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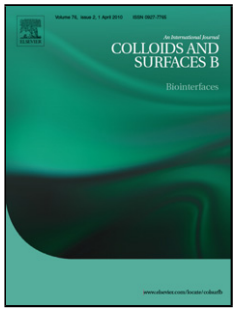

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Enhancing the evanescent field in TiO_2/Au hybrid thin films creates a highly sensitive room-temperature formaldehyde gas biosensor

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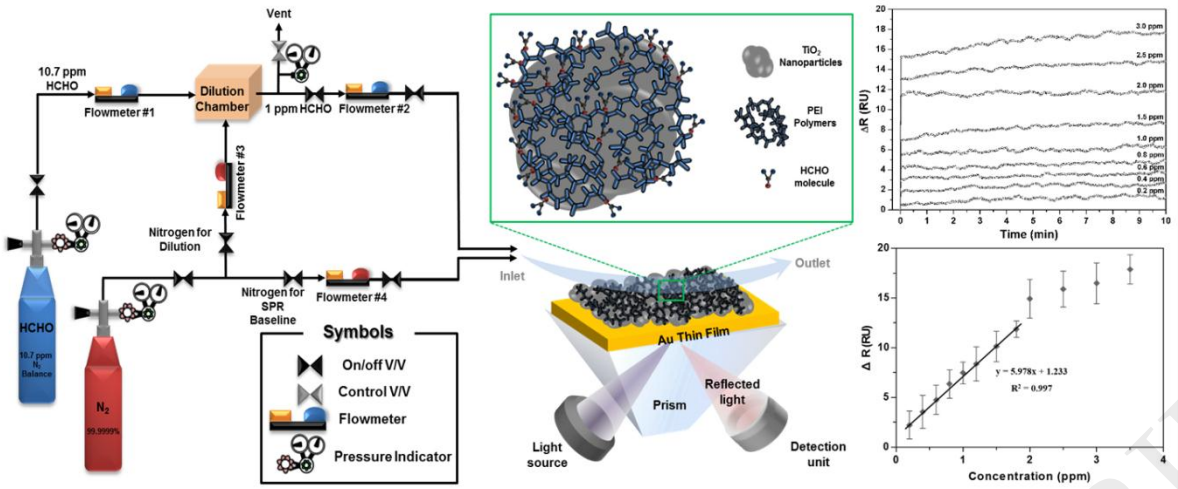
Graphical abstract



Research Highlights

- SPR gas sensors for the sensitive detection and quantification of formaldehyde
- Enhancement of the evanescent field in ligand-modified TiO_2/Au hybrid thin film
- Fast and linear sensing response at room temperature
- Applicable to real-time biomedical monitoring and diagnosis

ABSTRACT

Discovery of the relationship between disease and the volatile organic compounds (VOCs) contained in respiratory gas in human bodies has led to the development of analytical methods and detection systems that can be used for diagnosis. Recent studies, however, have encountered problems using these diagnostic tools when operation temperatures are too high and the detection range of the gas concentration falls beyond the limits of diagnosis criteria. In this study, we propose a highly sensitive surface plasmon resonance (SPR) biosensor that is based on an enhanced evanescent wave technique and can be operated at room temperature (RT) for the detection of formaldehyde. The detection system relies on an improved Kretschmann configuration with an enhanced signal transducer algorithm and a novel microfluidic gas channel that can accomplish highly sensitive quantification using ligand-modified TiO_2/Au hybrid thin film as a RT-operated sensing interface. The detection of formaldehyde was chosen to test this concept, because formaldehyde is a known breast cancer biomarker that exists in human exhalation. When the interface of our sensing system was exposed to formaldehyde, the interaction between the ligand and the analyte produced changes in the SPR profiles of the

gold thin film. The linear range of the detection system was 0.2 ~ 1.8 ppm with limit of detection at 0.2 ppm. The diagnostic criteria suggest this method could be applied to biological monitoring and diagnostics.

KEYWORDS: evanescent field, formaldehyde, gas biosensor, hybrid thin film, room temperature, sensitive detection

1. Introduction

The measurement of metabolites on media other than blood is becoming increasingly significant because of major demands for noninvasive and rapid analysis. Breath analysis is one of the most desirable noninvasive procedures. As a diagnostic tool, breath testing is traditionally used to measure hydrogen, carbon dioxide, and ammonia [1-4]. Normal human breath is known to contain 200 trace volatile organic compounds (VOCs) in addition to a large amount of H_2O and CO_2 [5,6]. Although most VOCs are derived from unknown metabolic pathways, recent studies have traced increased concentrations in exhaled air and correlated these with diseases: acetone in relation to diabetes [7,8], ammonia in relation to hepatitis [9,10], dimethyl sulfide in relation to cirrhosis [11], and ethylbenzene, styrene, and hexanal in relation to lung cancer [12-14]. The potential for a convenient and noninvasive diagnostic tool for a variety of diseases has encouraged researchers to develop a new generation of diagnostic methods for breath testing based on endogenous VOCs.

