FROM MATERIALS INVESTIGATION TO NON-INVASIVE DIABETES DIAGNOSIS*

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The paper presents some investigation on material properties which are candidates for a gas sensor. The best choice was semiconducting oxides such as WO_3, CuO, SnO_2, TiO_2. The materials properties were optimized to obtain the most sensitive gas sensor. Gas sensor matrix was used to build portable device for non-invasive diabetes diagnosis. The design of measuring device for glucose level in blood from the exhaled air gas content is presented. The components of device such as gas preconcentrator, gas sensor, integrated gas sensor matrix and a measuring method are described. The advantages of such a device were presented for portable, personal model as well as a hospital once.

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1. Introduction

John Whitehead, grandson of the founder of the world's largest clinical laboratory instrument company (Technicon Instruments), was visibly excited. The year was 1982, and the picture he was holding was a wristwatch, displaying "Blood Glucose = 107." "Wouldn't that be great!" he bubbled, "No more trips for diabetics to the doctor to measure blood sugar, no more need to stick a needle in your finger to make measurements at home."[1]

The only problem then, and for at least the next 40 years, was that it didn't work.

The gas sensors have been investigated for the last few decades, and the first commercially available gas sensor was launched on the market in 1968 by Figaro Company and is still available. Since then, the gas sensors market has increased year by year and it is now assumed to be worth 1.2 billion USD in 2022 [2]. Generally, the gas sensor consists of a gas-sensitive layer, gas

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sensor substrate with electrodes, package and front-end electronic circuits. The gas sensors properties such as sensitivity and selectivity are determined by the gas-sensitive layer, which can be realized in many different forms including organic and non-organic materials. One of the common group of the materials utilized for gas-sensing applications are metal oxides [3]. There is a number of papers, where gas-sensing behaviour of various MOXs is presented in various applications such as industrial environment monitoring [4], air pollution control [5], air quality control [6], automotive [7] and, recently, in the medical diagnostics for exhaled breath analysis [8–11]. The exhaled human breath consists of major elements and compounds such as nitrogen, oxygen, carbon dioxide, water vapour and volatile organic compounds, mostly in the ppb-ppm range. So far, 3500 different VOCs have been detected in the exhaled human breath and it was proven that a single breath consists at least of 500 various VOCs [12]. Some of them were named biomarkers, since their presence can be used for diagnostics, for instance, NO_2 (asthma) [13] H_2O_2 (chronic obstructive pulmonary diseases) [14], NH_3 (chronic kidney disease) [15], C_2H_6 (renal failure) [16], C_3H_6O (diabetes) [17]. One of the global disease is diabetes. The number of patients with diabetes is rapidly rising in middle and low income countries. The number of people with diabetes has risen from 108 million in 1980, 422 million in 2014, over 500 million in 2020, and an estimation for 2045 is 629 million (Fig. 1). About 1.6 million deaths were directly caused by diabetes and also it is a major cause of heart attacks, stroke and lower limb amputation or blindness. WHO estimates that this disease was the seventh leading cause of death in 2016 [18]. All these facts push us to start investigation on materials and develop a device for comfortable control of glucose level in blood.

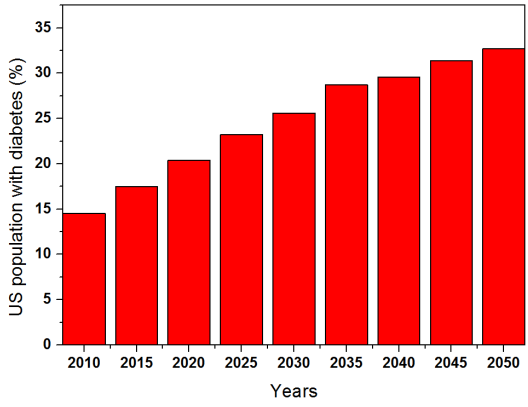

Fig. 1. Projecting the future diabetes population [19].

