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Highly selective real-time detection of breath acetone by using ZnO quantum dots with a miniaturized gas chromatographic column

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ABSTRACT

In this study, we developed a breath acetone analyzer based on a miniaturized gas chromatography (GC) column integrated with ZnO quantum dots (QDs); this analyzer is capable of analyzing a wide range of breath acetone concentrations within 2 min using a small volume (1 ml) of human breath without pre-concentration. The average size of the ZnO QDs, which were synthesized by a wet chemical method, was approximately 6 nm. The developed analyzer could detect acetone concentrations as low as 0.1 ppm. The response of the ZnO QDs increased with increasing acetone concentration and was strongly correlated with the concentration (R^2 = 0.9915). The miniaturized GC column effectively separated acetone from the breath. In addition, a preliminary testing of the breath acetone analyzer was performed through the breath analysis of volunteers who were on ketogenic and normal diets. The results showed that the acetone content in the breath of the volunteer who was on a ketogenic diet for three days was 1.2 ppm.

1. Introduction

Breath analysis using gas chromatography (GC) to identify more than 200 compounds in human breath first came into practice in the 1970s [1]. Endogenous compounds such as inorganic gases (NO, CO) and volatile organic compounds (acetone, ethanol, ammonia, ethane, pentane) in the human breath serve as biomarkers for several diseases [2]. Breath acetone is related to diabetes [3], fasting [4], fat metabolism [5], and numerous other diseases [6,7]. The main energy source of the human body is transformed from glycogen to fat when glycogen intake is reduced [8]. The ketone bodies acetoacetate and 3-hydroxybutyrate are produced by fat metabolism in the liver [9,10]. Acetone derived from acetoacetate is found in the blood and urine and is released as exhaled breath at the blood–air interface in the alveoli of the lungs [11]. The breath acetone concentration of a healthy human is 0.3–4.0 ppm [12,13], while that of an adult on a ketogenic diet (low amounts of carbohydrates and high amounts of fat) is higher, up to 40 ppm [14]. Breath acetone is affected by various physiological factors such as diet, obesity, and exercise. When a person is on a ketogenic diet, marked alterations in energy metabolism occur, with the ketone bodies replacing glucose as fuel [15]. The ketogenic diet can increase fat metabolism, which increases the breath acetone concentration [14]. The breath acetone concentration is measured by GC-mass spectrometry [1,16,17], selected-ion flow-tube mass spectrometry [18,19], ion mobility spectrometry [20,21], and proton-transfer-reaction mass spectrometry [22,23], which are commonly used in the laboratory. With increasing interest in smart healthcare, portable personal healthcare devices are in high demand. The conventional tools used for breath analysis are disadvantageous in terms of cost, portability, and complexity. Electrochemical sensors [2,5,24], biological sensors [11,25], and sensor arrays [26,27] are used to overcome these problems. The main drawback of electrochemical sensors, besides their low selectivity and large sampling gas volumes, is their inadequate sensitivity for trace acetone concentrations. Selectivity plays a vital role in accurately analyzing the biomarkers of human breath, which consist of more than 200 compounds. Above all, breath analysis must be normalized by end-tidal breath analysis as the exhaled substance concentration may depend on the ventilation/perfusion ratio of the lung. Here, the sampling volume of the breath must also be controlled, as it can cause interference with the end-tidal breath analysis. Although much progress has

Abbrevaitions: GC, gas chromatography; QD, quantum dot; SEM, scanning electron microscopy; TEM, tunneling electron microscopy; EDS, energy-dispersive X-ray spectroscopy; FFT, fast fourier transform

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been made in this regard, current electrochemical sensors do not show the desired sensitivity and selectivity for breath acetone analysis [28]. A pre-concentrator is used to enhance the sensitivity of the sensor by concentrating the target gas during the sampling process [29,30]; however, this increases the analysis time.