Various types of VOC gas sensors are already in use for the detection and monitoring of environmental air pollutants in the field. Gas chromatography (GC) is the most common form of analysis that is used to analyze trace VOCs. Although GC offers a high level of sensitivity and a broad linear range, the procedures of sample collection, preconcentration, and analysis are too complicated and time consuming. Over the past few years, many electrochemical methods for the detection of VOCs have been reported using a series of metal oxides such as TiO_2 [15,16], ZnO [17,18], In_2O_3 [19,20], WO_3 [21,22], and SnO_2 [23-25] as the signal-induced

materials for sensing layers. These methods have individual advantages that include high gas response and rapid response/recovery times. However, high operation temperatures of more than 200℃ are required to avoid interference from humidity, and the sensing concentration range for VOCs is on the ppm level, which is too wide for application as a diagnostic biosensor in breath testing. To overcome these limitations, colorimetric optical VOC sensors were developed and their performance has been reported [26-28]. These sensors are known for their easy fabrication, non-requirement of subsidiary circuits, and the ability to monitor VOC gases in real-time. However, these sensors lack the ability to detect VOC concentrations, which makes it difficult to use them as diagnostic tools.

An alternative optical method, surface plasmon resonance (SPR)-based optical detection, has garnered recent attention for its use in the quantification of target gases and *in situ* real-time monitoring such as with NH_3 gas sensors that use SnO_2 films [29], NO_2 gas sensors that use WO_3 thin films [30], toluene gas sensors that use SiO_2 films [31], and H_2S gas sensors that use ZnO thin films [32]. SPR is a powerful evanescent wave technique that is sensitive to the optical properties of metal surfaces, which involves the use of molecule/receptor interactions at the metal-dielectric interface in a Kretschmann configuration [33-38]. The SPR technique has certain advantages and its sensitivity is sufficient for the monitoring of target gas analytes, but its reliability as a diagnostic biosensor requires further signal enhancement. The determination of trace amounts of gas biomarkers in exhalation continues to be a challenging task because the VOC biomarker criteria for diagnosis are extremely low and the range of concentrations is narrow.

In this study, we propose a highly sensitive SPR biosensor comprised of an enhanced evanescent wave technique that can be operated at room temperature for the detection of formaldehyde. Formaldehyde is one of the VOC gases that exist in the air exhaled by humans. It is known as a biomarker that correlates with the occurrence of breast cancer. To achieve our purpose, we developed a signal-enhanced SPR biosensing system using a novel hybrid platform comprised of TiO_2 nanoparticles and thin gold film. The SPR biosensing system for formaldehyde has several advantages over existing sensing systems. First, our SPR sensing system involves an improved Kretschmann configuration, an enhanced signal transducer algorithm, and a novel microfluidic gas channel for the highly sensitive quantification of formaldehyde. In addition, we fabricated a

novel sensor chip surface composed of a ligand containing a polymer-modified TiO_2/Au hybrid thin film for the specific interaction between formaldehyde and molecular receptors. The combination of an enhanced SPR sensing system and a TiO_2/Au hybrid platform allows extension of the evanescent field and a dielectric spacing layer capable of containing a greater number of active receptors, which results in a more sensitive platform even at room temperature. Therefore, this SPR biosensor has considerable potential for use in diagnostic applications as well as for use in environmental monitoring.

2. Experimental

2.1. Materials

Titanium (VI) oxide (TiO_2), poly(ethyleneimine) solution (PEI), and sodium hydroxide were purchased from Sigma-Aldrich. Ethyl alcohol anhydrous (99.9 %), sulfuric acid (95 %), and hydrogen peroxide (30 %) were purchased from Daejung Ltd., Korea. N_2 (99.9999 %) and Formaldehyde gases (10.7 ppm) were purchased from RIGAS Ltd., Korea. The gold chips (Gold thin film on glass substrates) were purchased from K-MAC Ltd, Korea.

2.2. Preparation of ligand-modified TiO_2/Au hybrid thin film

The TiO_2/Au thin film was fabricated from a TiO_2 ethanol solution via spin coating onto Au thin film, followed by calcination at 400℃ for 20 min. Then the TiO_2/Au thin film was immersed in a PEI ethanoic solution of 1.0 mg/ml for 1 h to fabricate the amine-modified TiO_2/Au hybrid thin film.

2.3. Scanning electron microscopy and elementary analysis

Scanning electron microscopy (SEM) observation and energy-dispersive x-ray spectroscopy (EDS) measurements were obtained on a Carl Zeiss SIGMA field-emission scanning electron microscope. Prior to

analysis, samples were platinum sputter-coated to make them electrically conductive. The measurement magnification at the time of analysis was 150 K.

