main advantage of the $0.3 \mu\text{m}$ or 300 nm thick layer of P-TiO₂ is to provide a greater number of air voids to be accommodated in the mesoporous TiO₂ layer leading to higher absorption of condensed IPA and the sensitivity of the sensor.

D. Optimization of Porosity of TiO₂

After optimization of all physical parameters of the sensor to attain the maximum light coupling and confinement loss, the porosity percentage of TiO₂ is studied next to achieve the highest sensitivity for the sensor. As the porosity of the TiO₂ is a chemical parameter of the sensor in which the density and uniformity can be selected by controlling the temperature and other condition such as chemical concentration, calcination time, etc., during the synthesis process. In this paper, the porosity of the TiO₂ in a range from 10 to 40% is considered, and the loss spectra corresponding to each porosity percentage is shown in Fig. 7. The optical loss spectra illustrate a blue shift with increasing in porosity percentage and obtain a maximum loss of 39.62 dB/mm for 30% porosity, while 37.03 dB/mm , 37.95 dB/mm and 29.20 dB/mm has been achieved for

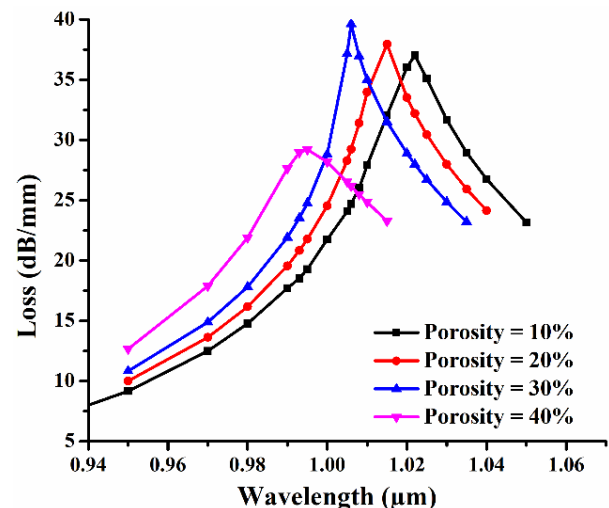


Fig. 7. Variation in confinement loss spectra with porosity fraction.

10%, 20% and 40% porosity, respectively. Therefore, the proposed optical fiber sensor to detect VOCs is designed to have a fix porosity percentage to be 30%.

E. Sensitivity

Next, after optimizing all the sensor parameters, the designed DSCPS is studied for its sensitivity with the presence of the various volume of IPA condensed in void. The absorption of various volume fractions of IPA mixed breath changes the equivalent refractive index of P-TiO₂ due to the capillary condensation. The equivalent refractive index of P-TiO₂ depends on the volume fraction of IPA which was estimated by using Lorentz-Lorenz formulation as discussed by relation (3) and also shown in Fig. 2. The confinement loss spectra due to the absorption of various volume percentage of IPA varying from 0-100 % is shown in Fig. 8. With the increase of the IPA volume fraction, a redshift is observed in the loss spectra, and the peak wavelengths are broadened due to the larger contrast of equivalent refractive index of P-TiO₂ in presence of IPA.

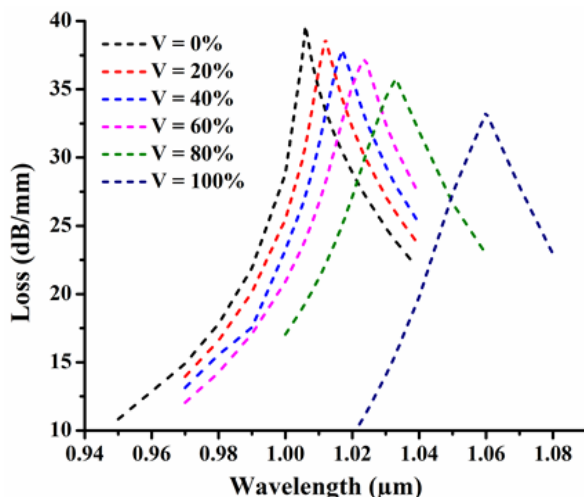


Fig. 8. Variation in loss spectra due to condensation of volume fractions of IPA.

