Microsystem in LTCC Technology to the Detection of Acetone in Exhaled Breath

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***Abstract*—An acetone is a well-known diabetes biomarker, since patients with diabetes tend to have higher acetone levels in their breath than healthy people. Exhaled acetone levels are usually in the range of 0.3-0.9 ppm (parts per million) for healthy subjects and over 3 ppm for patients with diabetes. Commercially-available gas sensors are under development for measuring samples at several tens ppm. Due to this fact, the microsystem with micropreconcentrator and sensor array is proposed as a solution that overcomes these limitations. The microsystem designed by author was manufactured in LTCC (Low Temperature Cofired Ceramics) technology. The microsystem based on micropreconcentrator structure as well as metal oxide gas sensors array. Acetone in diabetic breath was found to be higher than 1.11 ppm, while its concentration in normal breath was lower than 0.83 ppm.**

***Index Terms*—Breath analysis, low temperature cofired ceramics (LTCC), exhaled acetone measurements, micropreconcentrators.**

I. Introduction

Breath analysis has been developed for many years and there have been many instances of research into its potential for diagnosing diseases [1], [2]. It has the potential for the monitoring of early stages of lung cancer [3], [4], liver diseases [5], asthma [6], [7], halitosis [8], diabetes [9]-[11], and more. It is a promising tool for noninvasive, real-time illnesses diagnostics, metabolic status monitoring and for drug monitoring [12]. The main advantages of breath tests over conventional laboratory tests can be summarized as follows: non-invasive, safe and painless. They can be performed anywhere, especially at home without assistance of a well qualified personnel. Moreover, the breath analysis is fast, cheap, more flexible than a urine analysis and more comfortable than a blood analysis. Until now, more than 3500 compounds have been identified as present in exhaled human breath [13]. A part of them are known as biomarkers. It means that the certain biomarkers present in exhaled breath could be correlated to certain disease. Extensive studies have been conducted to identify and quantify correlation between exhaled VOCs and certain diseases [14]-[16]. The author focused on one of them - acetone [17]. It is produced normally in the human body, primarily results from the spontaneous decarboxylation of the acetoacetate and to a lesser extent from enzymatic conversion of acetoacetate to acetone [18]. The exhaled acetone is usually in the range of 0.3 - 0.9 ppm for healthy people, and over 3.0 ppm for people with diabetes [19]. Acetone and other volatiles in breath are present in nanomolar quantities. In order to measure such low concentrations the laboratory systems are applied. They can be divided into two groups: on-line methods, i.e. proton transfer reaction mass spectrometry (PTR-MS) [20], atmospheric pressure chemical ionization mass spectrometry (APCI-MS) [21] and off-line methods such as: gas chromatography - mass spectrometry (GC-MS) [22], selected ion flow tube mass spectrometry (SIFT-MS) [23] based on sample preconcentration. Those methods are in fact very expensive and required a well qualified personnel, therefore their use is exclusively restricted to the laboratories. Based on literature review, exhaled breath acetone measurement in its developmental stage is currently characterized by intensive studies and creation of experimental prototype devices [24]-[26].

In this paper the microsystem based on micropreconcentrator and gas sensors array manufactured in LTCC technology is presented.

II. Experimental

A. Measurement Setup

A schematic view of measurement setup is presented on Fig. 1. It consists a few parts as follows: microsystem in LTCC technology based on micropreconcentrator and gas sensors array placed in gas sensor chamber, gas valve, carrier gas – in this case nitrogen, RH (relative humidity) filter and Tedlar Bag with collected breath from diabetes patients and healthy controls. A LabView VI was written to control the data acquisition for the experiment.

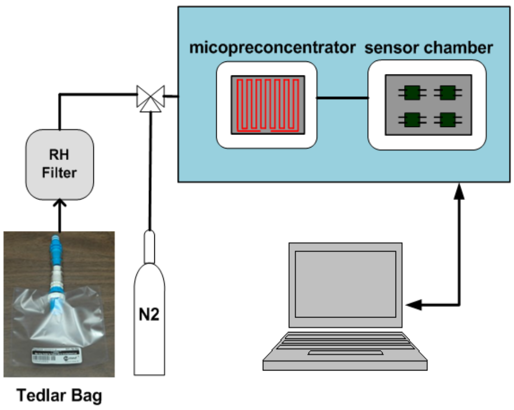

Fig. 1. A schematic view of measurement setup to the detection of exhaled acetone.

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B. Micropreconcentrator Structure

The micropreconcentrator structure was previously precisely described in [27]. Briefly, it consists eight layers of LTCC green tapes with spiral-shaped channel filled with adsorbing material. In this study, the commercial available Carboxen-1018 (Sigma-Aldrich) was used. The structure is 1.2-mm thick and has lateral dimensions of 25 × 20 mm. Two heaters covered by the ceramic foils are embedded over and below the channel. The heaters are required for heating the adsorbent to the desorption temperature. The best concentration factor obtained was 5250 for pure acetone and 100 for exhaled acetone. The top view of manufactured micropreconcentrator with assembled inlet/outlet nanoports is presented on Fig. 2.