2.4. SPR measurements

The SPR system was utilized in the Kretschmann configuration using attenuated total reflection (ATR). The light source of the SPR system was a light-emitting diode (LED, Opnext Inc., Japan) with a peak wavelength of 770 nm. The p-polarized light beam with a wedge shape reached a metal chip after having passed through a cylindrical prism (BK-7), in which the refractive index is 1.518. The incident angle of the light source was ranged from 38.76 to 45.47 degree. The intensity of the light reflected from the Au chip was acquired by using a Charge-Coupled Device (CCD, 1024 × 768 pixel, IDS Co., Germany). BK-7 glass of 12 mm (width) × 12 mm (length) × 0.3 mm (height) was used as a substrate of the Au thin film. The SPR sensing system had three channels. One of the three channels was used as a reference channel, and the others were used as sample channels. Interference signals were eliminated by subtracting signal of the reference channel from signal of the sample channels. Time-resolved SPR angle shifts were measured using a fixed-angle method that enabled the reflectance change, ΔR, to linearly correlate with the SPR angle shift, $\Delta\theta_{SPR}$. Reflectance data at a fixed-incident angle were acquired in real time via computer.

2.5. Gas generation and detection of formaldehyde

We developed a gas generation and SPR detection system that could operate at room temperature conditions (temperature of 25 ± 1 ℃ and relative humidity of 40 ± 5 %). The standard formaldehyde gas was prepared by ISO 6142, which specifies a gravimetric method for the preparation of calibration gas mixtures in cylinders with traceable values for the amount-of-substance fraction (amount fraction) of one or more components. The standard formaldehyde gas was comprised of vaporized formaldehyde and balanced nitrogen gas. The formaldehyde was introduced into the cylinder in liquid state, and completely vaporized in the cylinder. The final concentration of formaldehyde in the standard gas was 10.7 ppm.

The flow rate of the formaldehyde gas was set to a range of from 2.0 × 10^{-3} L/min to 49.6 × 10^{-3} L/min to prepare various standard forms of formaldehyde in concentrations ranging from 0.1 to 4.0 ppm. The flow rate of the N_2 gas was maintained at 102.0 × 10^{-3} L/min. The standard formaldehyde gases were injected into an inlet of the sample well on the PEI-modified TiO_2/Au hybrid thin film. The SPR signals of the interface of the PEI-modified TiO_2/Au hybrid thin film induced by the interaction between ligands and formaldehyde gases were then measured. Signal changes in reflectance were collected and the standard deviation for each concentration of formaldehyde gases was determined.

3. Results and discussion

3.1. Gas detection principle of ligand-modified TiO_2/Au hybrid thin film

A SPR biosensing platform was incorporated into the detection method using ligand-modified TiO_2/Au hybrid thin film in a gas phase-optimized SPR system, and was enhanced using a signal transducer algorithm. The detection method involved the use of polyethylenimine (PEI)-modified TiO_2 nanoparticles containing amines (NH_2) that functioned as a ligand that was selective for formaldehyde and an Au thin film with TiO_2 nanoparticles used as signal amplifiers to stabilize the surface chemistry in the sensing platform.

The overall scheme for the detection method is shown in Fig. 1. Formaldehyde molecules are known to have a specific affinity for amine groups via electron transfer, and the presence of cations considerably enhances the adsorption affinity for formaldehyde [39,40]. To induce electrostatic interaction and enhance the adsorption affinity for formaldehyde to the amine ligand, the terminal group of the PEI-modified TiO_2 nanoparticles was altered from $-NH_2$ to $-NH_3^+$ via treatment under acidic conditions.

PEI-modified TiO_2 nanoparticles provide a much higher concentration of formaldehyde receptors than a flat surface and specific adsorption is assumed to occur using this method. Therefore, the interface of an Au thin film that includes PEI ligand appeared to be an excellent candidate for use in detecting formaldehyde, and resulted in a lower detection limit. In addition, because the optical properties of TiO_2 nanoparticles lead to their functioning as a dielectric spacing layer that functions as spatially extended probes of interfacial electric fields

for amplified signal transducing in an SPR system, the sensing platform is more sensitive and stable. Therefore, the integration of widely distributed adsorption sites, the dielectric properties of the interfacial sensing layer as a signal amplifier, and the signal fitting algorithm can induce significant changes in the optical constants.

Base on the sensing principle, we integrated a gas dilution skid with a SPR sensing system to promote the accurate sensing of formaldehyde. The gas dilution skid was designed and verified by using a SimSci-ProII, which is a commercial process simulator supplied by Schneider-Electric. At first, 10.7 ppm of pressurized formaldehyde (balanced with nitrogen) went to a #1 flowmeter in Fig. 1. The metered formaldehyde flow was then mixed with highly pure nitrogen from the #3 flowmeter in the dilution chamber. To prevent a reverse flow, an effluent vent line of the dilution camber was depressurized automatically via a control valve. The diluted formaldehyde flow was metered again at the #2 flowmeter, and then supplied to the SPR sensor. In addition, in order to stabilize the baseline of the SPR sensor, pure nitrogen flow was metered at the #4 flowmeter, and injected into the SPR sensing system.

