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Determination of Volatile Organic Compounds in Exhaled Breath by Ion Mobility Spectrometry★

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In this paper, the possibility of determination of volatile organic compounds (VOCs) present in the exhaled breath using an ion mobility spectrometer (IMS) has been described. This device combines high sensitivity, analytical flexibility, low cost of individual analyses, and suitability for the real-time monitoring. The IMS is often coupled with multicapillary column (MCC), which enables the analysis of a mixture of gaseous substances in a very short time. The MCC–IMS system was calibrated for ethanol, 2-hexanone, 2-heptanone, 3-heptanone, limonene, and p-xylene. Linearity of the method was investigated in the concentration range from 0.3 to 83.8 ppb at the limit of detection ranging from 0.1 to 2.1 ppb. The presented method can be used for determination of VOCs in exhaled air, especially for early diagnosis of patients suffering from lung, larynx, mouth, and esophagus cancers.

W pracy opisano możliwość oznaczania lotnych związków organicznych (VOCs) w wydychanym powietrzu za pomocą spektrometru ruchliwości jonów (IMS). Aparat ten łączy wysoką czułość detekcji oraz niski koszt pojedynczej analizy z możliwością kontroli procesów w czasie rzeczywistym. Sprzężony z kolumną multikapilarną (MCC) umożliwia analizę lotnych substancji w mieszaninie w bardzo krótkim czasie. Układ MCC–IMS skalibrowano dla etanolu, 2-heksanonu, 2-heptanonu, 3-heptanonu, limonenu oraz p-ksylenu. Liniowość metody badano w zakresie stężeń od 0.3 do 83.8 ppb, przy granicy wykrywalności od 0.1 do 2.1 ppb. Opracowana metoda pozwala na oznaczanie VOCs w wydychanym powietrzu i może być użyteczna w szybkiej diagnostyce osób z chorobami nowotworowymi, płuc, krtani, ust i przełyku.

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★ Dedicated to Professor Rajmund Dybczyński on the occasion of his 75th birthday.

Ion mobility spectrometry (IMS) is a technique designed by Cohen and Karasek in 1970s [1]. Since that time IMS has been developing very fast. Now, various combinations of IMS and other techniques such as gas chromatography (GC–IMS) [2], liquid chromatography and mass spectrometry (LC–IMS–MS) [3], multi-capillary columns (MCC–IMS) [4], time-of-flight mass spectrometry (IMS–TOF–MS) [5], solid-phase microextraction surfaced enhanced laser desorption (SPME–SELDI–IMS) [6], and others are known. IMS is an effective, simple in practice, and, due to its small size, a very convenient detector. It combines high sensitivity (detection limits down to the ng–pg per liter and ppb_v–ppt_v ranges) and relatively low cost of a single analysis with a high-speed data acquisition. The time needed to record a single ion mobility spectrum is in the range of 20–50 ms [7]. The important feature of IMS is that no vacuum is required for its operation. Therefore, ambient air can be used as a carrier gas. As a consequence, the IMS detector can be miniaturized, which provides a benefit in commercialization of the system in comparison to other online techniques [8]. Due to these advantages, IMS is used in many branches of industry and by institutions such as the police and army. The IMS detector has been applied to the quality assurance and process monitoring in the pharmaceutical industry [9], for detection of trace explosives [10, 11], screening of chemical warfare agents [12, 13], environmental monitoring [14, 15], screening of illegal drugs [6, 16], and online breath analysis [7, 17]. IMS has also made great strides towards the analysis of biological materials, such as bacterial spores [18, 19].

