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Detection of human metabolites using multi-capillary columns coupled to ion mobility spectrometers

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Abstract

The human breath contains indicators of human health and delivers information about different metabolism processes of the body. The detection and attribution of these markers provide the possibility for new, non-invasive diagnostic methods. In the recent study, ion mobility spectrometers are used to detect different volatile organic metabolites in human breath directly. By coupling multi-capillary columns using ion mobility spectrometers detection limits down to the ng/L and pg/L range are achieved. The sampling procedure of human breath as well as the detection of different volatiles in human breath are described in detail. Reduced mobilities and detection limits for different analytes occurring in human breath are reported. In addition, spectra of exhaled air using ion mobility spectrometers obtained without any pre-concentration are presented and discussed in detail. Finally, the potential use of IMS with respect to lung infection diseases will be considered.

Keywords: Breath analysis; Volatile metabolites; Volatile organic compounds; Ion mobility spectrometry; Trace gas analysis; Metabolomics; VOCs; IMS

1. Introduction

It is well recognised in the medical community that humans exhale volatile compounds which potentially carry important information about the health status of the humans. Thus, a successful detection of potential products of different metabolic processes becomes attractive if the detection limits of the spectrometric methods used are low enough and the instruments becomes available on moderate price levels to be used as standard methods in hospitals. The vision of the authors is to contribute to use human breath as carrier of information of the health status of the body in addition to human blood and urine.

Human breath contains numerous volatile substances derived from both endogenous metabolism and external exposure to vapours and gases and their metabolites. Approximately 200 different compounds have been detected in human breath; some are correlated to various common disorders like diabetes, heart disease and evaluation of lung cancer [1].

The composition of different constituents in respired air is representative for blood borne concentrations detected through gas exchange at the blood/breath interface in the lungs [2]. Thus, the presence and also the quantitative variations of specific volatile organic compounds (VOCs) in respired air are directly linked to VOCs in the blood, which is in contact with diseased tissues or organs. On the other hand, metabolites derive from local bacterial infections in the airway system can be also detected using the breath. In hospitals, pulmonary infections carry a significant risk for people with weak immune systems especially for long-time inhaled and post-operative patients.

Investigations of breath were carried out using different techniques. The most popular sampling method is the use of Teflon bags into which the subject expels the air. The components of the exhale are then collected using a sorbent-trap or a cryo-trap followed by desorption into an analytical instrument like GC–MS, which is used in the majority of cases

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reported [3,4]. This is a rather time consuming process with numerous steps which may lead to loss of analytes [5,6]. Several substances may adsorb on the surface of the bag [7] such part can be significant, particularly if trace levels of analytes should be quantified.

In the literatures the number of the different compounds analysed from the exhaled air and their quantities can alter with the applied sampling and analytical methods. In the most cases, the major VOCs in the breath of healthy individuals found are isoprene (12–580 ppb_v), acetone (1.2–1880 ppb_v), ethanol (13–1000 ppb_v), methanol (160–200 ppb_v). All are products of the normal metabolic processes [8].

For the majority of the potential analytical methods for breath analysis, the high moisture content of the breath samples is a prominent problem. It can bother the sensitivity or the water should be frozen by using liquid nitrogen as cryo-trap necessary to use GC–MS effectively. Because of the status as laboratory instruments, which are comparatively large and expensive and offer an analysis time approx. 40–90 min (depending on the different sample preparation steps), a need for instruments applicable for direct and on-line analysis of the breath exists. If the sample handling procedure steps could be minimised, no additional laboratory steps becomes necessary and no additional carrier gas supplies like high purity nitrogen or helium as used in GC–MS are necessary for effective breath analysis procedures. In such cases, the investigations on humans could be handled direct in the hospitals by standard personal.