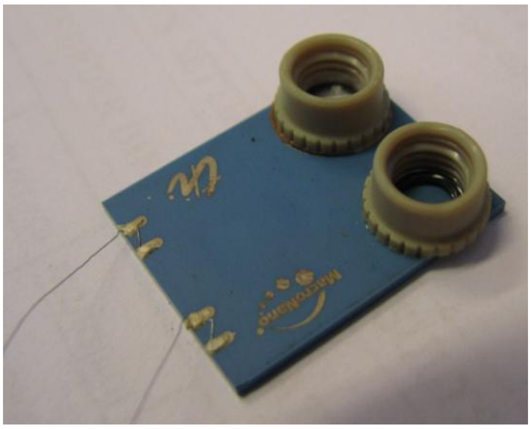

Fig. 2. Top view of manufactured micropreconcentrator with assembled inlet/outlet nanoports.

C. Gas Sensors Array

The author mounted the four metal oxide (MOX) gas sensors in a sensors chamber with Pt100 resistor (Fig. 3). The Pt100 resistor was used to measure the temperature inside the chamber with and without gas flowing through it. The MOX sensors work in higher temperatures, usually in the range of 300-500^{o}C or even higher [28], [29]. Due to this fact, the heater is embedded together with the sensitive part and a correct management of the sensor heating needs to be assured.

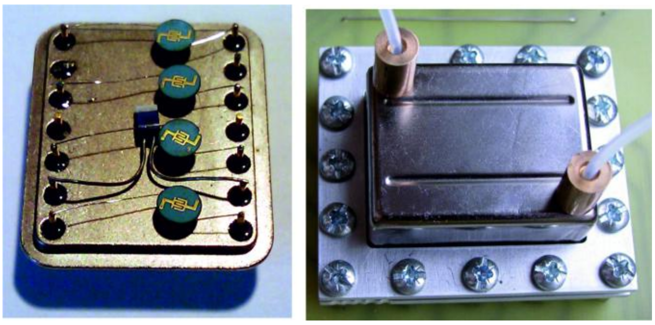

Fig. 3. The gas sensors chamber with Pt100 temperature sensor before and after the encapsulation.

To reduce the power consumption the novel topology of gas sensors array is under investigation. The four gas sensors will be placed in one cover (Fig. 4) also made in LTCC with lower thermal conductivity coefficient. In addition to a normal heating management, in which the sensor is kept at a constant temperature, in proposed solution the gas sensors temperature modulation will be applied. The proposed solution is still under investigation and it is patent pending.

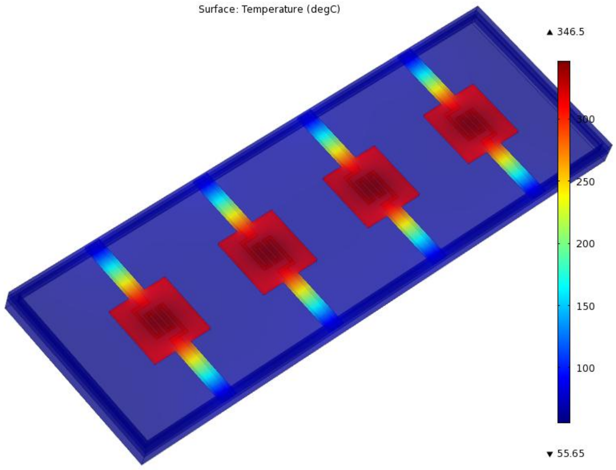

Fig. 4. Thermal simulation of gas sensors array made in LTCC technology.

D. Breath Collection

All experiments involving human subjects were performed according to the "Declaration of Helsinki" and in accordance with Polish law. All patients and volunteers declared a written consent to participate in the investigation. As a reference gas the certified acetone in the concentrations: 80 ppm, 8 ppm and 0.8 ppm (Air Products) was used. The breath samples were collected with Tedlar Bag of 1.0 L volume. Prior to the use, the new bags were cleaned three times by using pure (99.9999%) nitrogen. Additionally, after each measurement the bags were purified with pure N_2 to remove any contaminations. Twenty five volunteers (11 healthy controls, 14 patients with diagnosed diabetes) were asked to breath into breath bags and measured glucose in blood using conventional and commercial available glucometers. All patients and volunteers attended ten visits within a 2-week period.

E. Measurement Procedure

The experimental procedure consisted of few stages. Firstly, the micropreconcentrator is conditioned under specific parameters. The author used a typical time-temperature profile for adsorbent made with Carbon Molecular Sieve. To start with, the temperature was around 100^{o}C for at least 30 minutes. Then, it was increased to 200^{o}C and 300^{o}C for 1h, respectively. At the end, the temperature was set to 350^{o}C for around 30 minutes. The flow rate was set to 25 sccm (standard cubic centimeters per minute). The total measurement time was equal 32 min (the Tedlar Bags are filled with 800 ml exhaled breath). However, the stable response was obtained after 10 min preconcentration time.