The IMS detector is characterized by not very high selectivity. Therefore, application of a pre-separation technique is helpful for the analysis of complex mixtures. In practice, the IMS detector is often coupled with standard gas chromatographic columns [2] or multi-capillary columns (MCCs) [4]. MCC are characterized by a comparatively high flow rate and high sample capacity in comparison to the single tight columns. The application of MCC enables direct injection of a high gas volume into the column, isothermal separation of volatile organic compounds (VOCs) at the ambient temperature, and multidimensional data analysis of the peaks [4]. The peaks can be identified using chromatographic data (retention times) and specific ion mobil-ity data (arrival times at the Faraday plate). The retention times of the compounds separated by MCC and drift times of the analytes are plotted to obtain a so-called ion mobility spectrum.

In the last few years, the combination of MCC and IMS has been used for breath analysis more and more often [4, 19, 20]. The MCC–IMS technique is supposed to be competitive to GC–MS, which is generally used for breath analysis [21]. Volatile organic compounds present in human breath, such as ethanol, acetone, isoprene and other hydrocarbons were measured directly by the MCC–IMS with detection limits down to the ng L^{-1} and pg L^{-1} range. The application of MCC reduces the negative influence of humidity present in the exhaled breath samples, what improves selecti-

vity of the method. The decrease of the water vapor effect when using MCC improves the sensitivity of determination of the molecules with low proton affinities. Additionally, the presence of a lot of moisture in the system facilitates cluster formation reactions between the analyzed ions and water molecules [22]. The important advantage of this technique is that the analytes do not need to be preconcentrated. If the concentration of the analyzed compounds is too high, they are not efficiently ionized since then the amount of reactant ions is insufficient [7]. IMS has shown low sensitivity towards alkanes [23] and benzene-related compounds [24] – the analytes with low proton affinity. A product ion originating from benzene and alkanes can be easy formed under conditions of low moisture and high temperature [24]. If the moisture level is sufficiently high, the reactant ion can be converted and no reaction (no detector response) occurs. Some researches in the IMS area have shown that ketones can produce maximally three peaks: for a monomer, a dimer, and a trimer [4]. The number of the peaks and the relation between these peaks depends on the concentration of the sample molecules. If the analyte's concentration is higher, the probability of collision between the analyzed molecule and a neutral molecule and formation of a dimer ion is also increased.

In this paper identification of 18 standards has been performed and the drift and retention times have been determined for 10 of them. The method for determination of volatile organic compounds in exhaled breath using the MCC–IMS device has been presented. Our aim was to introduce a very fast, simple, and inexpensive method for identification of VOCs present in exhaled air, which in the nearest future might find an application in clinical diagnosis.

Principles and theory of IMS

The detection process in the IMS is based on the movement of ions in a drift gas. This process occurs at the ambient pressure under the influence of stable electric field, which is in the range from 100 to 350 V cm^{-1} [7]. The IMS can be operated in the positive and negative modes. In the first stage, the so-called reactant ions are created and undergo a series of reactions with the molecules in the second stage. In case of a positive mode, the molecules (M) are ionized by collision with the reactant ions ($H^+(H_2O)_n$) and generate product ions ($MH^+(H_2O)_{n-x}$) and water, according to Eq. 1 [25, 26].

$$\underset{\text{sample}}{M} + \underset{\text{reactant ion}}{H^+(H_2O)_n} \rightarrow \underset{\text{cluster ion}}{MH^+(H_2O)_n} \rightarrow \underset{\text{product ion}}{MH^+(H_2O)_{n-x}} + \underset{\text{water}}{xH_2O} \quad (1)$$

Product ions formed in this reaction are stabilized *via* the displacement of water molecules bound to the cluster ion, which can be stabilized afterwards by collision with another molecule. If the concentration of the sample increases, a second product

ion is often formed as a result of collision of a protonated monomer and a sample molecule (Eq. 2):

$$\underset{\text{protonated monomer}}{MH^+(H_2O)_n} + \underset{\text{sample}}{M} \rightarrow \underset{\text{proton-bound dimer}}{M_2H^+(H_2O)_{n-x}} + \underset{\text{water}}{xH_2O} \quad (2)$$