The electric field distributions corresponding to each volume fraction of IPA is shown in Fig. 9. A clear view of leaky field appeared in Fig. 9 (b) for each absorbed volume fraction of IPA. As the volume of IPA in the air void increases. A more profound view of the field appears for 80-100% condensation of IPA in comparison to 0-60% volume fraction. Hence, the sensor can achieve a high sensitivity for the maximum condensed volume of IPA around 80-100%.

Resonance wavelength peaks corresponding to the various volume fraction condensed in P-TiO₂ obtained in Fig. 8 is fitted

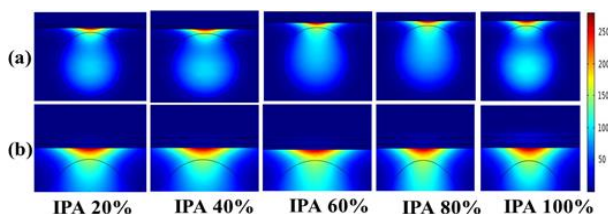


Fig. 9. a). Electric field distribution at various condensed volume fractions of IPA, b) Intuitive view of the SPR confinement at composite plasmonic material.

by a 3rd order polynomial and shown in Fig. 10. From Fig. 10, a nonlinear variation is observed with good redshift in λ_R with respect to the various volume of IPA varied from $\lambda_R = 1.006 \mu\text{m}$ to $1.060 \mu\text{m}$. The fitted curved of λ_R is then studied to obtain the sensor sensitivity.

The sensitivity of the designed IPA sensor, can be calculated by following relation [33], [34]:

$$S_\lambda = \Delta\lambda_{\text{peak}}/\Delta V_{\text{IPA}} \text{ nm}/\% \quad (5)$$

where $\Delta\lambda_{\text{peak}}$ and ΔV_{IPA} , represent the change in resonance wavelength and volume fraction of IPA, respectively. The sensitivity plot for the designed sensor is illustrated in Fig. 11 and the corresponding values are shown in Table.1.

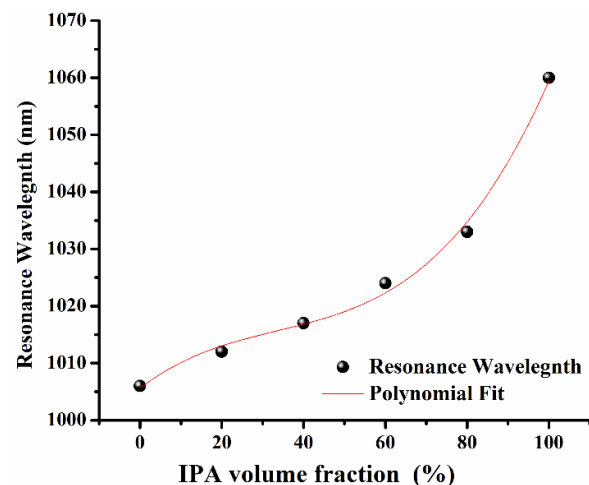


Fig. 10. Variation of resonance wavelength corresponding various condensed volume of IPA.