On the other hand, in the recent years ion mobility spectrometers (IMS) become comparatively small and effective devices to determine traces of quantities of VOCs down to the low ppb_v range, especially in air [9]. The primer advantages of IMS are that there is no vacuum required for the operation and ambient air can be used as carrier gas. As a consequence, the IMS can be miniaturised, which provides a benefit in the commercialisation of the system in comparison to other on-line techniques applied in the research for breath detection, like PTR–MS [10] and SIFT–MS [11].

World wide, more than 50,000 IMS units are in service, especially to detect chemical warfare agents, narcotics and explosives [12]. The instruments available on the market are handheld, too [13].

In the most recent years, miniaturised IMS [14–17] should be considered with respect to the potential for the analysis of rather complex mixtures of analytes as occurring in human breath.

The analysis with ion mobility spectrometers is based on characterising chemical substances through their gas phase ion mobilities in weak electric fields. Normally, an ion mobility spectrometer consists of an ionization chamber with a β- or UV-radiation source, an ion-molecule injection shutter (e.g. Bradbury–Nielsen-shutter), an ion drift tube and an ion collector (Faraday plate) [18].

A carrier gas, typically air on nitrogen transports the vapour analyte molecules into the ionization chamber, where they are ionised through a series of ion-molecule reactions. Conventionally, IMS comprise a β-radiation (typically ^{63}Ni) source. The ions are then injected into the drift tube by opening the shutter grid periodically and travelled through the drift region within a constant electric field against a counter-flow of neutral gas (e.g. drift gas) to the ion collector [19,20]. A high rate of collisions caused by such ions in the drift gas prevents the possibility to get neutral molecules into the drift region and to build clusters. Ions are then selectively detected on the basis of their unique drift times during the flow through the drift tube. The mobility of the analyte ions is determined from the drift velocity attained by ions in the electric field of the drift region at atmospheric pressure, which is in the range of 100–350 V/cm [18].

Because of the limited selectivity of the IMS, especially in the case of the detection of complex mixtures a pre-separation becomes helpful. For this reason, IMS are often coupled with standard gas chromatographic columns [21]. Actually, with respect to the analysis of exhaled air GC–IMS (or even a GC–MS) are not sensitive enough to obtain results by direct injection of the breath samples into the spectrometer, due to the very low concentration of the most breath constitutions normally occurring in low ppb_v and ppt_v ranges.

In the present case, so called multi-capillary columns (MCC) originally developed by the military of the former USSR should be considered because of the potential advantages like a comparatively high flow rate and a high sample capacity in comparison to single narrow-bore columns [22] are achieved. The MCC could be used for the direct injection of higher sample gas volume into the column, especially in the range of 10–50 mL. The high carrier gas flow, normally between 50 and 200 mL/min enables an isothermal separation of VOCs at ambient temperature. This is an important question with respect to the design of portable instruments, because an oven requires huge place, within a stable temperature program is insured.

Such MCC consists of a bundle of capillaries made from over 1000 individual capillaries, formed in a single small tube. The standard sizes of such a MCC is 50–300 mm in length and approx. 3 mm in bundle diameter which are adequate for packing portable instruments such as GC–IMS [23]. The stationary phases of the capillaries are conventional bonded silicones. Nowadays, MCC have become commercially available with a range of different stationary phases [24–26]. Thus, because of the high capacity, the gas flow conditions of MCC are comparable to IMS gas flows and retention times achieved at ambient temperature in the range of minutes [27] make the MCC favourable for combinations with IMS.