The formation of the reactant ions in the negative mode occurs between low-energy electrons and neutral species, such as oxygen. Ion molecule reactions proceed between the negative reactant ions ($O_2^-(H_2O)_n$) and sample molecule (M) forming the product ion ($MO_2^-(H_2O)_{n-x}$) and water (Eq. 3) [25]:

$$\underset{\text{sample}}{M} + \underset{\text{negative reactant ion}}{O_2^-(H_2O)_n} \rightarrow \underset{\text{product ion}}{MO_2^-(H_2O)_{n-x}} + \underset{\text{water}}{xH_2O} \quad (3)$$

When the concentration of the analytes is too high the amount of the formed dimers increases and the obtained spectra might be difficult to interpret [7, 26]. After ionization, the analytes drift through the cell under the influence of the electrostatic field. A shutter grid is opened periodically either to block the ions or to allow them to pass through into the drift region. The basic construction of the ion mobility spectrometer is presented in Figure 1. The ions are separated according to their unique mass and structure while flowing counter to the drift gas flow, which is introduced at the end of the drift tube. The IMS device is a specific ion filter, which sorts the ionized molecules according to their mobility (k). Ion drift time (t_d) is measured across the known tube length (L) with the known electric field (E). The mobility is given by the following Eq. 4:

$$k = L/t_d\, E \quad (4)$$

The velocity of ions (v) is calculated using Eq. 5 [14]:

$$v = L/t_d \quad (5)$$

Ion mobility k is characteristic for a given ion and depends upon temperature T, K and pressure p, kPa. k can be normalized to the reduced mobility k_0 using Eq. 6 [27]:

$$k_0 = k(273/T)(p/101) \quad (6)$$

In IMS smaller ions move faster through the drift tube than the larger ones and arrive earlier at the detector. Then, the ions are collected in a Faraday plate located at the end of the tube and time-dependent signal corresponding to the mobility of the arriving ions is registered. The ions generate a current, which is amplified and a drift

time spectrum is obtained. A microprocessor evaluates the spectrum for the target compound and determines the concentration based on the peak height. In the IMS detector different ionization sources for the analytes can be used: ^{63}Ni [28], ^{241}Am and ^{3}H [29], or UV light [30]. Corona [31] or partial discharges [32], as well as electrospray ionization have been also applied [33].

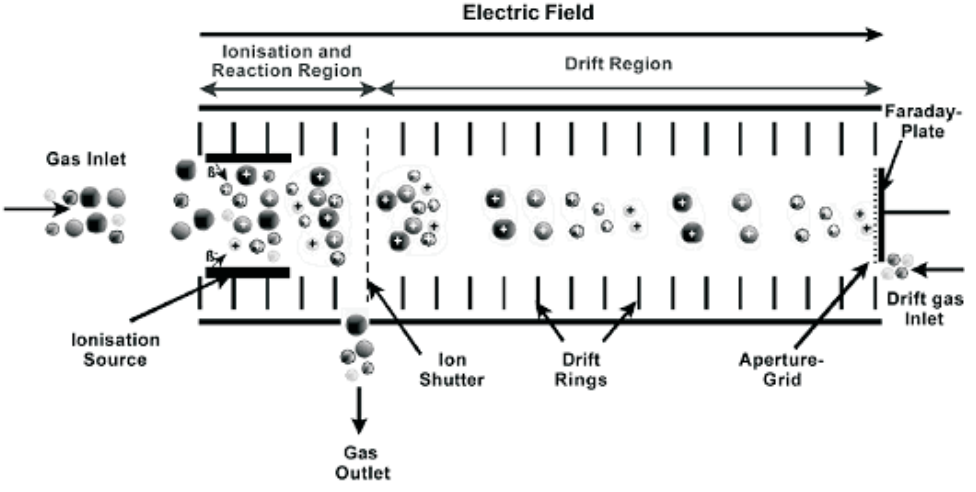

Figure 1. The scheme of the separation system in the ion mobility spectrometer ([14] with kind permissions of Elsevier)