Furthermore, in order to achieve gas sensing with a high degree of sensitivity, we developed an optical portion and a measurement algorithm. Our in-house-designed SPR sensor system allowed light to enter the low angular range and match the low refractive index of the gas phase. On the other hand, in terms of the measurement algorithm, we measured the signal in a fixed-angle mode to maximize sensitivity by using a feature whereby the full width at half maximum (FWHM) of the SPR curve was very narrow in the air phase. The fixed-angle mode generally measures the reflectivity on the SPR curve resulting from the shift of the SPR dip. The angle can be adjusted to find the inflection point of the SPR curve in order to obtain the maximum reflectivity change. The inflection point can be determined from the second derivative of the SPR curve, which gives the most sensitive starting angle or highest slope of the reflectivity shift versus angle shift. For this reason, the narrower the FWHM of the SPR curve, the more the variation in reflectivity increased, as shown in Fig. 2A. We also applied our new algorithm to determine the optimal fixed-angle in order to compensate for the narrow dynamic range of a typical fixed-angle mode. The algorithm used linear regression fitting and differentiation of the normalized raw curve by sigmoid asymmetric fitting to determine the optimal fixed angle with a minimum

of reflectance intensity in the linear range of $R^2 = 0.99$ on the left side of the SPR dip curve (Fig. 2B). Overall these incorporated efforts could allow us to achieve highly sensitive detection of formaldehyde at room temperature of 25 ℃ ± 1 ℃ and relative humidity of 40 ± 5 %.

3.2. Interfacial characterization of ligand-modified TiO_2/Au hybrid thin films

Electron microscopic analyses of the surface were used and characterized to investigate the morphology and structure of the TiO_2/Au thin film. To control both the spin coating of TiO_2 and PEI modification, the fabrication of the TiO_2/Au thin film was optimized to enhance the SPR signal for the detection of formaldehyde. In the SEM image shown in Fig. 3A, prior to PEI modification, the TiO_2 nanoparticles agglomerated in irregular semi-spherical shapes with sizes that averaged 300 ~ 400 nm. After fabrication of the TiO_2/Au thin film, close inspection of the SEM images revealed that the TiO_2 nanoparticles were deposited with *ca.* 570 nm on the Au thin film (Fig. 3A inset). The TiO_2/Au thin film was subsequently treated with PEI, and the thickness of the film was increased to *ca.*760 nm (Fig. 3B). The space of the extended evanescent field of SPR phenomena and the thickness of the TiO_2 nanoparticles were optimized via the modification by PEI, which was confirmed from the results showing that the sensing performance by this optimized TiO_2/Au thin film was optimal, given the concentration range for formaldehyde (data not shown). Fig. 3C uses the PEI modification of specific interactions with formaldehyde to show the elemental analysis of amine-functionalized TiO_2/Au thin film. These results showed that the amine-functional groups were well distributed on the surface of the TiO_2/Au thin film without inducing desorption of the TiO_2 nanoparticles.

The subsequent procedures of amine-functionalized TiO_2/Au thin film were confirmed using angle-resolved SPR measurements for native Au thin film, TiO_2/Au thin film, and PEI-modified TiO_2/Au thin film. Fig. 3D shows the angle-dependent SPR contour plots for the assembly of the Au bare thin film and PEI-modified TiO_2/Au thin film using an ambient dielectric of air. After treatment with a TiO_2 coating, the SPR contour plot showed not only a change in SPR resonance angle ($\Delta\theta_{SPR}$) but also a significant increase in the reflectance of light (ΔR). These results indicate that the changes in both $\Delta\theta_{SPR}$ and ΔR were caused by increases at the

TiO_2/Au interface in the thickness and dielectric constant of the adjacent layer, and, in particular, by an imaginary portion of the dielectric constant of TiO_2. Based on these optical characteristics, this phase of the TiO_2 nanoparticles is responsible for the increases in both $\Delta\theta_{SPR}$ and ΔR. The PEI modification also caused changes in both $\Delta\theta_{SPR}$ and ΔR due to the increase in thickness and the change in the dielectric constant of the layer adjacent to the TiO_2/Au thin film.

When formaldehyde is exposed to the sensor surface it undergoes selective adsorption onto the amine ligand on the TiO_2/Au thin film, which results in significant changes in the SPR curve profiles. The ΔR in our algorithm represents the useful SPR signals, and these were examined by carefully considering the optical properties of the sensing material.

3.3. Evaluation of formaldehyde detection

With the basic principles in hand, the real-time sensing performance of the sensor surface was first investigated to examine the dependence of the surface sensitivity originating from the interaction between the sensing layer of the PEI-modified TiO_2/Au and formaldehyde. In order to analyze the RT response of the sensor surface, the PEI-modified TiO_2/Au thin film was directly exposed to formaldehyde gas molecules. The changes in reflectance near the SPR angle were measured and the time-resolved ΔR data were obtained via the fixed-angle mode. We confirmed that the optimized detection time would be 10 min, which is sufficient time for the various formaldehyde concentrations used to reach equilibrium. Thus, in order to explore the sensitivity of the gas biosensor, the time-resolved changes in ΔR after a 10 min-exposure were determined for formaldehyde concentrations ranging from 0.1 to 3.0 ppm.

