Compact static mass spectrometer for medical diagnostics

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Abstract. Static mass spectrometer for detecting pathologies in the human organism from the composition of exhaled air is described in this paper. The instrument is equipped with the capillary and membrane sample intake systems for dynamic investigations of a number of components in the exhaled mixture as well as for determining trace amounts of specific volatile biomarkers accompanying diseases of the respiratory system, blood circulation system, interstitial tract, and endocrine system. Tests of the mass spectrometer with the membrane sample inlet system have shown for one of the markers that the monitoring of acetone vapor in air during the respiratory process can be carried out at a level of ~1 ppm. Mass spectrometric detection of a number of other markers with a higher (up to two orders of magnitude) penetrability through the membrane as compared to acetone becomes possible at the ppb level. The presented static mass spectrometer was tested for the possibility of working with a linear Ion CCD matrix designed to directly register ions in a wide energy range. The experimental results prove that the selected scheme of the mass spectrometer can be used in combination with both the IonCCD detector and the microchannel plate – IonCCD detector without significantly deteriorating the main performance characteristics of the instrument.

1. Introduction

Exhaled air analysis is a rapidly developing area of non-invasive medical diagnostics. More than 800 gases that are biomarkers of various diseases are currently known [1]. The possibility of early diagnosis of disease depends on the sensitivity of the instrument used to detect biomarkers and rapidity of measurements. Methods such as gas chromatography, mass spectrometry, gas chromatography-mass spectrometry, electrochemistry, UV chemiluminescence, IR spectroscopy applied now to determination of trace amounts of compounds in multicomponent mixtures.

Double focusing static mass spectrometers are promising tools for analyzing the composition of exhaled air. There is a possibility of increasing sensitivity in studying the composition of exhaled air through the use of membrane inlet systems. Coupling the membrane inlet systems with a portable static mass spectrometer [2] allows to create a compact and highly sensitive instrument for rapid multi-component analysis.

2. Mass spectrometer description

2.1. Mass analyzer

The choice of the ion-optical scheme of the mass spectrometer is determined, on the one hand, by the requirements for the analytical capabilities of the instrument, such as resolution and sensitivity, and, on the other hand, by the requirements imposed on small-sized instruments, such as size and power...
consumption. The parameters of the mass analyzer are determined in accordance with the methodology proposed in [2]. The parameters of the system were chosen using numerical simulation programs. A program for simulating ion trajectories in sector fields of a mass analyzer with different sector angles for different mass ranges of the investigated ions [3], modified for a magnet with a single curved output boundary, was used for preliminary calculations. This program was used for determining the ranges of optimal relations between the parameters for which the final analysis of the system was carried out using the SIMON program. Ion trajectories and contours of the ion-optical system in two projections are shown in Figure 1.

The matching of the curvature of the output boundary of the magnet, as well as the angles of entrance and exit of the ion beam relative to its boundaries, makes it possible to increase the mass dispersion without deteriorating the resolution of the instrument. The ion source of the Nier type was used in this instrument. The ion beam parameters at the source output were as follows: cross section 0.1 × 3.0 mm, angular spreads within ±1°, and energy spreads within ±1°. The results of numerical simulation have made it possible to determine the resolution of the mass analyzer (~250 for a transmission of ~50%).

![Figure 1. Ion–optical scheme of the mass spectrometer: projections of ion trajectories onto the yx and zx plane.](image)

2.2. Sample Inlet System

The requirements of high sensitivity and express analysis in determining the concentration of gases and volatile compounds in exhaled air are the most important because, on the one hand, the dynamics of changes in the content of a number of target compounds, including low concentrations, is studied, on the other hand, studies are carried out using portable mass spectrometers equipped with pumping systems of limited productivity. The mass spectrometer is equipped with sample intake systems the application of each of which is determined by the priority of the imposed requirements. Special electromagnetic and piezoceramic locks open the access to the sample during measurement and can rapidly block the flow of intake gas when required, sealing the vacuum part of the instrument.

The capillary sample intake system, shown schematically in Figure 2a with a photograph, is intended for studying the dynamics of variation in the ratio of the main components of exhaled air (O₂, CO₂ (for anesthesia), N₂O, etc.). This system makes it possible to directly introduce the sample into the instrument without a substantial change in its composition and ensures the response to a change in the gas content in the sample within 0.1 s. To reduce the condensation of moisture on the capillary walls, leading to instability of the sample flow fed to the instrument, the system is supplemented with evacuation tracts including a forevacuum pump and a diaphragm micropump. When the requirements of high sensitivity are prioritized over the requirements of express analysis, the mass spectrometer is equipped with a
relatively simple and compact membrane system of sample intake; the schematic diagram and photograph of this system are shown in Figure 2b.

![Schematic diagram and photograph of the intake system](image)

**Figure 2.** Design and photograph of the intake system: (a) capillary system: 1, 2—mini valves; 3, 4—capillaries with an inner diameter of 0.125 mm having lengths of 30 and 1 cm, respectively; (b) membrane system: 1—copper washer, 2—stainless steel shell, 3—silicon washer, 4—polydimethylsiloxane membrane with a thickness of 30 μm and effective area of 3 mm², 5—supporting grid, 6—metal washer, and 7—fastening nut.

The combination of the high sensitivity and fast response of the instrument is achieved by using a thin silicon membrane (SSP-M100, Special Silicon Products Inc., Ballston Spa, NY) with a thickness of 30 μm. The dependence of the results of measurements on the ambient temperature can be substantially suppressed by stabilized heating of the intake system [4]. The application of this membrane has made it possible to reduce the limits of detection of a number of volatile organic compounds in air by up to 1000 times as compared to the capillary system, but slightly increased the delay time of the response of the signal (up to 1–5 s). In the scheme proposed here, automatic blocking of the introduction of the sample to the membrane by a piezoelectric lock is envisaged in the case of breakdown, which is especially important when thin membranes are used in routine measurements. The combination of the capillary and membrane sample intake systems considerably simplifies the calibration of the instrument in the case of high sensitivity analysis.