ZnO has a wide bandgap (3.37 eV), high bond energy (60 meV), and high thermal and mechanical stability [31]. Thus, it has been applied in many fields, such as solar cells [32], lasers [33], and detectors [34]. In particular, ZnO is a pioneer material for gas sensing due to its high sensitivity and morphological and chemical stability. Various gases, such as C_2H_5OH, C_4H_9OH, CO, and C_6H_5Cl, can be detected using ZnO-based sensors [35]. In particular, ZnO-based sensors can detect acetone [36–38]. However, research on whether ZnO-based sensors show desirable sensing properties for breath acetone analysis is scarce. We have recently synthesized ZnO quantum dots (QDs) by a wet chemical method. The sensor based on ZnO QDs show a good response ($(R_a–R_g)/R_g = 1574$) and a low detection limit (0.01 ppm) to acetone (unpublished data). The good sensing properties can be attributed to the increased number of active adsorption sites and enhanced kinetics of the surface reaction due to the size effect. The ZnO QD sensor shows the best sensing properties for the analysis of breath acetone. The detailed sensing properties and physical and chemical characteristics of the ZnO QDs will be discussed in separate studies.

In this study, we report a breath acetone analyzer to overcome the shortcomings of existing breath analyzing systems. The developed breath acetone analyzer consists of a ZnO QD-based sensor and a miniaturized GC column. The ZnO QD-based sensor sensitively detects the acetone content (detection limit: 0.1 ppm) and is suitable for application to human breath acetone analysis, and the miniaturized GC column effectively separates acetone from the human breath. Additionally, preliminary results of the testing of the breath acetone analyzer for volunteers on ketogenic and normal diets are discussed.

2. Materials and methods

2.1. Breath acetone analyzer

The breath acetone analyzer comprised a sampling loop, a packed column, three solenoid valves, a mini-sized pump, and a sensor based on ZnO QDs. Fig. 1 shows a schematic of the analyzer and an optical image of the real breath analyzer. The dimensions of the breath acetone analyzer were $8 \times 13 \times 16$ cm^3. First, the sampling loop was filled with 1 ml exhaled breath without pre-concentration. Subsequently, acetone was separated from the exhaled breath by the packed column within

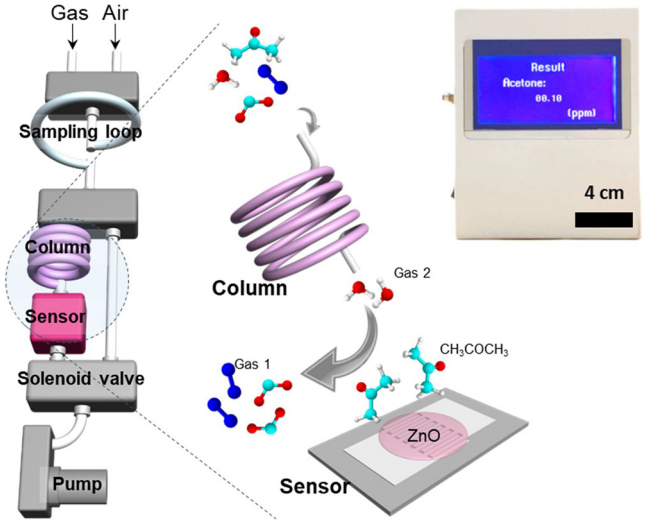

Fig. 1. Schematic of breath acetone analyzer and real image.

100 s at a carrier gas flow rate of 20 sccm. The operating temperature of the column was maintained at 30 °C. The separated acetone was detected by the ZnO QD-based sensor. The length and inner diameter of the packing column (Isenlab Inc.) were 20 cm and 0.15 cm, respectively.