When the PEI-modified TiO_2/Au surface is exposed to a formaldehyde solution, the reflectance of the SPR signal is upward-shifted, compared with that of the PEI-modified TiO_2/Au thin film prior to detection. The SPR signal was proportionally increased with increases in the concentration of formaldehyde. The subsequent changes in ΔR for different concentrations are shown in Fig. 4. As the concentration of formaldehyde is increased, the SPR reflectance signal increases. Interestingly, an exposure time of less than 10 sec was needed

for the discrimination of formaldehyde concentrations in the measured range. Based on the shape of the graph and the changed in the SPR signal of each formaldehyde concentration, it would be possible to estimate the concentration of formaldehyde within a period of 1 min. It should be also noted that although the sensing test was performed at room temperature, the fast response time of our SPR gas sensor may challenge comparison with any previously reported studies on electrochemical gas sensors [41-43].

To construct a calibration curve, the sensor response was read after 10 min and determined as a function of formaldehyde concentration. Fig. 5 shows the calibration curves of the SPR gas biosensor for formaldehyde. The results were created using SPR responses for a minimum of 3 substrates. The ΔR for limit of detection (LOD) and limit of quantification (LOQ) for formaldehyde gas could be commonly calculated from the signal-to-noise ratio, which was correspond to 3 and 10 times the noise level, respectively. The noise level was measured by acquiring a baseline fluctuation when the SPR sensor surface was exposure to N_2 gas without formaldehyde. Considering the signal to noise in N_2 media in the absence of formaldehyde ($\Delta R = 0.162$), the LOD and LOQ were determined to be less than 0.2 ppm and 0.6 ppm respectively, which makes the method approximately 5 ~15 times more sensitive than the currently reported detection range for formaldehyde [44-46]. The high sensitivity of the method at room temperature resulted from a large distribution of binding sites for formaldehyde and a spatially extended probe for interfacial electric fields on the hybrid platform that was comprised of a TiO_2/Au surface and a gas-phase-optimized SPR sensing system.

It is noteworthy that the response of the SPR signals for formaldehyde were quite linear and ranged from 0.2 ~ 1.8 ppm. The slope of the linear range (from 0.2 to 1.8 ppm) in the calibration curve was determined to be 5.978 as shown in Fig. 5. At higher concentrations of formaldehyde, the formation of complexes based on the electron transfer between the ligand and the formaldehyde became saturated, leading to a nonlinear response and a plateau, at concentrations above 3.5 ppm. The nonlinear response at higher formaldehyde concentrations was caused by the amine ligand on the TiO_2/Au surface becoming almost saturated with formaldehyde, which caused the complex formation between the ligand and formaldehyde to decrease drastically. As a result, the change in SPR reflectance initially increased in the formaldehyde concentration, and then ultimately reached a

limiting value (∆R = *ca.* 1.4 RU). Considering the reported range of diagnostic formaldehyde concentrations, such as *ca.* 0.45 to 1.20 ppm for breast cancer criteria [47], the results showed that the developed SPR gas biosensing platform would be applicable to the diagnostic tool for the detection of target gas biomarker.

For the practical use of the sensing system, the effects of humidity and CO_2 gas on the SPR sensing signal would be important issue. Therefore we carefully investigated the effects of humidity and CO_2 gas on the proposed sensor. At first, we fabricated exhalation-simulated gas mixture comprising O_2 (15.70 $\pm$ 0.30 %), CO_2 (3.2 $\pm$ 0.06 %), and N_2 (balanced). And sensing tests were performed to evaluate the effect of CO_2 in the human exhalation gas on the SPR sensing signal. In addition, for the investigation of the effect of humidity, additional sensing tests were also conducted on simulated conditions such as native air (relative humidity of 40 $\pm$ 5 %) and water medium. Fig. 6A shows time-resolved changes in the SPR signals for various simulated conditions. The simulated conditions included 0.6 ppm and 0.2 ppm concentration of formaldehyde, pure nitrogen, exhalation-simulated gas mixture, native air (relative humidity of 40 $\pm$ 5 %), and water medium. The sensor surfaces were exposure to each simulated condition for 60 sec. The reflectance changes (∆R) in SPR signals of the exhalation-simulated gas mixture, native air and water medium were much less than that of N_2 baseline (Fig. 6B). These results indicate that CO_2 gas and humidity have little or no influence on the sensing signals of our SPR sensing system. Therefore we believe that our sensing system can be used to measure the concentration of formaldehyde in human breath, and it has the potential for application to the breath analysis of actual exhalation samples.

4. Conclusions

In conclusion, a SPR gas biosensing platform for the sensitive and room temperature-operated detection and quantification of formaldehyde using ligand-modified TiO_2/Au hybrid thin film is described. The basis for the gas biosensing method involves an improved Kretschmann configuration with an enhanced signal transducer algorithm, a novel microfluidic gas channel for highly sensitive quantification, and an amine-modified TiO_2/Au hybrid thin film as a sensing interface. The results showed significant changes in the SPR profiles with a fast

response time even when the sensing system was operated at room temperature. The limit of detection was determined to be 0.2 ppm, which is about 3 ~ 6 times more sensitive than the current diagnostic criteria level for breast cancer. A linear response was observed for formaldehyde concentrations ranging from 0.2 to 1.8 ppm. It is noteworthy that the range of breast cancer criteria is *ca.* 0.45 to 1.20 ppm, which falls within the linear range of sensing responses for our system at room temperature. We concluded that our SPR gas biosensor could be applied to other biosensing areas such as other cancers and metabolic disorders.

