Analysis of Acetone Absorption Spectra Using Off-axis Integrated Cavity Output Spectroscopy for a Real-time Breath Test

Lim Lee*, Yonghee Kim, Byung Jae Chun, Taek-Soo Kim, Seung-Kyu Park, Kwang-Hoon Ko, Ki-Hee Song, and Hyunmin Park
Quantum Optics Research Division, Korea Atomic Energy Research Institute, Daejeon 34057, Korea
(Received August 11, 2023 : revised September 20, 2023 : accepted September 27, 2023)

We analyzed the absorption spectra of acetone in the 3.37 µm mid-infrared range using the off-axis integrated cavity output spectroscopy technique to develop a real-time, in-line breath analysis device. The linear relationship between acetone concentration and absorption increase was confirmed as 0.32%/ppm, indicating that the developed device allows for a quantitative analysis of acetone concentration in exhaled breath. To further confirm the feasibility of using our device for breath analysis, we measured the acetone concentration of human breath samples at the sub-ppm level.

Keywords: Acetone, Laser sensor, Off-axis integrated cavity output spectroscopy, Volatile organic compounds
OCIS codes: (280.1545) Chemical analysis; (300.6340) Spectroscopy, infrared; (300.6390) Spectroscopy, molecular

1. INTRODUCTION

Currently, hospitals use a plethora of invasive methods for disease diagnosis. However, these methods require the collection of patient’s blood or tissue, which may cause discomfort and require expensive equipment. Furthermore, it takes a large amount of time to obtain the diagnostic results. In contrast, disease diagnosis based on breath gas analysis is a non-invasive and convenient technique for patients that is low-cost and allows for real-time measurement and diagnosis. As a result, the number of studies using human breath gas analysis in clinical disease diagnosis has been continuously increasing and breath analysis-based techniques have shown great potential.

In 1970, a gas chromatography (GC) analysis reported the presence of approximately 250 types of volatile organic compounds (VOCs) in human breath gases [1]. There have also been many studies published on the relationship between the components of human breath gases and diseases. Recently, it has been reported that there is a correlation between specific VOCs and diseases (i.e. acetone for diabetes patients and benzene and isoprene for cancer patients) [2].

The most commonly used method for breath gas analysis is mass spectrometry, such as gas chromatography-mass spectrometry (GC-MS) [3–5]. However, GC-MS-based techniques are limited in commercial development due to several disadvantages, such as the difficulty of direct breath sampling, the need for high levels of expertise, and relatively slow analysis time. For these reasons, much research has been conducted to develop a wide range of alternative methods that enable rapid operation and sensitive analysis.

Laser-based spectroscopy, which is a key alternative method, provides quick and accurate quantitative analysis results. Furthermore, it offers low cost and a real-time measurement analysis. Accordingly, several studies have been conducted in various fields based on the analysis of VOCs contained in pure breath using laser-based spectroscopy. For example, gastrointestinal disorders in patients are diag-
nosed by measuring methane (CH₄) concentrations in their breath using infrared spectrometry [6]. Also, the diagnosis of diabetes, which is related to abnormal metabolism, can be implemented by measuring the concentration of acetone using the cavity ring-down spectroscopy (CRDS) technique [7].

These successful implementations demonstrate the potential commercialization of diagnostic systems based on optical spectroscopy in actual clinical applications. Notably, laser-based spectroscopy enables either single or multiple real-time measurements with sub-second temporal resolution and ppb level sensitivity. These are advantageous for elucidating the physiology models for VOC gas exchange or biomarkers in various breathing phase stages by continuous measurement. Furthermore, it enables detailed monitoring of changes in disease-related biomarkers by sampling real-time breathing cycles and accumulating a large amount of data with high precision and accuracy. When using isotopic tracer substances to track metabolic substances in biological activities such as pathogen attacks, drug therapy, or eating, detection limits of ppt levels are required [8].

In this work, we developed an efficient breath analysis method based on the off-axis integrated cavity output spectroscopy (OA-ICOS) technique. Our method offers comparable sensitivity to CRDS or photo-acoustic spectroscopy (PAS) while minimizing system complexity. Since the OA-ICOS adopts the time integrated measurement, the device makes real measurement more convenient than the device using other techniques such as CRDS [9–11].

As the OA-ICOS technique allows for simultaneous measurement of multiple absorption spectra over a wide range of wavelengths, it can identify various molecules in the breath. Our OA-ICOS system uses the mid-IR wavelength range, where the absorption cross-sections of most VOCs are relatively large, allowing it to measure minute gas absorption precisely.

Our method has a sufficient observation range for broad absorption lines, especially for acetone, which is clearly distinguished from the absorption lines of ethane, methane, and other compounds. This provides advantages for analyzing multiple VOC concentrations and commercializing the technique [12]. In this study, we describe our OA-ICOS system in detail and present a quantitative measurement method for acetone concentration, considering the aforementioned properties of acetone. We also propose how the measurement results can be used for breath diagnosis.

