ISSN 8756-6990, Optoelectronics, Instrumentation and Data Processing, 2014, Vol. 50, No. 4, pp. 411–416. © Allerton Press, Inc., 2014.
Original Russian Text © S.N. Atutov, N.A. Danilina, S.L. Mikerin, A.I. Plekhanov, M.M. Andrushkevich, E.N. Surkov, 2014, published in Avtometriya, 2014, Vol. 50, No. 4, pp. 107–113.

OPTICAL INFORMATION TECHNOLOGIES

Detection of a Small Admixture of Acetone in the Exhaled Air for Noninvasive Diagnosis of Type I Diabetes

S. N. Atutov[a], N. A. Danilina[a], S. L. Mikerin[a], A. I. Plekhanov[a], M. M. Andrushkevich[b], and E. N. Surkov[c]

[a] *Institute of Automation and Electrometry, Siberian Branch, Russian Academy of Sciences, pr. Akademika Koptyuga 1, Novosibirsk, 630090 Russia*
[b] *Presidium of the Siberian Branch of the Russian Academy of Medical Sciences, ul. Timakova 2, Novosibirsk 630117 Russia*
[c] *Research Institute of Physiology and Fundamental Medicine, Siberian Branch, Russian Academy of Medical Sciences, ul. Timakova 4, Novosibirsk, 630117 Russia*
E-mail: Natalia.d@russia.ru

Received June 7, 2013

Abstract—A method for measuring the concentration of a biomarker (acetone in human's breath), which is based on the use of glow-discharge emission spectroscopy in air is proposed for the purpose of noninvasive glucose monitoring in diabetes patients' blood. The experimental setup and measurement techniques are described, and preliminary results of clinical trials of the developed system under ambulatory conditions are presented.

Keywords: gas analyzer, glow discharge, spectroscopy, noninvasive medical diagnostics.

DOI: 10.3103/S8756699014040141

INTRODUCTION

It is well known that diabetes is a complex of metabolic disorders accompanied by an increased blood glucose level. This can lead to serious health complications, such as blindness, kidney failure, heart disease, and gangrene. Type I diabetes, which occurs as a result of the lack of insulin caused by autoimmune destruction of insulin-producing β-cells of the pancreas, requires an expensive life-long treatment with insulin. Many patients need daily multiple and painful capillary blood sampling for glucose monitoring, which makes patients frequently deviate from this virtually important procedure. It is particularly problematic for sick children. We also note rather low accuracy of blood glucose level measurement at home, which, according to the ISO 15197 standard, does not exceed $\pm 20\%$ for the available glucose meters [1]. Development of the method of noninvasive blood glucose level monitoring would allow patients to monitor this level and perform insulin therapy more accurately and effectively without a great psychological stress; moreover, diseases can be detected at an early stage if the method is sufficiently sensitive.

There are many publications on the study of the relationship of a number of gaseous compounds with different kinds of pathological processes in the human body and their possible use for diagnosis, monitoring, and treatment of various diseases [2]. For example, it was found that the substance concentration measurement (biomarkers in the exhaled air) can be used as a basis for diagnosing a number of serious diseases.

Several successful attempts to control the blood glucose level by measuring the acetone concentration in the exhaled air were described in [3–5]. Turner et al. [6] discovered a linear dependence of the acetone concentration on the blood glucose level, which demonstrates the feasibility of the method of noninvasive diagnosis of type I diabetes. However, it should be noted that all these experiments were carried out by using

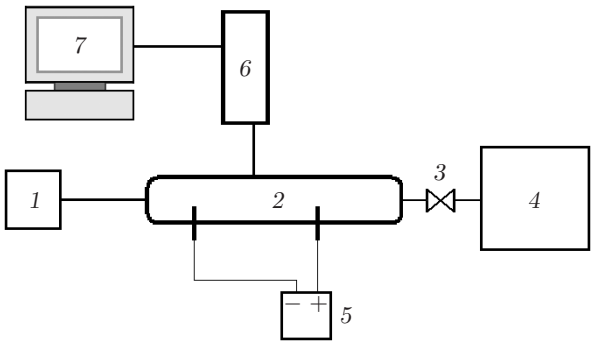

Fig. 1.

chromatographic and ion-drift mass spectrometers whose complexity, crockness, and high cost significantly constrain the widespread application of this technique. An analysis of the market of equipment for medical diagnosis of diabetes patients also shows the lack of commercially available low-cost devices that use this promising noninvasive method of glucose monitoring.