EXPERIMENTAL

Apparatus

An ion mobility spectrometer (ISAS Institute for Analytical Sciences, Dortmund, Germany) was used for the measurements (Fig. 2). The device was equipped with a radioactive ionization source – ^{63}Ni. Ionization of the analytes occurred in the ionization chamber under ambient pressure. After ionization, the ions were let through to the drift region by periodically opening the shutter grid. They flowed against a synthetic air (*i.e.* drift gas) in the constant electric field (electric field strength 300 V cm^{-1}, positive drift voltage 4 kV) to the ion collector. The shutter opening time was 300 µs, and the length of the drift region was 120 mm. The flow rate of the synthetic air used as a drift gas was 84 mL min^{-1}. The flow rate of the synthetic air passing through the sampling loop was 83 mL min^{-1}.

For separation of the analytes polar multicapillary column (Multichrom, LTD. Novosibirsk, Russia) was applied. The column was an assembly of approx. 1200 capillaries packed with the cross-linked liquid phase OV-5. The length of the MCC was 0.2 m, the inner diameter of the capillary was 40 µm, and the film thickness was 0.2 µm. The flow rate of the carrier gas was 127 mL min^{-1}. The column was coupled to the IMS. Separation was performed isothermally at 30°C. A 10 mL dose loop and an electric six-port valve were positioned before the MCC (Fig. 2).

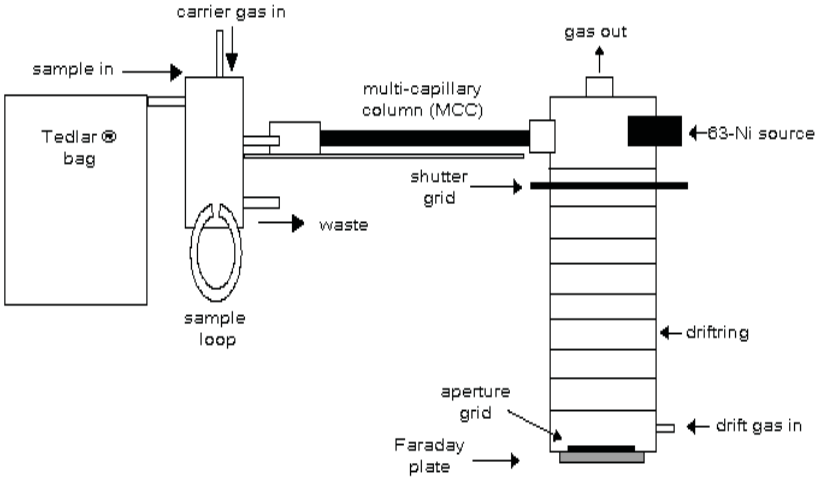

Figure 2. Schematic representation of the measuring system

The data were acquired using an IMS Tool program (Department of Anesthesiology and Critical Care Medicine, Medical University of Innsbruck, Innsbruck, Austria). This software has been written specially for the IMS device. It provides information about drift and retention times of the analyzed compounds and integrates a peak volume.

Reagents

Nitrogen of 6.0 purity and synthetic air (20% O_2 (5.6), 80% N_2 (6.0)) were purchased from Linde (Munich, Germany).

Standards of ethanol (99.8%, Riedel-de-Haen, Seelze, Germany), methanol (99.9%, Sigma–Aldrich, Steinheim, Germany), 1-propanol (99.5%, Fluka, Steinheim, Germany), 2-propanol (99.5%, Fluka, Steinheim, Germany), formaldehyde (36.5%, Sigma, Steinheim, Germany), acetaldehyde (99.5%, Merc, Darmstadt, Germany), 3-heptanone (98%, Alfa Aesar, Karlsruhe, Germany), 2-heptanone (98%, Aldrich, Steinheim, Germany), 2-hexanone (98%, Aldrich, Steinheim, Germany), benzene (99.8%, Aldrich, Steinheim, Germany), toluene (99.8%, Aldrich, Steinheim, Germany), p-xylene (99%, Aldrich, Steinheim, Germany), furan (99%, Aldrich, Steinheim, Germany), 2-methylfuran (99%, Aldrich, Steinheim, Germany), isoprene (99%, Aldrich, Steinheim, Germany), acetonitrile (99.8%, T.J.Baker, Deventer, Holland), and limonene (98%, Fluka, Steinheim, Germany) were detected using the IMS.