The development of non-invasive method to replace the conventional invasive one is a driving force for researchers all over the world. The material investigation is focusing on gas-sensitive materials that can be used for portable exhaled acetone detectors. There are several requirements for such devices: the sensitivity in the sub-ppm range, since exhaled acetone is in the 0.2–0.8 ppm and over 2.5 ppm for healthy and diabetes, respectively; the high selectivity due to high presence of interfering compounds in the exhaled breath, including humidity; long-term stability comparable to conventional blood glucose analyzers-glucometers. All mentioned above properties are realized by developing all parts of the gas sensors, however, the gas-sensitive layer is the most crucial due to the chemical–physical reactions that occur. The most common MOX used for the exhaled acetone detections are: SnO_2, TiO_2, In_2O_3, ZnO, WO_3, Fe_xO_y, CuO, all of them were recently presented and discussed in the review paper [20].

In this paper, the development path from material investigation to portable exhaled breath analyzers for acetone detection is presented.

2. Selected metal oxides for acetone detection

As it was mentioned above, the main role in the gas sensors play the gas-sensitive layer, mostly based on the metal oxides, including single compounds as well as heterostructures [21]. There are various depositon methods for metal oxide deposition such as sol-gel [22], CVD [23] and vacuum-based magnetron sputtering (MS) technology [24]. The MS technology which is well-known technique for industrial applications mostly takes the possibility to be integrated in CMOS processes, where gas-sensitive layers as well as gas sensors substrates, and front-end electronics can be realized in one technology during the designed technological process. Moreover, the MS technology has been used by the authors since 1985, therefore, such a technique was used for MOX deposition.

2.1. CuO

CuO phase with *p*-type semiconducting property is reported as a gas-sensitive material. Copper compounds are mainly in the oxidation states +1 and +2 in its normal chemistry. The authors have demonstrated the Cr:CuO thin films with the highest response at 450°C (3.2 ppm of acetone). The obtained detection limit was $\sim$ 0.4 ppm — it is below 1 ppm, so this sensor is a very good candidate for acetone detection in sensor matrix for diabetes measurements. Next experiments are necessary for lowering the operating temperature.

2.2. WO_3

Tungsten oxide WO_3 is the most common metal oxide used in sensors for exhaled acetone detection. The tungsten oxide exhibits *n*-type conducting behaviour for both types of surface reaction (oxidation and reduction). Li *et al.* [25] have presented the investigation of Ru-loaded WO_3 nanoparticles with the highest response (R_a/R_g) obtained for 1 w.t.% Ru and it was around 7.3 at 300°C/1.5 ppm [25]. The acetone sensors based on WO_3 nanofibers were proposed by Kim *et al.* [26] with hierarchically interconnected porosity with 10.80 response at 1 ppm of acetone and high humidity atmosphere (90% RH). The acetone sensing characteristics for gravure-printed WO_3/Pt-decorated rGO nanosheets composites were shown by Chen *et al.* [27]. The top response value was 12.2 to 10 ppm at 200°C [27]. The selective acetone sensor based on iron and carbon codoped WO_3 with hierarchical walnut-like microstructure were presented by Shen *et al.* [28]. The maximum response (~ 17) was obtained for 0.992 at % Fe/WO_3 at 300°C to 10 ppm of acetone [28]. The main goal of the investigations carried out by the authors is to develop the device for analysis of the exhaled acetone concentrations based on the metal oxides' sensors. Low Temperature Cofired Ceramics (LTCC) technology was used in sensor substrates. The view of such an array is presented in Fig. 5 and more details could be found elsewhere [29]. The authors [20] have developed the Si-doped WO_3 thin films deposited by GLAD magnetron sputtering for the acetone detection (Fig. 2). The highest signal of (R_a/R_g) was observed for thin film deposited and annealed in 300°C, and under exposure to 1 ppm of acetone. Detection limit for such a sensor was below 1 ppm and it was equal to 0.16 ppm. It means that Si-doped WO_3 sensor is the great candidate for diabetes sensor for integrated sensor matrix [29, 30].