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Competing Interests

The authors declare that they have no competing interests.

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Figures

Fig. 1. Schematic diagram for the detection of formaldehyde gas using a hybrid platform of PEI-modified TiO_2/Au thin film via a SPR gas-sensing system.

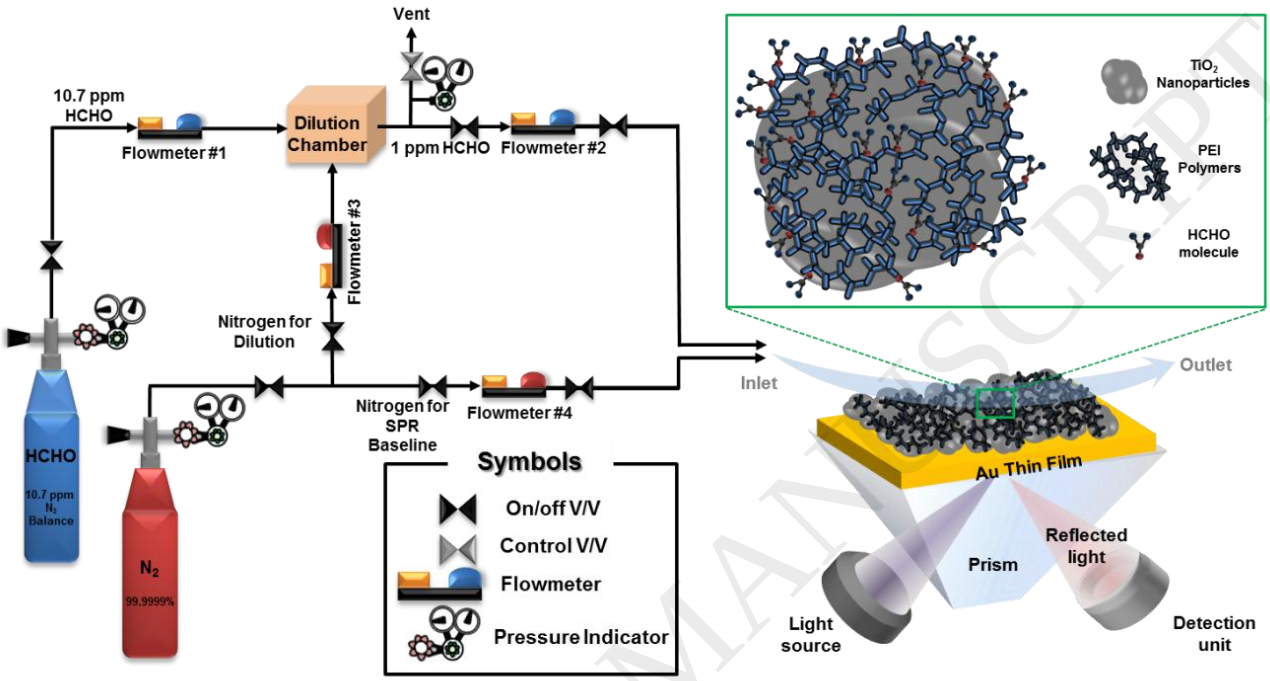

Fig. 2. (A) A comparison of the SPR spectra of native Au thin films under air (gas phase, red line) and water (liquid phase, black line) using the algorithm that features the full width at half maximum (FWHM) of the SPR curve. (B) The algorithm used to determine the optimal fixed angle with minimum reflectance intensity in the linear range on the left side of the SPR dip curve using linear regression fitting and differentiation of the normalized raw curve by sigmoid asymmetric fitting.