Preparation of gaseous standards

Calibration gases were obtained by evaporation of the liquid standards listed above in a 500 mL glass gas bulb. Before use, the bulb was cleaned with methanol and dried in an oven at 75°C for at least 24 h. Then, it was purged with the ultra-clean nitrogen. Afterwards, the bulb was vacuumed for 10 min using a vacuum pump. Calibration vapor mixture was obtained by the syringe injection of 1 μL of each liquid standard through the membrane into a glass bulb. The appropriate amount of the vaporized standard (0.3–83.8. ppb) was removed using a gas-tight syringe and introduced into a 500 mL-in-volume Tedlar bag with nitrogen.

The presented procedure is widely used for the preparation of standard mixtures for gas analyzes, *e.g.* breath samples [21].

Identification of VOCs

Identification of compounds was performed in the gaseous standards diluted with nitrogen and in the exhaled breath collected earlier. For each compound the identification analysis was repeated three times. The concentration of a standard in the sample was increased every time. Breath sample was used as a control for standards diluted with the exhaled air. The drift and retention times were measured for 18 compounds; (Tab. 1). They were determined using the IMS Tool program. The calibration curves were plotted for six compounds often present in breath samples.

Table 1. The drift and retention times of the analyzed standards

Compound	In nitrogen		In breath		CAS-number
	Drift time, ms	Retention time, s	Drift time, ms	Retention time, s	
Ethanol	19.78–19.82	18.00	19.82–21.48	18.00–19.20	64-17-5
Methanol	19.72–19.76	18.00	19.80–19.86	15.80–19.60	67-56-1
1-Propanol	20.20–20.22	6.70–7.80	17.64–17.70	22.50–25.90	71-23-8
2-Propanol	in RIP area		in RIP area		67-63-0
Formaldehyde	not detected		not detected		50-00-0
Acetaldehyde	21.06–21.10	9.00–10.10	20.96–21.02	10.10	75-07-0
Acetone	in RIP area		in RIP area		200-662-2
3-Heptanone	25.36–25.42	18.00–20.20	25.60–25.66	18.00	106-35-4
2-Heptanone	26.00–26.02	19.10	25.98	18.00–19.10	110-43-0
2-Hexanone	23.94	10.10–11.20	23.96	10.10–11.20	591-78-6
Benzene	not detected		not detected		71-43-2
Toluene	not detected		not detected		108-88-3
p-Xylene	18.56–18.58	40.50–51.70	18.54 – 18.58	41.70	106-42-3
Furan	not detected		not detected		110-00-9

(Continuation on the next page)

Table 1. (Continuation)

Compound	In nitrogen	In breath	CAS-number	Compound	In nitrogen
	Drift time, ms	Retention time, s	Drift time, ms		Drift time, ms
2-Methylfuran	21.14–21.16	6.70	17.70	7.80–9.00	534-22-5
Isoprene	not detected		not detected		78-79-5
Acetonitrile	in RIP area		in RIP area		75-05-8
Limonene	21.12–21.24	54.20–54.30	21.00–21.06	50.70–53.00	138-86-3

Breath collection

Breath – ambient air samples were collected into 3 L-in-volume Tedlar bags (SKC Inc, Eighty Four, PA). Before breath collection, all bags were cleaned by flushing with nitrogen gas. Then, they were filled with nitrogen and heated at 95 °C for several hours to remove all contaminations. Each time, two bags of the exhaled breath per patient and one of the indoor air were collected.