II. EXPERIMENTAL SETUP

Figure 1 shows the experimental setup of our home-built OA-ICOS technique. A high-reflective optical cavity with two mirrors (R = 97.0% at 3.37 μm, ROC = 1 m, Calcium Fluoride (CaF₂); Optogama, Vilnius, Lithuania) was mounted on a 30-cm stainless tube with an inlet consisting of selectable injection ports and an outlet connected to a vacuum pump. The inlet connector was designed to be switchable for use with injection ports for a gas mixture, syringe and breathe sample.

A distributed feedback laser (DFB interband cascade laser, DFB-280400; Nanoplus, Dreißigacker, Germany) was used as the light source, and a FiberPort 1 (PAF2-11E; Thorlabs, NJ, USA) with a focal length of 11 mm was used as a beam coupler. The beam is guided by a single mode fiber (P3-32F-FC-1; Thorlabs) to a FiberPort 2. Its transmission output was about 2 mW with the improved beam mode due to the spatial filtering effect by using the single mode fiber. A FiberPort 2 (PAF2-4E) with a focal length of 4 mm was used as the collimator at the end of the fiber. The output beam diameter of the FiberPort 2 is 1.2 mm, smaller than that of the FiberPort 1 (3.2 mm). This reduces the interference effect between the reflected beams inside the absorption cell, making the alignment of the OA-ICOS system more straightforward.

The signal-to-noise ratio (SNR) of the OA-ICOS is basically proportional to the beam path length, satisfying the resonance condition of the successively reflected beams, and is limited by the interference noise as a result of the overlapped beams inside the cavity. Therefore, by optimizing the divergence and position with the angle of the incident beam on the cavity, the absorption path can be maximized while minimizing the interference. Instead of multiple lenses, only one FiberPort was used as a collimator to simplify the configuration and make it easier for maintenance.

The transmitted beam passes through two lenses (L1, 2-inch diameter with f = 50.8 mm; L2, 1-inch diameter with f = 25.8 mm) and subsequently focuses on a thermoelectrically-cooled MCT (HgCdTe) photovoltaic detector (PD) (time response: 80 ns, Pvi-4TE-5 with PIP-UC-LS preamplifier; VIGO system, Mazowiecki, Poland). The PD requires low-temperature operation to reduce the dark current and increase the sensitivity. The output voltage offset of the
PD varies with changes in external temperature and cooling cycles. To correct the variations in the offset, we applied the current of the laser from the threshold to the maximum value. When the current region is lower than the threshold current, it is identical to when the light is blocked. We can calibrate the PD offset to zero using the obtained value.

We scanned the wavenumber region of 2,968–2,973 cm\(^{-1}\), as shown in Fig. 2, by modulating the current at a laser diode (LD) temperature of 15 °C using the LD controller (ITC4001; Thorlabs). This modulation range is sufficient for simultaneously measuring the absorption signals of acetone and several VOCs such as ethane and methane. The wavelength of the light source was measured by a Fourier transform optical spectrum analyzer (OSA205C; Thorlabs) and compared with the absorption lines of water, ethane, and methane in the HITRAN database [13]. To confirm the absorption wavelength values in the OA-ICOS system, we first obtained individual absorption lines by injecting acetone, methane, ethane, and water into the absorption cell. They were then mixed inside the cell and the corresponding mixed absorption line was obtained. For this, water was directly injected into the inlet using a syringe port, while acetone, ethane, and methane were injected using another port for a gas mixture. By comparing the obtained values, we experimentally confirmed the absorption wavelength values using the OA-ICOS. This process has been performed slowly at a scan rate of sub-Hz level in order to obtain accurate measurement values using OSA205C, and then the acetone concentration measurement was performed quickly at a level of several kHz for rapid measurement and analysis.

**III. RESULTS AND DISCUSSION**

Acetone gas samples with concentrations ranging from 1 to 100 ppm were prepared by mixing a 500 ppm acetone gas sample (500 µmol/mol; Airkorea Co., Yeoju, Korea) with dry air. The sample was mixed for an hour before measurement. The total pressure of the gas mixture in the absorption cell was set to be 500 Torr. The distance between the cavity mirrors of the OA-ICOS is changed by the O-ring compression corresponding to the internal pressure of the absorption cell. It is well known that the cavity alignment of cavity enhanced absorption spectroscopy (CEAS) techniques such as the OA-ICOS is highly sensitive to changes in the distance between the mirrors.

After optimizing the cavity mode matching conditions in a vacuum state, the transmittance of the light change was measured while injecting nitrogen gas without absorption in the corresponding wavelength region. We observed that the transmittance increased by 0.56% as the pressure inside the cell increased by 100 Torr, indicating that the effective length of the optical path of the cavity is shortened as the mode matching efficiency decreases. The path of the beam incident on the mirror plane and the divergence of the beam were rearranged to optimize the mode matching in a 500 Torr environment, and the measurement errors were reduced by performing each measurement at the same pressure.