The aim of this work is to create a method of noninvasive medical diagnosis of type I diabetes based on detection of the biomarker traces (acetone in human's breath) by means of high-discharge resolution spectroscopy in air in the visible wavelength range. The advantage of emission spectroscopy over other well-known techniques is that it does not require the use of ultra-high vacuum and cryogenic temperatures. Emission spectroscopy in the visible wavelength range is insensitive to the presence of water vapors in the exhaled air due to the lack of strong water lines in this range and has a high spectral selectivity limited only by broadening of the emission lines because of the Doppler effect. Moreover, the high selectivity of this method is combined with a wide spectral range covering virtually all biomarkers needed for medical applications. The method is simple to implement, requires neither a carrier gas nor expensive consumables, and allows manufacturing compact devices that also suitable for using at home.

EXPERIMENTAL RESULTS AND DISCUSSION

The experimental setup shown in Fig. 1 consists of a vacuum pump *1*, glass cell *2*, adjustable gas inlet valve *3*, sample pretreatment chamber *4*, high-voltage source *5*, spectrometer *6*, and computer *7*.

The setup operated as follows: a sample of air in a mixture with a calibrated portion of acetone was prepared in the chamber and then introduced into the cell through the adjustable valve. Under ambulatory conditions, patients or volunteers breathed into the chamber to achieve a desired flow of the studied air in the receiving part of the setup. During this process, the pressure at a level of 10 Torr was maintained in the cell with the adjustable valve. Upon reaching the operating pressure, the glow discharge with a constant current of 8 mA was ignited in the cell. The emission radiation of the discharge was directed through a fiber-optic cable to the spectrometer, whose signal was recorded and processed by the computer. In this study, we used an Avantes AvaSpec-2048TEC fiber-optic spectrometer with high photometric sensitivity in the visible spectral range. A 50-μm wide spectrometer entrance slit and a diffraction grating with 600 lines per 1 mm provided a spectral resolution equal to 1.2 nm.

Spectrometer signals were processed in the following way: a laboratory air spectrum was recorded without introducing the test substance and then was used as a reference, after which the next analyzed discharge spectrum was recorded; then the relative emission spectrum was calculated by dividing the test spectrum by the reference spectrum.

The reference spectrum of laboratory air recorded in the spectral range from 335 to 882 nm is shown in Fig. 2. The dominant lines of this spectrum are due to N_2 band systems: the first and second positive systems are in the ranges from 600 to 882 and from 335 to 500 nm, respectively [7]. The atomic oxygen line in the 845 nm is due to O_2 dissociation in air. The line of 811.5 nm corresponds to Ar whose fraction in air is approximately 1% [8]. It should be noted that there are no water lines in the recorded spectra in the above-mentioned spectral range because they are mainly concentrated in the infrared, terahertz, and millimeter ranges of the electromagnetic spectrum. These lines often create serious interference in accurate spectroscopic measurements performed in certain spectral ranges.

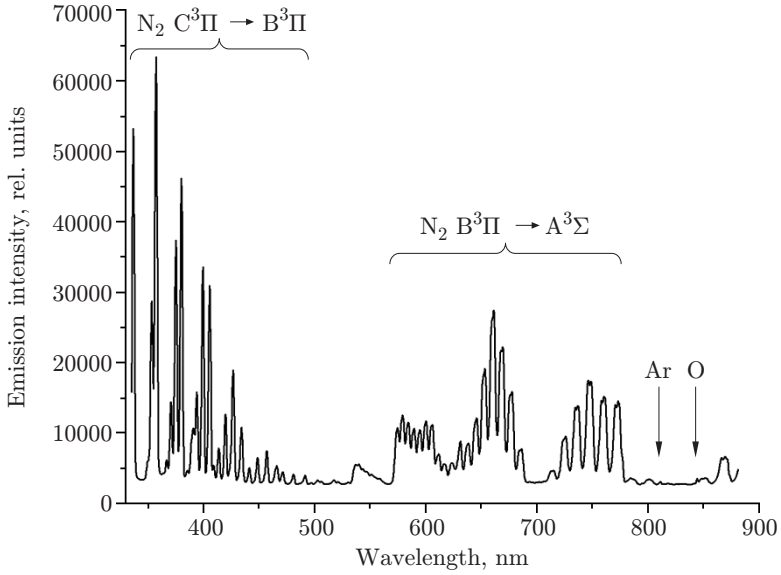

Fig. 2.