RESULTS AND DISCUSSION

Identification of analytes

The drift and retention times were presented in the range in which they were observed in the ion mobility spectrum. Their variations might result from different flow rates of the carrier gas or from the change in the concentration in the analysed sample. In case of some substances, the drift and retention times for the standards diluted with nitrogen and breath sample were different. The presence of moisture in the exhaled air influenced the drift and retention times of the analytes.

Formaldehyde, benzene, toluene, furan, and isoprene were not detected by MCC–IMS. The peaks of acetonitrile, acetone and 2-propanol were observed within the reactant ion peak (RIP), because the analyzed ions had the same mobility as the reactant ions. Therefore, the IMS Tool program could not integrate them. 2-hexanone, limonene, and 2- and 3-hexanone produced three peaks originating from the protonated monomer, a proton-bound dimer, and a trimer. These peaks were observed in the ion mobility spectrum at the same retention times but at different drift times. The number of and the relation between these peaks depended on concentration of the sample molecules. For calculation, the larger volume peak of ketones and limonene was taken into account.

Quantification and validation method

The calibration curves were calculated on the basis of the results obtained in the analysis of the gaseous mixture of the compounds diluted with nitrogen. They are shown in Figure 3.

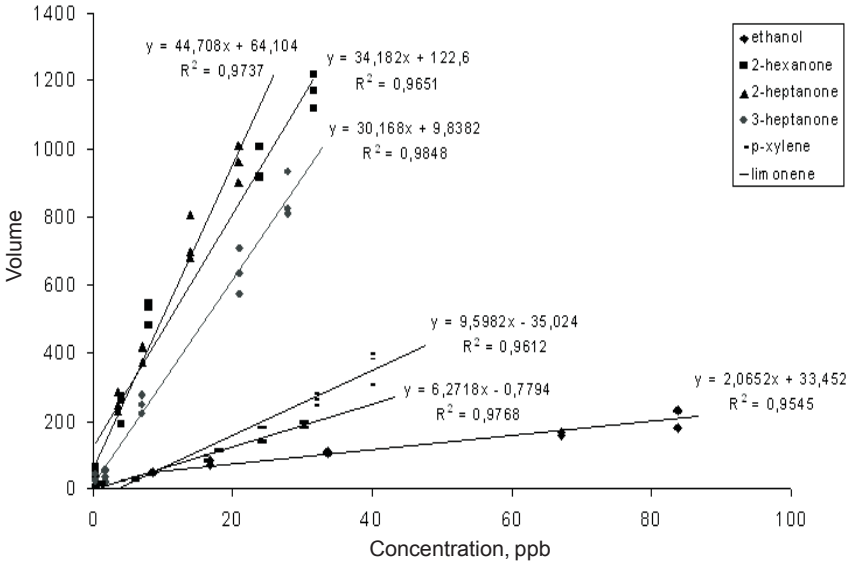

Figure 3. Calibration curves for the standard compounds (see text for details)

Table 2 shows precision, linearity, and detection limits for ethanol, 2-hexanone, 2- and 3-heptanone, limonene, and p-xylene. Precision of the method was determined in four consecutive analyses. Linearity between the analytical signal and the amount of the analyte was another important characteristic in the quantitative analysis. A linear regression analysis of the peak volume *vs* analyte's concentration dependence was performed using the standard mixture. Concentration ranges depended on the analysed compounds: 0.3–31.7 ppb for ketones, 8.4–83.8 ppb for ethanol, 4.0–39.7 ppb for p-xylene, and 1.2–30.2 ppb for limonene. Linearity was quite satisfactory - correlation coefficient (R^2) ranged from 0.955 for ethanol to 0.985 for 3-heptanone (Tab. 2).