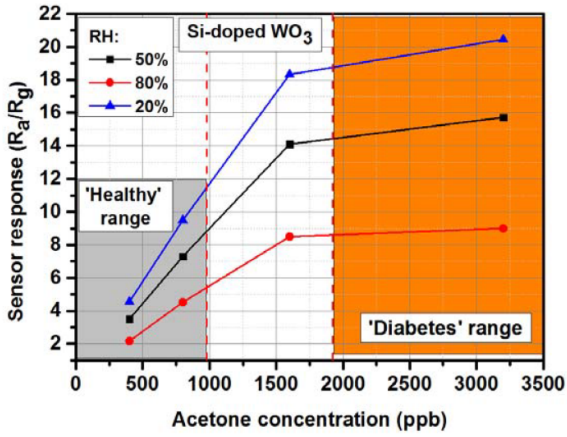

Fig. 2. The "healthy" and "diabetes" regions in Si-doped WO_3 acetone sensor (RH: Relative Humidity). Reprinted from [20] CC BY 4.0.

2.3. SnO_3

Among the semiconducting metal oxides, tin oxides have the longest story of investigations as a gas-sensing material. The SnO_2 was extensively studied material for enhanced acetone detection. The recently published results are summarized in Table I.

2.4. TiO_2

Titanium dioxide is most thoroughly studied metal oxide, and it exhibits n-type behaviour. Its composition strongly influences its gas sensing properties, hence many scientific groups are working currently on this material with special emphasis on its different nanostructures. Park [31] has presented the investigation results of TiO_2 nanoparticles functionalized In_2O_3 nanowires for exhaled acetone measurements. The measurements were carried out as a function of acetone content starting from 0.1 ppm to 10 ppm at 250°C. The sensor responses (R_a/R_g) were equal to 4.07 up to 33.34, respectively. The detection mechanism was precisely described, so this material becomes very attractive for a commercial use [31].

TABLE I

Parameters of different acetone sensors.

Material	Maximum response (R_a/R_g)	Acetone concentration [ppm]	Operating temperature [°C]	Reference
NiO/SnO_2	20.18	50	300	[32]
2D C_3N_4-SnO_2	11	20	380	[33]
GO-SnO_2-TiO_2	60	5	200	[34]
WO_3/SnO_2	66.5	50	200	[35]
SnO_2 decorated SiO_2	2193.7	300	270	[36]

3. Gas sensors arrays

Exhaled air analysis is not an easy case while it contains about 4000 components. There are few selected gases which are the markers for particular disease. It is the reason we designed an integrated gas sensor matrix [37] to collect data for selected disease (in our case diabetes). The matrix consists of several sensors for diabetes marker detection, and additionally for CO_2 and water vapour. The design of sensor arrays is presented in Fig. 7 together with all other components of the diagnostic device.

3.1. Preclinic tests

The preliminary preclinic tests were made for eleven healthy volunteers with no history of any respiratory disease. Two persons participating in the research were special. The first one was a heavy smoker (male) and the second one a pregnant woman. There were five young women with an average age of 31 years and six men with the average age of 33 years. Volunteers attended ten visits in the Department of Electronics AGH, Kraków, Poland within two weeks. The analysis of exhaled acetone was performed in two periods. In the morning between 8:00 am and 3:00 pm for nine volunteers, and in the afternoon between 3:00 pm and 8:00 pm for another two. The similar preparation to blood investigation were used. The subjects were asked to inhale moderately after five minutes of rest and then to exhale in the 1-l breath bags and once more after 2 h following the consumption of 75 g of glucose. Gas samples in the breath bags were analyzed using the MS with micropreconcentrator structure. The glucose content in the blood was measured using a commercial glucometer Accu Check Active (Roche Diagnostics©, Basel, Switzerland). Both the breath acetone measurement as well as the blood glucose content measurement were performed at least twice to avoid any incidental results.