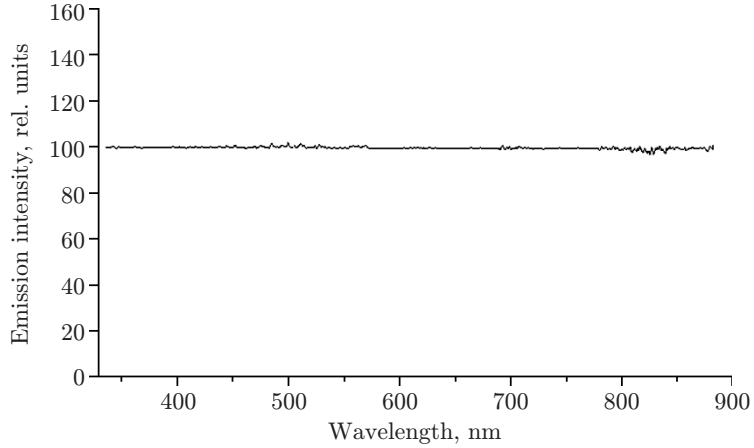

Fig. 3.

The relative spectrum obtained without introducing acetone into analyzed air is shown in Fig. 3. The spectrum is actually the result of dividing the reference spectrum of laboratory air by itself, which is why it is shaped as a straight horizontal line with noise, which varies from 1 to 5%, depending on the spectrum range.

It was found that addition of acetone vapors into analyzed air (the acetone concentration is 30 ppm) significantly modifies the relative spectrum (Fig. 4). This modification was due to changes in the discharge conditions. Due to the appearance of acetone vapors, a decrease in the discharge emittance lowered the overall signal level from 100% (see Fig. 3) to 70% (see Fig. 4), and the redistribution of intensities between nitrogen lines was manifested in the presence of two narrow dips in the ranges of 777 and 845 nm. Acetone is represented in the recorded spectrum by ten closely spaced lines in the spectral range from 380 to 580 nm. The bright lines with the wavelengths of 656 and 486 nm correspond to the hydrogen lines H_α and H_β of the Balmer series. The spectrum has also a number of unidentified weak lines and spectral bands.

We performed experiments on recording the acetone spectra in the absence of oxygen through the use of pure nitrogen and argon as a carrier gas. The resulting acetone spectra were indistinguishable from the spectra recorded in the air discharge. This result excludes the hypothetical possibility of distortion of the acetone emission spectrum due to acetone oxidation by atmospheric oxygen in the glow discharge.

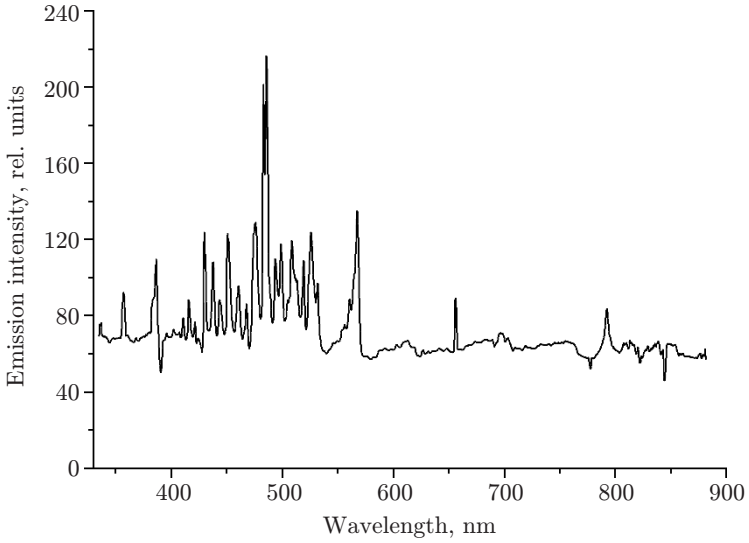

Fig. 4.

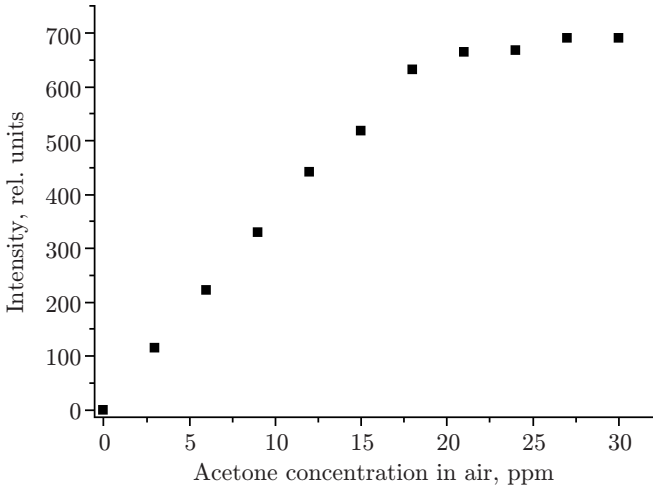

Fig. 5.