The ZnO QDs were synthesized by a wet chemical method. The ZnO precursor solution was prepared using Zn acetate ($Zn(O_2CCH_3)_2$, Alfa Aesar). In brief, 1.975 g Zn acetate was dissolved in 90 ml *N,N*-dimethylformamide ($((CH_3)_2NC(O)H)$, Duksan). The ZnO precursor solution was injected into a methanolic solution of tetramethylammonium hydroxide ($N(CH_3)^{4+}(OH)^-$ (methanol:tetramethylammonium hydroxide = 1:8) using a syringe pump for 1 h at 30 °C. The synthesized ZnO QDs were rinsed with acetone and dispersed in methanol. The ZnO QD-based sensor was prepared by dispersing the ZnO QD solution on an Al_2O_3 substrate, followed by heat treatment at 350 °C for 30 min to remove the residue. The microstructure of the ZnO QDs was investigated by scanning electron microscopy (SEM, JEOL-7001 F) and tunneling electron microscopy (TEM with energy-dispersive X-ray spectroscopy (EDX), JEM-F2000), which were also used for the compositional analysis of the ZnO QDs.

2.2. Sensor characterization

To fabricate acetone sensors, the ZnO QDs were dispersed on an alumina substrate (0.5×0.25 mm^2) supplied with interdigitated Pt electrodes and heating elements. The devices were dried at 90 °C and heat-treated at 350 °C for 30 min to remove the residual organic compounds. The ZnO QD sensors were tested at various temperatures (394, 417, 430, and 446 °C) to optimize the operation temperature of the breath acetone analyzer system. The breath acetone analyzer was used to detect air-balanced acetone. The concentration of air-balanced acetone was in the range 0.1–50 ppm at the optimal temperature of 430 °C. Acetone was directly injected into the breath acetone analyzer, without any pre-concentration, for 10 s. The sampling volume of the acetone was limited to 1 ml. Ambient air was used as the carrier gas at a flow rate of 30 sccm.

The resistance of the ZnO QD sensor was converted to a sensor signal (*log(R)*) by the breath acetone analyzer. The response of the ZnO QD sensor was defined as Δ(*log(R)*):

$$\Delta(\log(R)) = \log(R)_{max} - \log(R)_{min} \quad (1)$$

where $log(R)_{max}$ is the maximum resistance before exposure of the acetone and $log(R)_{min}$ is the minimum resistance at exposure. These values are related to the resistance of the ZnO QD sensor.

2.3. Breath characterization

Three healthy subjects (three male volunteers) were tested. One volunteer was on a ketogenic diet (daily carbohydrate intake of less than 5%) for three days, and two volunteers were on a normal diet. The volunteers fasted for 8 h before the breath analysis. The volunteer who was on the ketogenic diet for three days was made to consume 300 ml apple juice, which contained 50 g carbohydrates; immediately, the breath acetone concentration was measured consecutively for 50 min at 5-min intervals and finally after 800 min. The volunteers were made to directly blow into an end-tidal sampling loop, which was connected to the breath acetone analyzer. The end-tidal breath remaining in the sampling loop was forced into the breath acetone analyzer and detected within 2 min. The breath acetone concentration was determined by the equation defined below. This equation was related to the acetone concentration and resistance change of the ZnO QD sensor and was derived from the experimental data. The change in the sensor signal was measured for various concentrations of air-balanced acetone in the range of 0.1–5 ppm. As the sensor's resistance change is linearly related to the acetone concentration in the ZnO QD sensor, the equation was

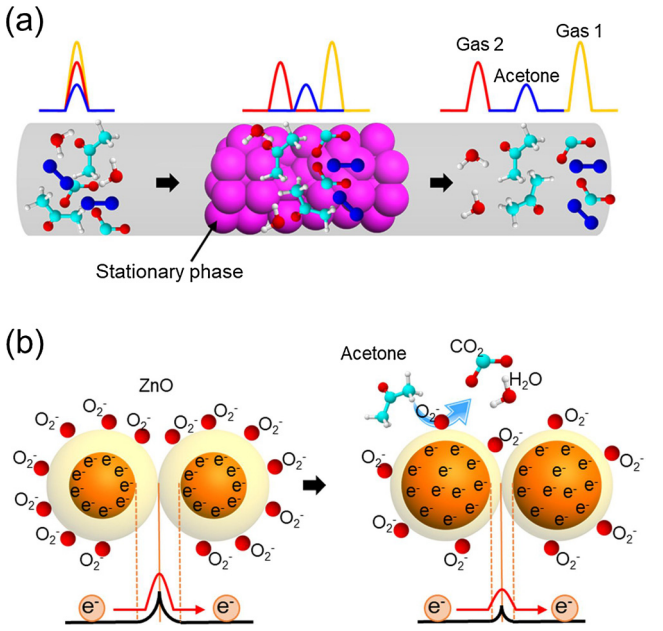

Fig. 2. Schematic of (a) mechanism of separation of mixture gas in packed column and (b) mechanism of acetone gas sensing on ZnO QD surface.