F. Concentration Factor

The concentration factor is defined as a ratio of gas concentration after and before the preconcentration process (i.e. the ratio of peak area before and after desorption). The concentration factor is different for different adsorbent material and measurement conditions. Based on investigation results, the author used Carboxen-1018 as an adsorbent material. It is also recommended by Sigma-Aldrich company as a suitable for preconcentration volatile organic compounds present in exhaled breath. Fig. 5 shows acetone concentration before and after preconcentration for three different adsorption times: 5 min, 10 min, and 30 min.

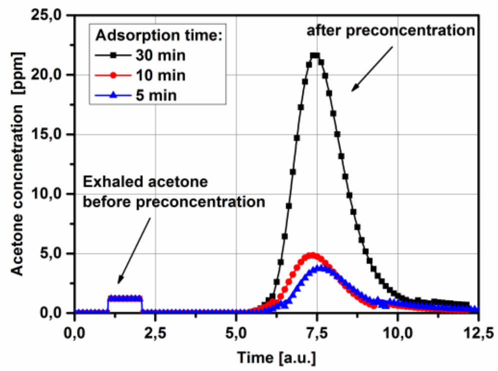

Fig. 5. Acetone concentration before and after preconcentration for three different adsorption times: 5 min, 10 min, 30 min.

III. Results

Based on the successful sample preconcentration with the micropreconcentrator structure, breath acetone samples taken from diabetes patients and healthy volunteers were determined. Acetone concentrations in 14 diabetic patients and 11 healthy volunteers were summarized in Table I. The median acetone in healthy group was 0.63 ppm, while in diabetic patients breath was 2.08 ppm. The acetone concentration in normal breath was ranged from 0.49 to 0.83 ppm and was in the range of 1.11 to 3.11 ppm for diabetic patients. The obtained results are in accordance with the results reported in [30]-[32].

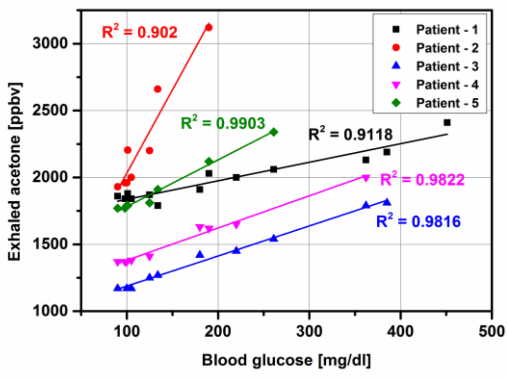

Fig. 6. Blood glucose concentration vs. exhaled acetone concentration for patients with type-1 diabetes.

Fig. 6 shows relations between breath acetone as measured by microsystem and blood glucose. There is a linear correlation between breath acetone and blood glucose concentration for each diabetic patients. Therefore, it is obvious that a direct and absolute relationship between blood glucose and exhaled acetone does not exist [33]. However, the high value of the linear coefficient allows to conclude that there is a possibility to use exhaled acetone as a supplementary tool in diabtets diagosis.

It is obvious, that some calibration measurements are necessary before using exhaled breath acetone as the supplementary tool for diagnostic diabetes. The microsystem can be calibrated i.e. by performing OGTT (Oral Glucose Tolerance Test). The response drift of gas sensors has to be taken into consideration as well. Currently, the response drift is under investigation by author.

TABLE I: The Mean Breath Acetone Level for Healthy Volunteers and Diabetic Patients

Subject no	Group	Mean Breath acetone [ppm]	Age	Male
1	Diabetic	1.61	33	Female
2	Diabetic	2.32	23	Male
3	Diabetic	2.28	22	Male
4	Diabetic	1.73	29	Female
5	Diabetic	2.31	23	Male
6	Diabetic	1.45	25	Female
7	Diabetic	2.32	21	Female
8	Diabetic	2.17	40	Female
9	Diabetic	1.77	23	Female
10	Diabetic	2.50	20	Male
11	Diabetic	1.83	24	Male
12	Diabetic	2.14	22	Female
13	Diabetic	2.30	55	Female
14	Diabetic	2.37	35	Female
15	Diabetic	2.78	60	Male
16	Healthy	0.53	43	Male
17	Healthy	0.50	30	Female
18	Healthy	0.73	28	Male
19	Healthy	0.77	41	Male
20	Healthy	0.69	32	Female
21	Healthy	0.58	28	Male
22	Healthy	0.65	30	Female
23	Healthy	0.63	39	Female
24	Healthy	0.59	26	Male
25	Healthy	0.71	29	Male

IV. Conclusion

The main goal of the proposed microsystem in LTCC technology based on sensors array and micropreconcentrator structure is a fast and quantifiable determination of acetone in the exhaled breath for real time measurements and low costs. It is an alternative for the microsystems in silicon technology, widely discussed in literature [34]-[36]. The LTCC technology provides possibility to manufacture stacked multi-chip-modules (MCM). The micropreconcentrators in MCM technology ensures a higher concentration factor without a significant increase in adsorption time. Such solution is under investigation and it is in the process of patent pending.

Further basic research studies in this area may provide additional insight into diabetes diagnostic using exhaled acetone analysis. According to the data provided by the World Health Organization, in 2004, an estimated 3.4 million people died from consequences of high fasting blood sugar. Therefore, the investigation

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