Figure 5 shows the dependence of the acetone spectrum intensity on the acetone concentration in air. The sample was pretreated by injecting precision portions of liquid acetone into chamber *4* (see Fig. 1), and the mixture was introduced into the cell after acetone evaporation. This dependence is linear with good accuracy at low acetone concentrations, and the curve reaches saturation at a concentration of approximately 17.5 ppm.

The saturation is due to a drop in the total discharge emission intensity because of the reduced temperature of electrons with a significant concentration of easily ionized components, which are acetone molecules. Note that the expected maximum concentration of acetone in the patients' breath is a value of the order of 10 ppm [9]. This makes it possible to work in the linear portion of the graph, which greatly simplifies the blood glucose level measurement process.

PRELIMINARY RESULTS OF CLINICAL TRIALS

Before each measurement, the emission spectrum of laboratory air was recorded and taken as a reference. Further on, we performed blood tests in order to find the glucose level by using a "Yellow Springs Instruments" glucometer. Then the patients breathed into the chamber for sample pretreatment until a

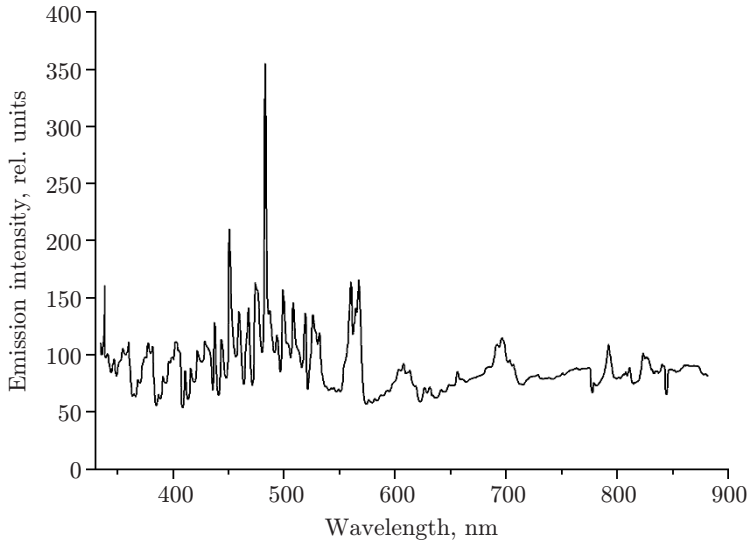

Fig. 6.

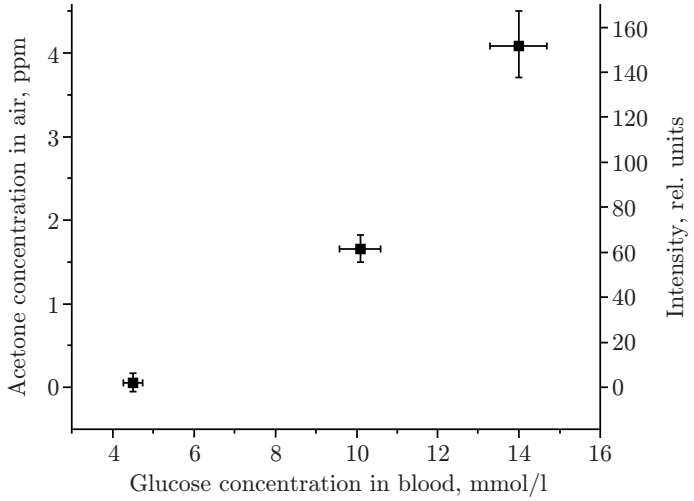

Fig. 7.

desired air flow in the receiving part of the setup was reached. These tests were performed for all patients on an empty stomach. Figure 6 shows the spectrum of exhalation of a patient who suffered from diabetes for ten years. The figure clearly shows the characteristic spectral lines of acetone similar to those presented in Fig. 4. The line at 337 nm corresponds to a molecular gas NO, which is a biomarker of such diseases as cancer of digestive organs, asthma, gastritis, and others [2]. In the range from 350 to 430 nm, there are wide spectral bands corresponding to methane, which is an indicator of a gastrointestinal tract disorder. Note the complete absence of water lines, although the water vapors constitute a significant proportion of the breath. In the spectrum, there are also a number of unidentified molecular bands and lines that require a further study.