given as $Y = 69.79 \times X + 0.07$, with a linear correlation coefficient of $R^2 = 0.998$, where Y is the acetone concentration balanced in air and X is $\Delta(log(R))$.

3. Results and discussion

Fig. 2(a) shows a schematic of acetone separation from the mixture gas. The column was packed with stationary phase-coated packing material. The mixed gas was passed through the column for the separation of acetone. The carrier gas controlled the flow of the mixed gas, thus separating the components. The separation of acetone was based on the difference in the strengths of interactions of the component gases with the stationary phase. Non-polar gases such as CO_2 and N_2 were rapidly released from the column due to their weak interaction with the stationary phase. On the other hand, polar gases such as acetone and water vapor were released slowly. The vapor was released after acetone due to its high polarity.

Fig. 2(b) shows a schematic of the mechanism of the ZnO QD sensor for acetone. When the ZnO QDs were exposed to air, oxygen was adsorbed on the ZnO surface. The adsorption of oxygen resulted in the formation of ionic species such as O_2^-, O^-, and O^{2-} depending on the operating temperature. At low temperatures ($T < 100$ °C), O_2^- was chemisorbed. At high temperatures, however, O^- ($T = 100$–300 °C) and O^{2-} ($T > 300$ °C) were chemisorbed [39,40]. In the temperature range selected in our study, only the most stable O^{2-} species (compared to O_2^- and O^-) reacted with acetone [39]. A thick depletion layer was formed on the surface as the O^{2-} species reacted with electrons, which were initially in the conduction band of the ZnO QDs. When the ZnO QDs were exposed to acetone, the O^{2-} species reacted with the surface gas as follows:

$$CH_3COCH_{3(ads)} + 4O^{2-}{}_{(ads)} \rightarrow 3CO_{2(gas)} + 3H_2O_{(gas)} + 8e^- \quad (2)$$

Acetone was thus decomposed into CO_2 and H_2O on the surface of the ZnO QDs. The thickness of the depletion region decreased due to the release of electrons into the conduction band of the ZnO QDs, which in turn increased the conductivity owing to a decrease in resistance. Acetone was detected based on the changes in resistance of the ZnO QD sensor.

Fig. 3(a) shows the top-view SEM image of the ZnO QD sensor. The dark area represents the Al_2O_3 substrate, the bright area denotes the Pt electrode, and the area indicated by the circle shows the dispersed ZnO QDs [Fig. 3(a)]. The interdigitated Pt electrodes were positioned 5 μm apart from each other on the Al_2O_3 substrate. ZnO QDs were then dispersed on the Pt electrodes. Fig. 3(b) shows the low-resolution TEM image of the synthesized ZnO QDs. The QDs were predominantly clustered, but some of the isolated particles had a spherical morphology. The average size of the QDs was about 6 nm. The high-resolution TEM image in Fig. 3(c) displays the clear lattice structure of the ZnO QDs, indicating their high crystallinity. The inset in Fig. 3(c) shows the fast Fourier transform (FFT) images of the ZnO QDs. The FFT image shows a spotted pattern that demonstrates the crystallization of the QDs. The crystal structure of the ZnO QDs could be ascribed to hexagonal wurtzite. The measured d-spacing values of the (010) and (−101) planes of the ZnO QDs were 0.281 and 0.248 nm, respectively. Fig. 3(d) shows the scanning tunneling electron microscopy and EDS images of the ZnO QDs. EDS elemental mapping of both Zn and O revealed that the QDs were composed of uniformly distributed Zn and O. We also performed X-ray diffraction of the ZnO QDs; the patterns showed peaks corresponding to the (100), (002), and (101) planes, confirming the presence of a hexagonal wurtzite phase (JCPDS #36-1451) without any secondary phase. The characterizations of the ZnO QDs were reported elsewhere [41].