2. Experimental

2.1. Instrumentation

For the measurements described below, a custom designed IMS equipped with radioactive ionization source was used

Table 1
Main parameters of the ^{63}Ni-IMS

Parameter	
Ionization source	^{63}Ni (510 MBq)
Length of the drift region	120 mm
Electrical field strength	326 V/cm
Drift volthage	4 kV
Shutter opening time	300 μs
Drift and sample gas	Synthetic air
Drift gas flow	100 mL/min
Sample gas flow	150 mL/min (optimised for breath analysis)
Temperature	25 °C (ambient)
Pressure	101 kPa (ambient)

[28,29]. All parts of the IMS, which are in contact with the analytes were formed from inert materials. Teflon was used for the ionization chamber and the drift tube. The shutter grid was built from parallel nickel wires, which is closed by an electric field established. As conducting surface, drift rings were constructed from brass (Ms 63, material Nr: 2.0321), because it can be better handled as stainless steel and the rings are outside of the drift tube without any contact to the analytes. The drift tube was designed on the basis of modelling the homogeneity of the electric field inside the tube by Soppart and Baumbach [30]. The electric field in the drift tube is established by using a high-voltage supply with a voltage divider connected to the drift rings placed in equal distance. The relevant parameters of the IMS are summarised in Table 1.

2.2. Multi-capillary column

To separate complex mixtures a 17 cm long polar MCC (OV-5, Sibertech Ltd., Novosibirsk, Russia) made by combining approx. 1000 capillaries with an inner diameter of 40 μm and a film thickness of 0.2 μm was coupled to ^{63}Ni-IMS. The total column diameter of 3 mm allows operating with a carrier gas flow up to 150 mL/min, which is the optimum flow rate for IMS.

The heating of the column is indispensable for the reproducibility of the chromatographic results. To get constant retention times the MCC was hold at 30 °C during the breath analysis procedure. With an isothermal separation, a simpler heating construction is needed, which means a significant size decline of the instrument.

2.3. Practical importance of the MCC

In the detection of trace compounds the lost of the analytes must be avoided. Especially in the on-line analysis mentioned above, which operates with an on-column injection step, the capacity of the column and the efficiency of the separation are very important factors. In an experiment the separation of a test gas mixtures using two different columns, a metal capillary column (MXT-Volatiles, Silcosteel, Restek Corp., Bad Homburg, Germany) and a MCC described above were compared. An isothermal separation was investigated with both columns to keep in view the constructional advantages of an isothermal analysis by the miniaturisation of the device.

Table 2
Parameter of the columns examined

Parameter	Capillary column	Multi-capillary column
Stationary phase	VOCOL (polar)	OV-5 (polar)
Number of capillaries	1	approx. 1000
Length of the column	15 m	17 cm
Film thickness	0.3 μm	0.2 μm
ID of a single capillary	0.53 mm	40 μm
Temperature of the column	70 °C (isothermal)	30 °C (isothermal)
Flow rate of sample gas	60 mL/min	50 mL/min

The test gas mixture was prepared from four ketones. After separating with the different columns the compounds were measured by ^{63}Ni-IMS. A summary of the parameters of both columns is shown in Table 2.

3-Pentanone (for synthesis 99% (GC), Merck, Hohenbrunn, Germany), 2-hexanone (purum 98% (GC), Fluka, Steinheim, Germany), 2-heptanone (purum 98% (GC), Fluka, Steinheim, Germany) and 2-octanone (purum 97% (GC), Fluka, Steinheim) were used as test compounds and mixture was made from neat liquid substances with the help of permeation tubes. As permeation source 1 mL glass flasks (CS, Chromatographie Service GmbH, Langerwehe, Germany) with cap with 2 mm hole diameter were used. Under the cap a polydimethylsiloxane-membrane (thickness: 1 mm; Reichelt Chemietechnik GmbH + Co., Heidelberg, Germany) was arranged, which exhibits a good permeability for volatile organic compounds. The tubes were hold in 60 °C, the permeation rates were determined gravimetrically. Concentrations were calculated for 3-pentanone 1300 ng/L (363 ppb_v), for 2-hexanone 1200 ng/L (288 ppb_v), for 2-heptanone 800 ng/L (168 ppb_v) for 3-octanone 600 ng/L (112 ppb_v).