3.2. Diabetes patients breath analysis

Exhaled air of fourteen patients diagnosed with type-1 diabetes was analysed pararelly to measuring glucose in blood using their own glucometers. There were two groups. First one — eight women with an average age of 31 years and the second one — six men with an average age of 25 years. The patients used different glucometers. Ten of them used Acuu Check Active (Roche Diagnostics©, Basel, Switzerland), four patients used One Touch Mini Select (LifeScan, Inc.©, Milpitas, CA, USA), Contour TS (Bayer GmbH©, Leverkusen, Germany), Acuu Check Go and Acuu Check Performa (Roche Diagnostics©, Basel, Switzerland), respectively (Fig. 3). The breath testing procedure was the same for patients as well as for the healthy volunteers. Relations between breath acetone as measured by mass spectrometry and blood glucose is presented in Fig. 3.

3.3. Device components

Two types of the devices for glucose level determination from diabetes marker measurements in exhaled air were designed and tested. All important components were developed and patented. First component of a measuring line is a gas preconcentrator. It is an important part, because diabetes marker levels are still below sensitivity range of the commercial sensors. The preconcentrator permits to collect residual gases to overcome the problem.

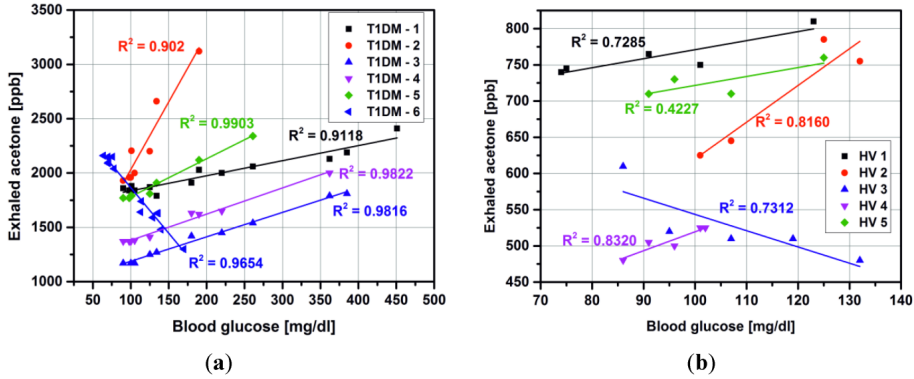

Fig. 3. Relations between breath acetone as measured by mass spectrometry and blood glucose for T1DM subjects (a) and healthy volunteers (b) (copyright CC BY 4.0) [38].

The Low Temperature Cofired Ceramics LTCC version of preconcentator is presented in Figs. 4 (a) and 4 (b). The concentrator channel is filled with nanoballs which selectively adsorb diabetes markers. After the temperature from the heater desorbes the measured gas, then one can measure the marker content even with a commercial sensor. Gas sensor is next and the most important component of both types of the devices. The LTCC version of three layers design is presented in Fig. 4 (c). The sensor consists of three layers. The top one is a thin film semiconducting capacitor. The middle one is a layer of heater and the bottom one is a layer of electrical path and contacts. All thin and thick films are deposited on LTCC. This design could be used for different gas sensing materials such as WO_3, CuO, SnO_2 *etc.*, and we can detect different gas markers of diabetes. The level of all 4 diabetes markers have to be measure as well as CO_2 and water vapour level.

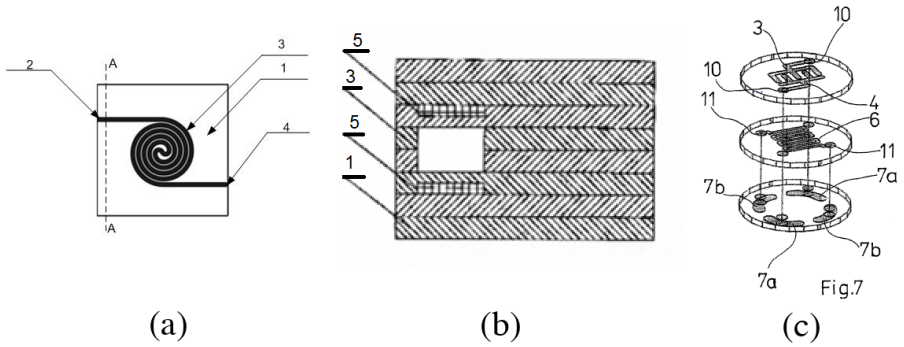

Fig. 4. Gas preconcentator. (a) — top view (1-LTCC, 2-inlet, 3-channel, 4 outlet), (b) — cros section (right) [39, 40], (c) — LTCC type sensor design, (3 — sensor, 6 — heater, 10,11,7 — metallic contacts) [41].