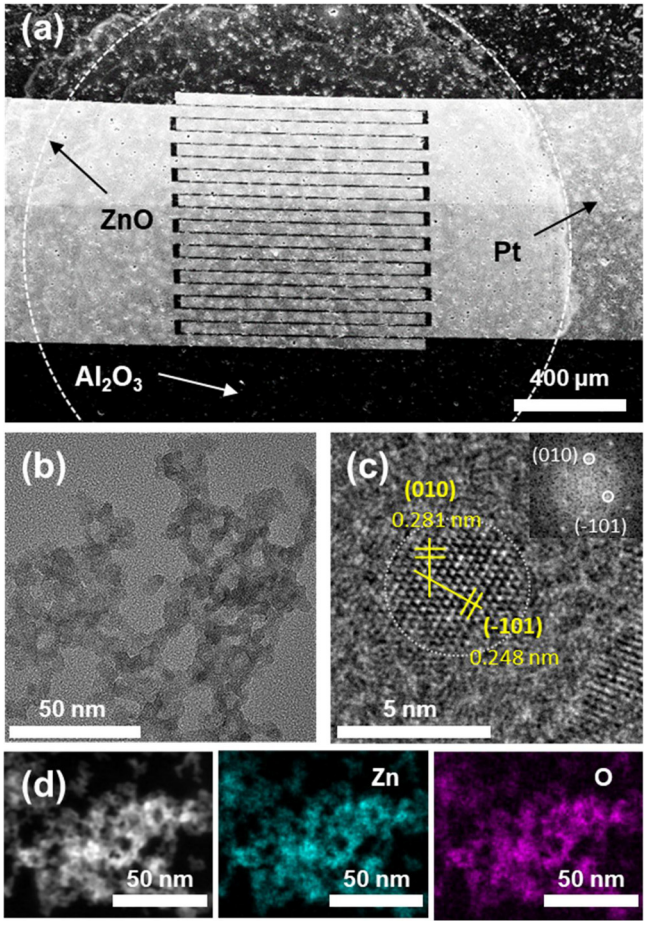

Fig. 3. (a) Top-view SEM image of ZnO QD sensor. (b) Low- and (c) high-resolution TEM image with FFT pattern (inset). (d) EDS images of ZnO QDs.

Fig. 4(a) shows the air-balanced acetone responses ($\Delta(log(R))$) for various acetone concentrations at 430 °C. The responses of the ZnO QD sensor at 430 °C were 0.027, 0.054, 0.088, and 0.261 for acetone concentrations of 0.1, 0.5, 1, and 5 ppm, respectively. Clearly, the response increased with increasing acetone concentration. The figure also shows the strong correlation between the response and the acetone