2.4. Test gas of selected breathe VOCs markers

Samples of acetone (puriss., p.a. 99.5%, Fluka, Germany), ethanol (Abs. 99.9%, J.T. Baker, Griesheim, Germany), ammonia (25%, Riedel-de Häen, AG, Seelze, Germany), isoprene (purum., 98%, Fluka, Steinheim, Germany), isopropanol (purum, 99.0%, Fluka, Steinheim, Germany) and pentane (puriss. p.a., >99.5%, Fluka, Neu-Ulm, Germany) were detected using ion mobility spectrometer. The preparation of the vapour gases was similar described above; tubes were hold at 30 °C.

2.5. Breath sampling procedure and on-line analysis with MCC-^{63}Ni-IMS

In the sampling process subject blows through a mouth piece coupled with a brass adapter designed at ISAS to a Teflon tube (1/4 in., Bohlender GmbH, Lauda, Germany), which is connected to a 10 mL stainless steel sample loop of an electric six port valve (Nalco, Macherey-Nagel, Düren,

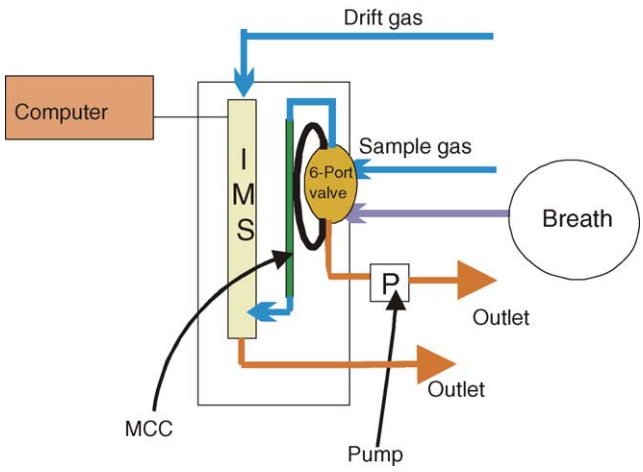

Fig. 1. Schematic draw of the breath sampling and analysis using MCC-Ni-IMS.

Germany). By switching the six-port valve breath is transported by the carrier gas from the sample loop into the MCC. The separated substances can be directly analyzed by IMS. Therefore, the results can be achieved within 600 s depending on the separation time of the compounds. This construction enables a direct and rapid sampling at a known breath volume. The schematic draw of sampling and detection the breath using MCC-^{63}Ni-IMS is shown in Fig. 1.

3. Results and discussion

The combination of the multi-capillary column with the IMS enables a multidimensional data analysis and allows identification by the chromatographic data (retention times) and also by using of the specific ion mobility data of the analytes. Therefore, retention times of the compounds separated by the MCC are shown in the *x*-axis and drift time of the single substances is displayed in the *y*-axis of the IMS-plot. The advantage of these topographic plots is the easy handling by comparing their pattern keeping all parameters of the analysis constant.

Results of separations using the two different columns are displayed in Figs. 2 and 3.

In both topographic plots a peak (drift time: 16.4 ms, $K_0 = 2.08\ \mathrm{cm^2/V\,s}$ for both peaks) existed continually during the whole analysis can be found. This is the so-called reactant ion peak (RIP), which is formed by chemical ionization of the carrier- and drift gas in ambient pressure by ion mobility spectrometers equipped with radioactive ionization source. If there is no any sample molecule in the system RIP has the maximum amount of ions. In the presence of sample molecules product ions are formed through collisions between the sample molecules and reactant ions. In the majority of cases product ions of organic molecules possess smaller mobility values (higher drift times) then the reactant ions. Table 3 gives a summary of the retention times and the mobilities of the product ions of the ketones separated.