Figure 3 shows the OA-ICOS absorption spectra of the measured acetone gas. The intensity of the transmitted beam decreased with an increase in the concentration of acetone, indicating that the absorption increased along with the concentration. In OA-ICOS technology, the beam alignment is to allow the beam that is incident off-axis to be repeatedly reflected between the mirrors that constitute the cavity. As a result, a significant portion of the beam overlaps, resulting in noise due to interference effects. This noise depends on the geometric structure of the cavity, and can be effectively removed by using a suitable LPF [14]. A cutoff frequency of 500-kHz for a low-pass filter (LPF, EF506; Thorlabs) was applied for noise reduction. The scanning rate of the LD was 5 kHz and the average number

**FIG. 2.** Typical acetone absorption spectrum observed by scanning the laser wavelength. The tunable range by current modulation at a fixed temperature of 15 °C is shown as wavenumbers.

**FIG. 3.** OA-ICOS absorption spectra of the measured acetone gas with different concentrations. The scanning rate was 5 kHz and each signal was averaged 128 times. OA-ICOS, off-axis integrated cavity output spectroscopy.
of spectra was 128. As shown in Fig. 3, the acetone absorption spectrum is broad and has structural changes of molecules with the concentration, making it difficult to define the size (peak height) of the absorption line.

The shape of the spectrum was changed according to the pressure, so the absorption was defined as the averaged value of the signal in the $40 \pm 2 \mu s$ region.

Figure 4 shows the calibration curve for acetone concentration and absorption level of the combined measurement results. The absorption of the spectrum increased linearly with a slope of 0.32%/ppm as the concentration of acetone increased. The average noise level of the spectrum was measured as $\pm 0.02\%$, indicating that the distinguishable minimum concentration difference is less than $\pm 0.06$ ppm. The error bars for each data represent the standard deviation of the absorption and are not distinguishable on the given scale.

Figure 5 shows the real-time measurement results of the exhaled gas. A Nafion filter (0.108-inch diameter, 6-inch length; Chromservis, Praha-Petrovice, Czech Republic) was attached to the inlet of the exhaled gas to remove moisture, and the filtered gas was injected in-line into the absorption cell. Figure 5(a) shows the absorption spectra of lab air (gray line) and the breath sample (red line) from one of the researchers. The absorption lines, indicated by the asterisk, were identified as the absorption line of water at wavenumber 2,969.52 cm$^{-1}$. Although the moisture in the lab air and breath samples was successfully removed by the nafion filter, but absorption line still observed. The subtraction result of the lab air spectrum from the breath sample is illustrated in Fig. 5(b). The complete compensation of water absorption peak by subtraction showed that the performance of the filter used was sufficient.

The black line represents the Voigt fitting result. This spectrum is the result of absorption by acetone, and the concentration calculated using the obtained calibration curve (Fig. 4) is 0.53 ± 0.06 ppm. This result correlates well with the value reported in a previous study; the acetone concentration in the exhaled breath of a healthy person is between 0.39 and 0.85 ppm [15].

**IV. CONCLUSION**

In this study, we analyzed the absorption spectra of acetone with the aim of developing a breath analysis device based on laser absorption spectroscopy. To develop a real-time, in-line breath analysis technology, we assembled an analyzer using the OA-ICOS technique and analyzed the absorption spectrum of acetone. We confirmed the linear relationship between the acetone concentration and the absorption, indicating that the developed device allows for quantitative analysis of acetone concentration in exhaled breath.
To further assess the feasibility of using our method as a breath analysis device, we measured the acetone concentration of human breath samples at the sub-ppm level. However, this result was obtained under the assumption that there were no other VOCs that could affect the observed absorption spectrum, and it was not measured in an environment that meets all the conditions proposed as a preprocessing process for breath analysis. Nevertheless, the measurement and analysis results show the possibility of quantitative analysis and commercialization. We confirmed the development potential as a more accurate and precise breath analyzer through the development of methods for measuring and analyzing multiple VOCs, standardization of in-line injection devices and measurement procedures.

Therefore, we believe that our presented technique offers an opportunity to simultaneously investigate multiple VOCs with the standardization of in-line injection and measurement procedures. Furthermore, this study will pave the way towards better and more practical breath analysis devices in clinical applications.

**FUNDING**

KAERI Institutional Program (Project No. 524430-23).

**ACKNOWLEDGMENTS**

This work was supported by the KAERI Institutional Program (Project No. 524430-23).

**DISCLOSURES**

The authors declare no conflicts of interest.

**DATA AVAILABILITY**

Data underlying the results presented in this paper are not publicly available at the time of publication, which may be obtained from the authors upon reasonable request.

**REFERENCES**