### 2.3 Design and Characteristics
Figure 3a shows the block diagram of the mass spectrometer. It includes:
(1) mass analyzer with the ion source described above and magnum-5901 detectors manufactured at Photonics;
(2) Edwards evacuation system including the XDD1 forevacuum pump, EXT75DX turbomolecular pump, APG100-XLC low-vacuum pressure gauge, APG-M high-vacuum monitoring sensor, NW16 LCPV electromagnetic gate, and TIC 200W vacuum system controller;
(3) capillary system for sample intake described above;
(4) membrane system of sample intake [4];
(5) diaphragm micropump manufactured at Thomas 5002 VD DC, ensuring the circulation of the sample in the intake systems; and
(6) electronic block with a processor ensuring operation of the entire mass-spectrometer system and permanently controlling its state.

The main parameters and characteristics of the instrument are as follows: mass up to 30 kg, size 250 × 450 × 650 mm; power 200 W; operation conditions: temperature from 10 to 35°C, humidity <80%; range of masses being measured up to 300 u, and mass resolution up to 250. Figure 3b shows the photograph of the mass spectrometer described here.

**Figure 3.** Mass spectrometer: (a) block diagram of the instrument; 1, 2—capillaries; 3, 4—microvalves with electromagnetic lock, BURKERT, G1/8; 5—piezoelectric lock [5]; 6—membrane; 7—block of
heating and temperature stabilization; 8—electromagnetic vacuum valve; (b) photograph of the instrument.

3. Results of test
The tests of the instrument on the laboratory bench revealed that both the capillary and the membrane intake systems make it possible to trace the variation of the concentration of oxygen and carbon dioxide in each respiratory movement. The response of the instrument equipped with the membrane system and that equipped with the capillary system differ in the ratio of intensities of the characteristic molecular peaks of the compounds in view of different penetrabilities of the membrane for each of them [4] and in the delay relative to the instant of variation of the sample composition due to diffusion in the membrane. Tests of the mass spectrometer with the membrane sample intake system have shown for one of the markers that the monitoring of acetone vapor in air during the respiratory process can be carried out at a level of ~1 ppm. This corresponds to the level of a healthy person, and information about the excess over this level or about a change in the dynamics of acetone release with breathing upon an increase in physical activity can be treated as the basis for diagnostics of deceases of liver and kidneys of a patient or can be used for selecting the exertion regime for sportsmen. Mass spectrometric detection of a number of other markers with a higher (up to two orders of magnitude) penetrability through the membrane as compared to acetone becomes possible at the ppb level.

4. Possibilities of application
The results of analysis of the composition of exhaled air described in [5-9] make it possible to attribute the elevated concentration of certain substances in it to certain diseases. Quantitative analysis of exhaled air using these biological markers (target approach) is used for various purposes for heart-disease patients and those with problems of respiratory and endocrine systems and those suffering from cancer and infectious diseases. The molecules being analyzed in the gas phase are also the markers of tolerance to physical loads (like oxygen and carbon dioxide), efficiency of hemodynamics (nitrous oxide, sulfur hexafluoride), and indicators of intensity of metabolic processes and functioning of liver and kidneys (acetone), and oxidative damage of tissues.

Conversely, synchronous semi-quantitative analysis of most substances contained in exhaled air is interesting for “integral” diagnostics (i.e., analysis of the so-called “respiratory print” of a certain pathological state (disease air fingerprint) that envisages the search for new biomarker molecules.

5. Instrument development prospects
Most small-sized mass spectrometers used for research, both in the laboratory and outside it, implementing in situ online control in industry and monitoring in medicine, geophysics, ecology, or space research work in a scanning mode. To solve these problems, mass spectrometers of different types are used [10]. In the case of rapid multicomponent analysis of various media, static instruments have some advantages over other mass spectrometers. These include the main characteristics of the device, like rapidness, sensitivity, and resolution. It is not easy to attain these advantages, but it can be achieved by the use of ion detection systems based on a coordinate-sensitive detector, which enables the simultaneous recording of ions in a broad mass-spectral range without deforming the shape of the response of the detector. The presented static mass spectrometer was tested for the possibility of working with a linear Ion CCD matrix [11, 12] designed to directly register ions in a wide energy range.

The experimental results prove that the selected circuit of the mass spectrograph can be used in combination with both the IonCCD detector and the MCP (microchannel plate)– IonCCD detector without significantly deteriorating the main performance characteristics of the instrument. In the former case, the detectors can be used in devices with ion sources operating at atmospheric pressure and serve for the analysis of low-volatile and nonvolatile compounds, including in chromatography–mass spectrometers. In the latter case, it is advisable to use them for quantitative analysis of traces of gases, vapors, or volatile compounds in the sample using ion sources located in a vacuum chamber. The use of the considered versions of the detector in combination with the ion-optical circuit proposed in this work
makes it possible to expand the possibilities of using mass spectrometry, especially in situ online monitoring in ecology and medicine.

6. Conclusions
Static mass spectrometer for detecting pathologies in the human organism from to the composition of exhaled air is described in this paper. The instrument is equipped with the capillary and membrane sample intake systems for dynamic investigations of a number of components in the exhaled mixture as well as for determining trace amounts of specific volatile biomarkers accompanying diseases of the respiratory system, blood circulation system, interstitial tract, and endocrine system.

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