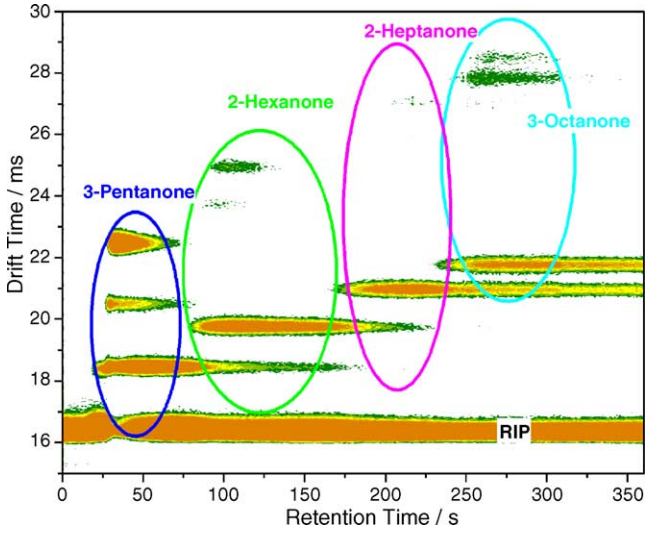

Fig. 2. Isothermal separation using MXT-capillary column coupled to ^{63}Ni-IMS.

In the analysis using IMS ketones can exhibit maximum three peaks: monomer, dimmer and trimer. The number and the relation of these peaks are depending on concentration of the sample molecules, so on the amount of the formed product ions. The more product ions are in the system the higher is the probability of the collisions between the ions and to build adducts. Because of adducts exhibit bigger masses and cross-sections, their mobilities are smaller than in the case of the monomers. In the separation using MXT-capillary column a higher peak diffusion effect can be observed, which reduces peak intensities as found on the 2D-plot (Fig. 2). Thus, in the case of the MCC in addition to the monomers of the separated compounds dimers and trimers with higher intensities can be detected.

Regarding the values of Table 3, a good correspondence can be observed between the reduced mobilities of the

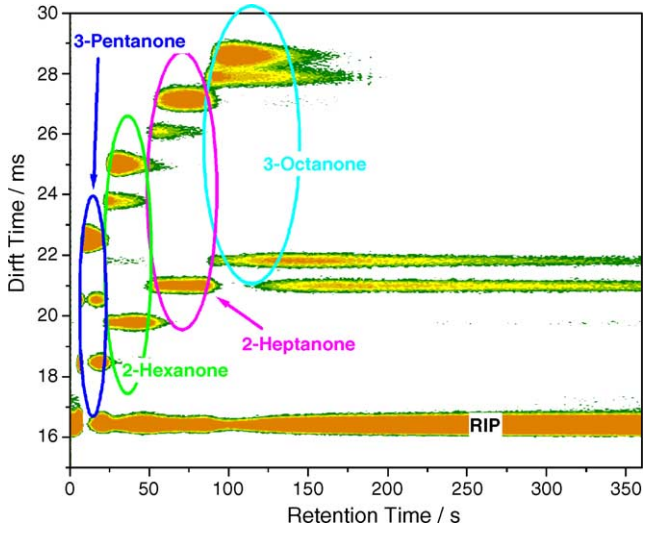

Fig. 3. Isothermal separation using MCC coupled to ^{63}Ni-IMS.

Table 3
Reduced mobilities and retention times of the ketones separated

Substances	MXT-capillary column				Multi-capillary column			
	Reduced mobilities (cm^2/V s)			Retention times (s)	Reduced mobilities (cm^2/V s)			Retention times (s)
	Peak 1	Peak 2	Peak 3		Peak 1	Peak 2	Peak 3	
3-Pentanone	1.85	1.67	1.52	30	1.85	1.66	1.52	18
2-Hexanone	1.73	1.44	1.37	100	1.73	1.43	1.37	25
2-Heptanone	1.63	–	1.26	205	1.63	1.31	1.26	68
3-Octanone	1.56	1.23	1.19	283	1.57	1.23	1.20	98

adequate peaks of the different substances in the two analyses investigated.