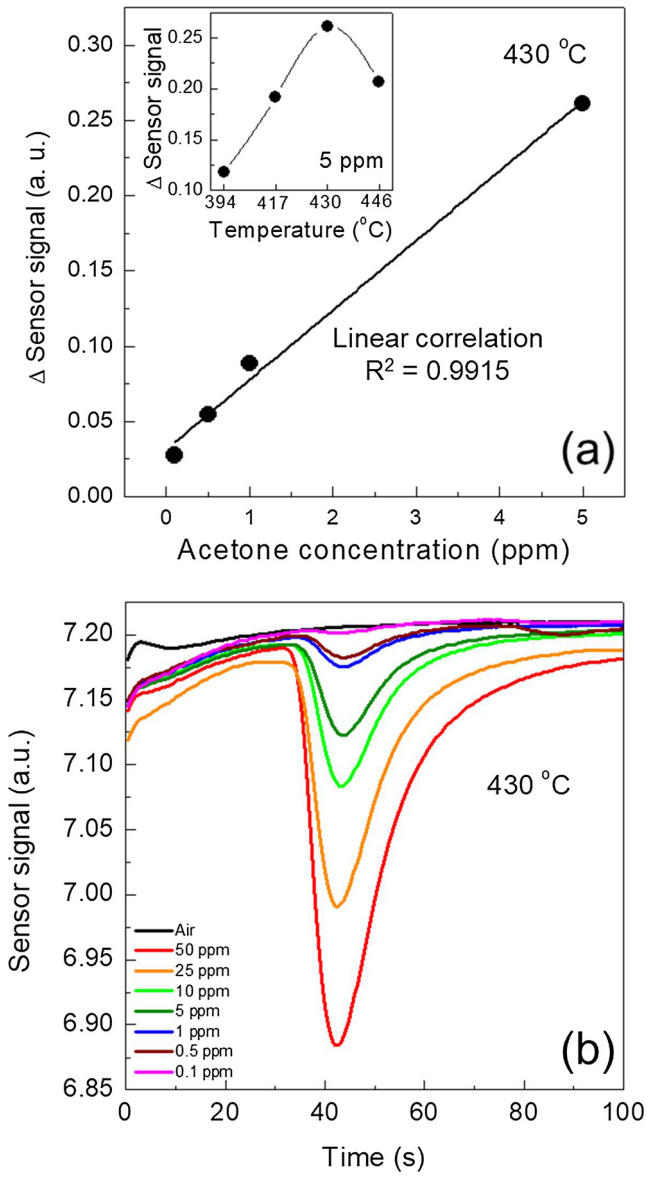

Fig. 4. (a) Responses with various acetone concentrations (0.1–5 ppm) at 430 °C and response with 5 ppm acetone at 394–446 °C (inset). (b) Sensor signal changes for various acetone concentrations (0–50 ppm) at 430 °C.

concentration. A linear fit of the data revealed an R^2 value of 0.9915, indicating the linearity of the sensor response. The inset image shows the air-balanced acetone sensing properties at various temperatures. The responses of the ZnO QD sensor for an acetone concentration of 5 ppm were 0.118, 0.192, 0.260, and 0.206 at temperatures of 394, 417, 430, and 446 °C, respectively. The response of the sensor increased with temperature up to an operating temperature of 430 °C and decreased above 430 °C. The optimal operating temperature of the ZnO QD sensor was thus determined to be 430 °C. Fig. 4(b) represents the *log (R)* changes of the ZnO QD sensor with time for various acetone concentrations (0–50 ppm) at 430 °C. No resistance changes in the ZnO QD sensor were detected when the acetone concentration was zero. The resistance of the ZnO QD sensor for acetone began to decrease at 32 s, reached the minimum value at 42 s, and then recovered. Consequently, acetone was released from the column at 32 s due to the interaction with the stationary phase, and the ZnO QD sensor maximally reacted with acetone at 42 s. The signal changes of the ZnO QD sensor at 32 and 42 s were 0.305, 0.188, 0.108, 0.070, 0.023, 0.017, and 0.001 for acetone concentrations of 50, 25, 10, 5, 1, 0.5, and 0.1 ppm,