The measured dependence of the acetone concentration in the exhaled air on the glucose concentration in the blood of three patients is shown in Fig. 7. Each point of this dependence is a single measurement for one patient. The leftmost point is the result of measurements for a healthy person. The acetone concentration measurement error is caused by the statistical error of the setup and the blood glucose level measurement error was taken from [10].

It is interesting to note the following feature. Within the error of the clinical trial, the graph bending observed in the range of 10 mmol/liter can be considered statistically true. This may indicate the presence of a nonlinear increase in the acetone concentration in the breath at extremely high blood glucose levels, which is the subject of further studies.

CONCLUSION

In this paper, the possibility of measuring the concentration of the biomarker (acetone in human's breath) with the help of glow-discharge emission spectroscopy in air is demonstrated in order to noninvasively monitor blood glucose levels in diabetic patients. The minimum sensitivity of acetone detection by the proposed method (at the level of noise) amounts to 20 ppb, which allows this method to be used to detect diabetes at an early stage, when it is still possible to cure the patient. With the use of the photodesorption effect [11], a further increase in the sensitivity of the proposed method is expected. This work demonstrates a potential for creating a portable sensitive breath analyzer suitable for diabetes control, including that at home. Due to the wide spectral range covering almost all biomarkers, the proposed method can be used to control several other socially important diseases.

This work was supported by the Russian Foundation for Basic Research (Grant No. 14-02-31099 mol_a).

REFERENCES

1. G. Freckmann, A. Baumstark, N. Jendrike, et al., "System Accuracy Evaluation of 27 Blood Glucose Monitoring Systems According to DIN EN ISO 15197," Diabetes Technology & Therapeutics **12** (3), 221–231 (2010).
2. E. V. Stepanov, "Methods of Highly Sensitive Gas Analysis of Molecular Biomarkers in Exhaled Air Studies," Proc. Prokhorov General Physics Institute **61**, 5–47 (2005).
3. A. W. Jones, A. Sagarduy, E. Ericsson, and H. J. Arnqvist, "Concentrations of Acetone in Venous Blood Samples from Drunk Drivers, Type I Diabetic Outpatients, and Healthy Blood Donors," J. Analytical Toxicology **17** (3), 182–185 (1993).
4. C. Deng, J. Zhang, X. Yu, et al., "Determination of Acetone in Human Breath by Gas Chromatography-Mass Spectrometry and Solid-Phase Microextraction with On-Fiber Derivatization," J. Chromatography **810** (2), 269–275 (2004).
5. N. Yamane, T. Tsuda, K. Nose, et al., "Relationship Between Skin Acetone and Blood β-Hydroxybutyrate Concentrations in Diabetes," Clinica Chimica Acta **365** (1–2), 325–329 (2006).
6. C. Turner, C. Walton, S. Hoashi, and M. Evans, "Breath Acetone Concentration Decreases with Blood Glucose Concentration in Type I Diabetes Mellitus Patients During Hypoglycaemic Clamps," J. Breath Research **3** (4), 046004 (2009).
7. R. W. B. Pearse and A. G. Gaydon, *The Identification of Molecular Spectra* (J. Wiley & Sons, inc., 1941).
8. D. Staack, B. Farouk, A. Gutsol, and A. Fridman, "DC Normal Glow Discharges in Atmospheric Pressure Atomic and Molecular Gases," Plasma Sources Sci. Technol. **17** (2), 025013 (2008).
9. V. L. Vaks, E. G. Dormacheva, A. V. Maslennikova, et al., "Application of Methods and Means of Transient Spectroscopy at Subterahertz and Terahertz Frequency Bands for Noninvasive Medical Diagnostics," Opt. J. **79** (2), 9–14 (2012).
10. P. J. Twomey, "Plasma Glucose Measurement with the Yellow Springs Glucose 2300 STAT and the Olympus AU640," J. Clinical Pathology **57** (7), 752–754 (2004).
11. S. N. Atutov, N. A. Danilina, S. L. Mikerin, and A. I. Plekhanov, "Photodesorption of Molecular Nitrogen from the Glass Surface," Avtometriya **49** (6), 98–106 (2013) [Optoelectron., Instrum. Data Process. **49** (6), 608–614 (2013)].