Table 2. Linearity, limit of detection (LOD), limit of quantitation (LOQ), and calibration range for the investigated standards

Compound	Calibration range, ppb	R^2	LOD, ppb	LOQ, ppb
Ethanol	8.4–83.8	0.955	2.1	6.3
2-Hexanone	0.4–31.7	0.965	0.1	0.3
3-Heptanone	0.4–28.0	0.985	0.1	0.3
2-Heptanone	0.3–20.9	0.974	0.1	0.3
Limonene	1.2–30.2	0.977	1.0	3.0
p-Xylene	4.0–39.7	0.961	1.0	3.0

Limit of detection and quantitation

To characterize the sensitivity of the MCC–IMS method, the limit of detection (LOD) was determined for individual compounds. We defined the limit of quantitation (LOQ) as 3× detection limit. Detection and quantitation limits for VOCs are shown in Table 2. Generally, the lowest detection limit was achieved for ketones. LOD for 2-hexanone and 2- and 3-heptanone was 0.1 ppb. The highest LOD of 2.1 ppb was achieved for ethanol. For limonene and p-xylene the determined LOD value was 1.0 ppb.

Application of IMS

The IMS device was applied to the analysis of exhaled breath samples. The exemplary ion mobility spectrum of patient's breath with lung cancer is shown in Figure 4. In the chromatogram ethanol, acetaldehyde, 2-hexanone and limonene were identified based on the retention and drift times determined previously for the standard compounds.

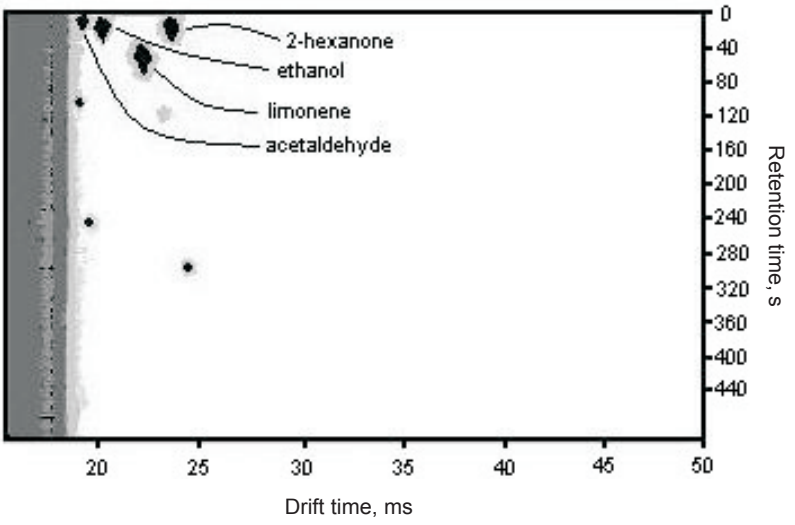

Figure 4. Ion mobility spectrum of patient's breath with lung cancer

CONCLUSIONS

The drift and retention times were determined for 18 compounds often identified in breath samples by other analytical technique. Unfortunately, some of them, i.e. formaldehyde, benzene, toluene, furan, and isoprene were not detected. Identification was performed for the standards diluted with nitrogen and breath sample. The obtained data might be used for identification of VOCs present in a gaseous mixture using the MCC–IMS method. The peaks of acetonitrile, acetone and 2-propanol were not observed because the mobility of the respective ions was the same as that of the reactant ions. Therefore, the used computer program could not integrate them. The calibration curves calculated for ethanol, 2-hexanone, 2-heptanone, 3-heptanone, p-xylene, and limonene were fairly linear and could be used for the quantitative analysis of these compounds. The MCC–IMS method was very sensitive for detection of ketones. The LOD value obtained for 2-hexanone and 2- and 3-heptanone was 0.1 ppb.

The aim of our work is to implement the MCC–IMS device for quantitative and qualitative online analysis of VOCs present in the exhaled breath. Our future goal is to use the MCC–IMS system as a potential non-invasive diagnostic method.

Acknowledgments

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