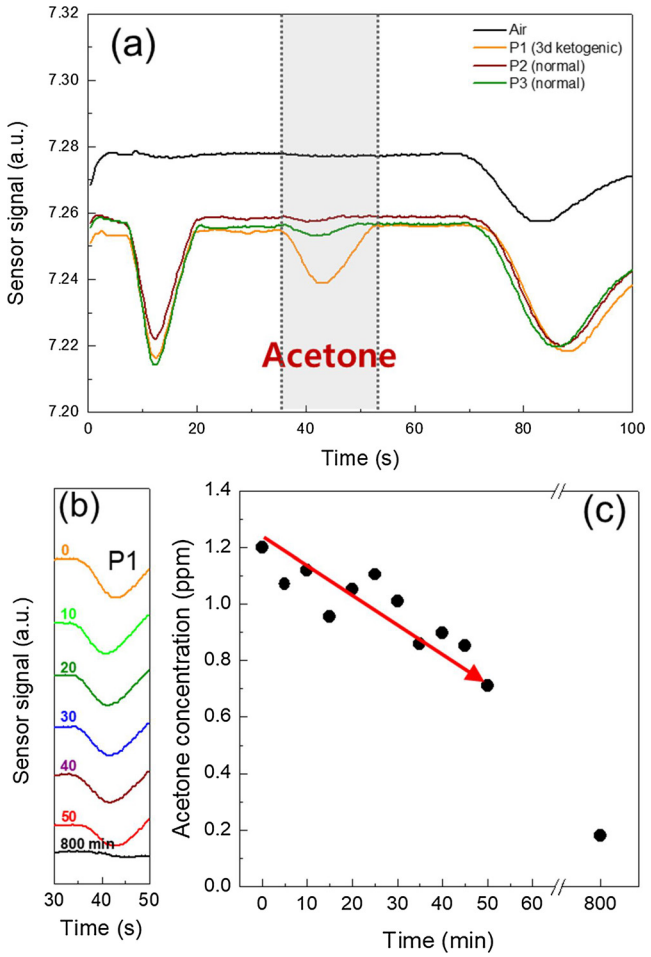

Fig. 5. (a) Breath analysis results for volunteers on ketogenic diet and normal diet for three days. Results for volunteer who was on ketogenic diet and then consumed carbohydrates: (b) sensor signal and (c) breath acetone concentration as a function of time.

respectively. The changes in the resistance due to reaction with acetone decreased with decreasing acetone concentration. As the acetone concentration decreased, the thickness of the depletion region decreased due to reaction of O^{2-} with the surface acetone.

Fig. 5(a) shows the air and breath test results for the three volunteers. The results of the air test showed a peak only near 80 s. However, three peaks at 12 s, 42 s, and 86 s were detected from human breath. The second peak represented the emission of acetone, and the corresponding time matched the detection time of air-balanced acetone. These values were similar to those mentioned in a previous report (before ketogenic diet: 0.17 ppm; after ketogenic diet for three days: 0.98 ppm) [13]. Fig. 5(b) shows the breath analysis data of subject P1, who was on a ketogenic diet for three days; as shown in the figure, the acetone concentration changed with time after the consumption of a quantity of carbohydrates. The change in *log(R)* at 0 min for P1 (after the ketogenic diet and before consuming carbohydrates) was higher than that for the other volunteers. Further, the changes in the signal decreased with time. Fig. 5(c) shows the breath acetone concentration change for P1 with time, from 0 to 800 min, after the consumption of carbohydrates. The breath acetone concentration was 1.2 ppm before carbohydrate intake, and it steadily decreased with time, reaching 0.71 ppm at 50 min. The breath acetone concentration after 800 min was 0.18 ppm, which was similar to that for the volunteers on a normal diet.

4. Conclusions

In this study, we developed a breath acetone analyzer integrated with a sensor based on ZnO QDs and a miniaturized GC column filled with a packing material. This sensor could be used for the analysis of small volumes of human breath (1 ml), and could detect breath acetone without pre-concentration in real time with high sensitivity and selectivity. The 6 nm ZnO QDs synthesized by a wet chemical method could detect up to 0.1 ppm acetone. The response of the ZnO QD sensor increased with increasing acetone concentration and was strongly correlated with the gas concentration (R^2 = 0.9915). Breath acetone was effectively released from the packed column at 32 s. This analyzer was used to perform breath analysis on volunteers who were on a ketogenic diet and a normal diet. The breath acetone concentration of the volunteer on a ketogenic diet for three days was 1.2 ppm. After carbohydrate intake, the acetone concentration steadily decreased to 0.18 ppm, which was almost identical to that for the volunteers on a normal diet. We demonstrate that the breath acetone analyzer can be used for clinical applications as it is cost-efficient and portable, facilitates real-time analysis, and has high selectivity and sensitivity.

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