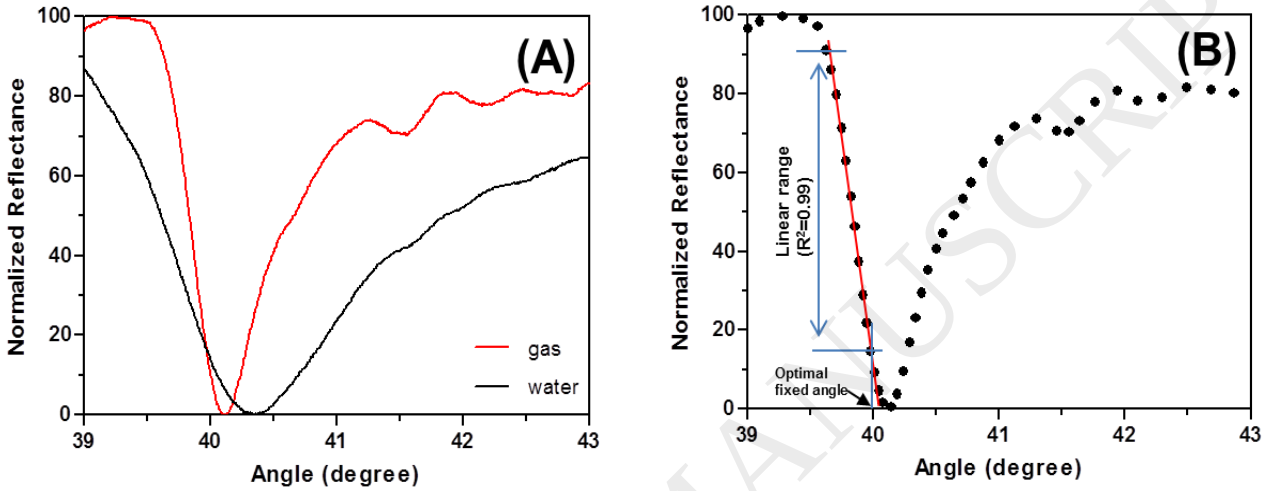

Fig. 3. (A) SEM images of the TiO_2-coated Au thin-film surface (inset: cross section) and (B) polymer-modified sensing layer on the TiO_2 coated Au thin film surface (inset: cross section) using PEI polymer. (C) EDS analysis of polymers modified as sensing layers on a TiO_2-coated Au thin film surface using PEI polymer. (D) SPR spectra for spin-coating chip fabrication. Spin coated with 0.05 M concentrations using TiO_2 nanoparticles.

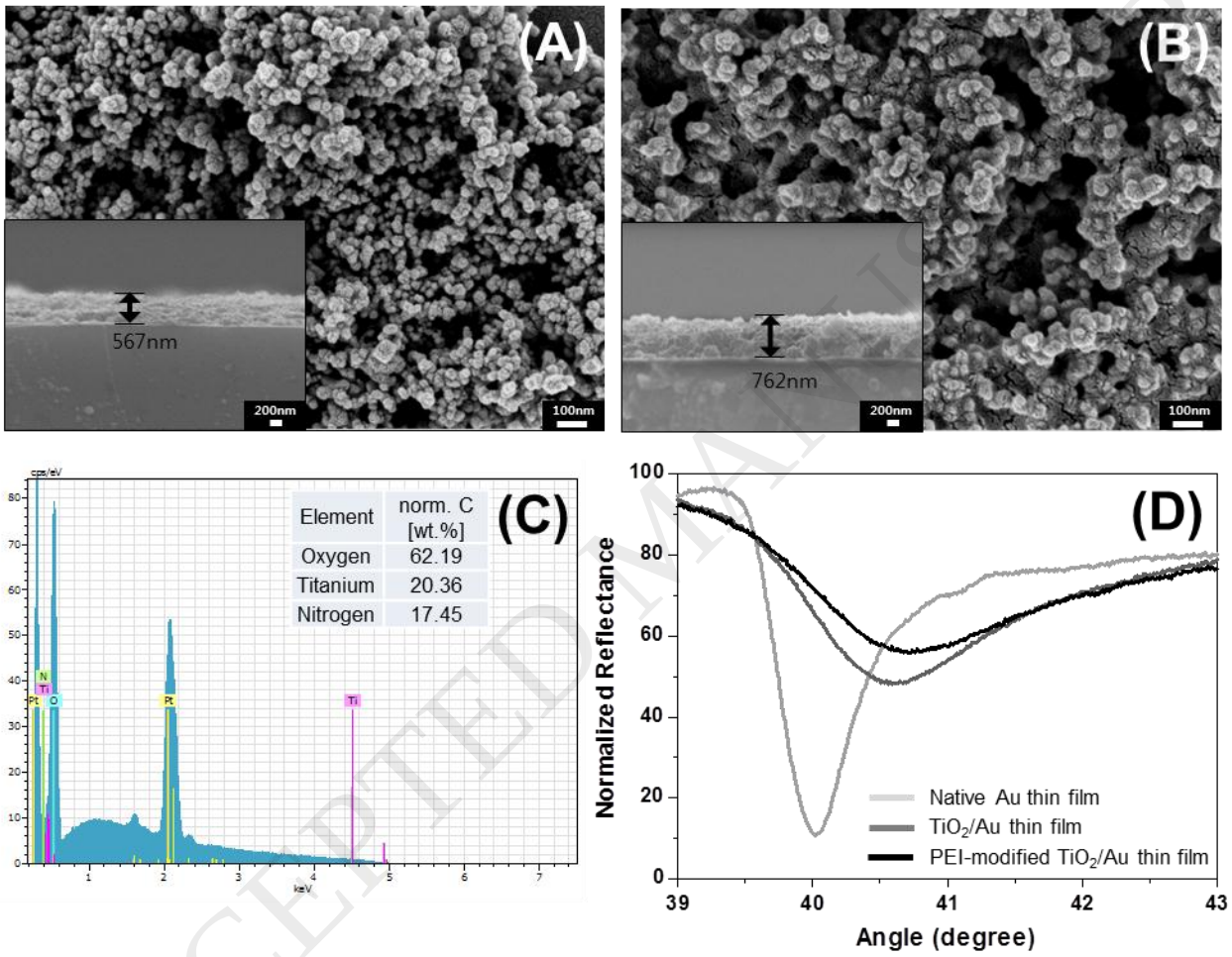

Fig. 4. Time-resolved changes in the SPR signal (reflectance, ΔR) in the fixed-angle mode for the in situ monitoring of formaldehyde gas concentrations ranging from 0.2 to 3.0 ppm.