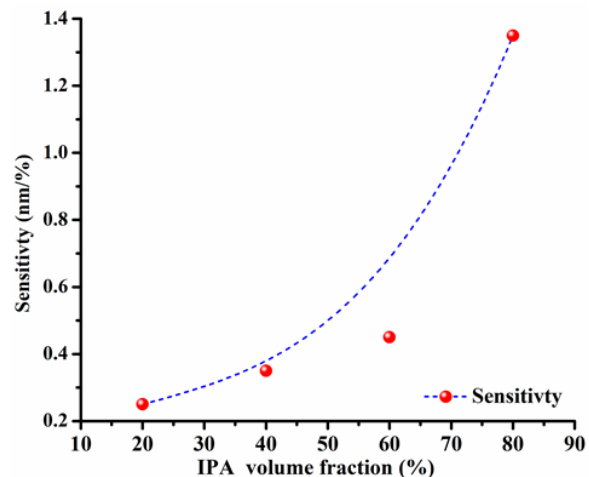


Fig. 11. Sensitivity of the designed sensor

TABLE I DETAILED STUDY OF THE DESIGNED SENSOR AND ITS SENSITIVITY		
IPA Volume fraction (%)	Resonance Wavelength (nm)	Sensitivity (nm/%)
20	1012	0.25
40	1017	0.35
60	1024	0.45
80	1033	1.35
100	1060	-

V. POSSIBLE FABRICATION TECHNIQUE OF DSCPS

The designed sensor can be fabricated and reliable to deploy for real-time monitoring of diabetes. As a basic idea of fabrication, a D-shaped fiber can be prepared before the deposition of the Ag/P-TiO₂ composite. A D-shaped fiber can be simply fabricated by using the side polishing and laser micromachining techniques, the polishing depth can be controlled using these micromachining technique [35]. The major advantage of this D-shaped configuration is to attain the maximum light at the metal-dielectric interface and sensitivity enhancement of the device [36]. Additionally, the D-shaped structure are robust in nature in comparison to the tapered fiber sensor [37]. Later a precise thin film of Ag can be deposited on polished by using thermal evaporation technique or sputtering machine. At the final stage, a mesoporous TiO₂ can be synthesized by a sol-gel technique and deposited using dip or spin coater. The porosity of the TiO₂ can be controlled by calcination time, mass fraction of polystyrene spheres in TiO₂ paste, etc., [38].

VI. APPLICATION

The sensing response of the sensor exhibits that the device performed very well in presence of IPA. IPA has been considered as one of the main VOCs along with acetone, available at high concentration in in exhaled breath of diabetic patient (mean 85.44 ppbv) in comparison to healthy group (mean 17.99 ppbv, $p < 0.001$) [39]. The proposed sensor is based on previously reported experimental works for VOC monitoring in which TiO₂ film, nanorod, etc. has been demonstrated to be a selective material for alcohol sensing. As a first report, in 2015, Alev *et al.* reported the selectivity feature of TiO₂ for IPA in comparison to various other VOCs such as ethanol, methanol, carbon tetrachloride, chloroform and acetone [23]. Later in 2017, the finding was supported by Shao *et al.*, in which the group has demonstrated the selectivity of TiO₂ material for alcohol sensing [24]. In the reported work the group has utilized graphene quantum dot along with TiO₂ for the detection of multiple VOCs such as toluene, acetone, ethanol, isopropanol, among which IPA has been observed to be more selective towards the configuration and sensing material and gives good response among other VOCs. Hence, from these experimental findings, our proposed sensor will be more selective for IPA in comparison to other similar alcohols or VOCs. Therefore, the proposed sensor developed to detect IPA is proposed to be used as the diabetes screening and monitoring tools which is possible for the early detection of the disease as IPA is considered to be one of the biomarkers of diabetes.

VII. CONCLUSION

In conclusion, a DSCPS for early detection of diabetes biomarker, IPA have been designed and analyzed. The sensor is based on wavelength interrogation technique and all the modal analysis and characterization is performed using the FEM technique based on COMSOL multiphysics. The sensor is composed of a thin Ag film followed by a thick layer of P-TiO₂ on polished D-shaped fiber. The sensing response of the sensor has been examined at various volume fractions of IPA

condensed in P-TiO₂, varying from 0-100%. The designed sensor realized a maximum sensitivity of 0.25, 0.35, 0.45 and 1.35 nm/% for 20%, 40%, 60% and 80% volume fraction of IPA condensed in P-TiO₂, respectively. An excellent response of the sensor illustrates that the idea of the development of such kind of sensor could be helpful in the early detection and monitoring of diabetes.

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