Hence, the design of six sensor matrix is used in both types of the device. The overview of integrated sensor matrix is presented in Fig. 5. This matrix was mounted in a standard IC case. An insuline pump could also be integrated with this devices. The scheme as well as the idea of measuring of diabetes marker starting from gas sensor via gas sensor matrix to measuring devices is presented in Fig. 6. The portable orange device from Fig. 6 could collect data on inner SD card or using low voltage bluetooth (LVB) in mobile phone send data to medical centre or personal doctor via data transfer or WiFi.

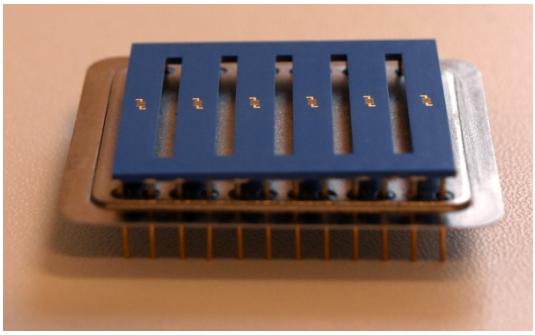

Fig. 5. Integrated gas sensor matrix [37].

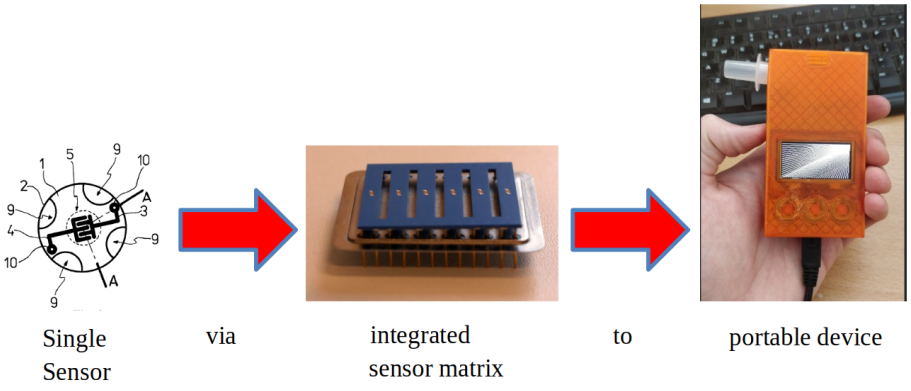

Fig. 6. (Colour on-line) From gas detection to diagnosis [38–44].

The measuring device contains also digital display for immediate presentation of the test result. Similar construction but different shape have hospital-type measuring devices. Some changes are done because of some additional needs. It means many fast measurements for different patient and obligatory printed personal data and the result of blood test.

The overview of one type of device is shown in Fig. 7 (a). The display of the device date, name and result of test is shown in Fig. 7 (b). Both devices were tested in lab with gas-chromatography method and some preclinic tests were done with several volunteers. Correlation between breath and blood (made with a standard glucometer) analysis was over 95%. Clinical tests are planned for the beginning of 2020 year.

Fig. 7. Diabetomat dedicated to hospitals (a), device display with result of measurement (b).

4. Conclusions

— The possibility to measure exhaled acetone as a biomarker for diabetes was proven;

— The linear correlation between exhaled acetone and blood glucose was confirmed;

— The various MOX have been tested, however, further investigations are still required to improve 3S parameters: selectivity, stability and sensitivity;

— Personal- and hospital-type devices were designed, tested and presented;

— A novel flexible solution was introduced [42–44].

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