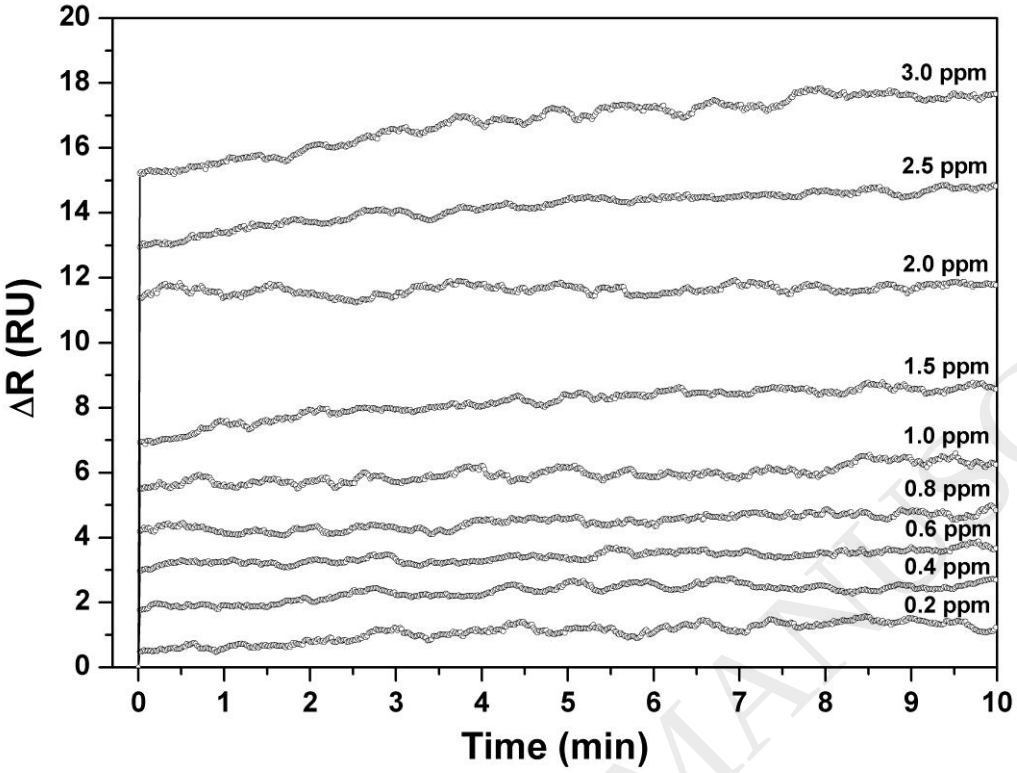

Fig. 5. The calibration curve for formaldehyde gas as a function of concentrations from 0.2 to 3.5 ppm. The error bar shown is the standard deviation from the mean (n = 4).

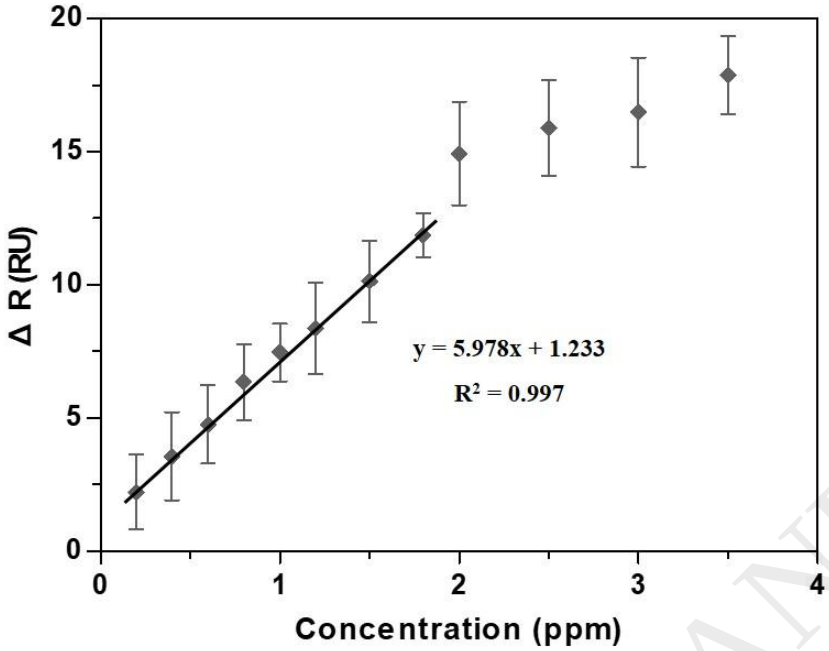

Fig. 6. (A) Time-resolved changes in the SPR signals for various simulated conditions including 0.6 ppm and 0.2 ppm concentration of formaldehyde, pure nitrogen, exhalation-simulated gas mixture, native air, and water medium. (B) Comparison of ΔR values measured after 60 sec exposure to the various simulated conditions.

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