Comparing the separation times in both analyses, the measurement using MXT- capillary column exhibits nearly three times longer retention times for 2-hexanone, 2-heptanone, 3-octanone against the higher column temperature and sample flow rate used. Thus, MCC occurs a faster isothermal separation in lower temperature and due to the smaller peak diffusion effect, detection limits of the compounds detected are reduced, so it is well applied for trace gas analysis.

3.1. Breathe VOCs

Reduced mobility's (K_0) of the breath VOCs described above were calculated for peaks found in ion mobility spectra of the analytes as shown in Table 4. To achieve the reproducibility threefold determination was accomplished.

The spectra were obtained in positive polarity at room temperature and ambient pressure. Detection limits were calculated considering 3σ values on exponential dilution investigations.

These detection limits are comparable to the concentration values of the VOCs detected in the breath with other analysis methods [31,32]. Therefore, in principle the detection of these components in the breath using IMS is achievable.

3.2. Applicability of the MCC-^{63}Ni-IMS in the clinical diagnostic

In cooperation with the lung hospital in Hemer on-site measurements were carried out with the exhaled air of 40 subjects included 22 patients suffering from different pulmonary lung infections. As a control group 18 healthy persons were analysed. A strategy for the sampling was defined. The full

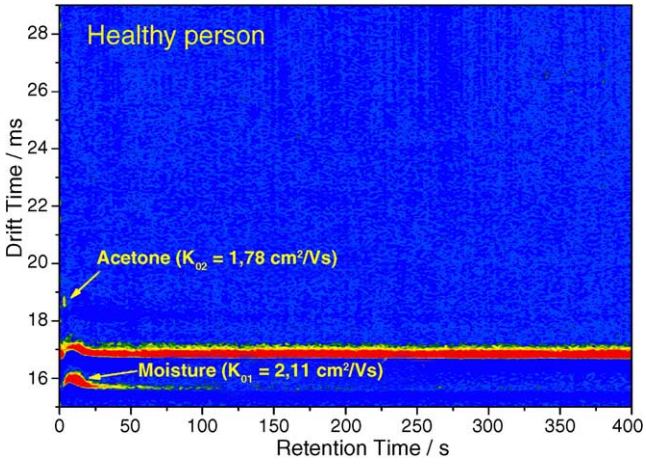

Fig. 4. IMS-topographic plot from the breath of a healthy person.

analysis was accomplished always in the same room, where room air was determined before each of the breath measurements. To reduce the risk of cross contaminations coming from other processes the subjects did not drink, eat and smoke 2 h before the breath measurements.

In Figs. 4 and 5, IMS-chromatograms from the exhaled air of a healthy person and a patient suffering from bacterial lung infection are displayed. From both plots the room air values were subtracted.

The formation of reactant and product ions in IMS can be altered by moisture; therefore, the separation of water is very important in case of working with samples containing high moisture level, like breath. Pictures show that the high breath moisture (K_{01} = 2.11 cm^2/V s) could be separated by the multi-capillary column at the beginning of the spectra, so it does not have any disturbing effect for the peaks coming at longer retention times. In the topographic plot of the exhaled

Table 4
Ion mobility's and detection limits of the substances selected

Substances	Reduced mobility (cm^2/V s)			Detection limits	
	Peak 1	Peak 2	Peak 3		
Acetone	1.80 ± 0.02			50 pg/L	20 ppt_v
Ammonia	2.02 ± 0.02			10 pg/L	14 ppt_v
Ethanol	1.89 ± 0.03	1.73 ± 0.03		1 μg/L	525 ppt_v
Isobutanol	1.66 ± 0.02	1.41 ± 0.02		200 pg/L	65 ppt_v
Isopren	1.64 ± 0.02	1.40 ± 0.03	1.20 ± 0.03	8 pg/L	3 ppt_v
Pentane	1.68 ± 0.02	1.39 ± 0.02		5 μg/L	2 ppm_v

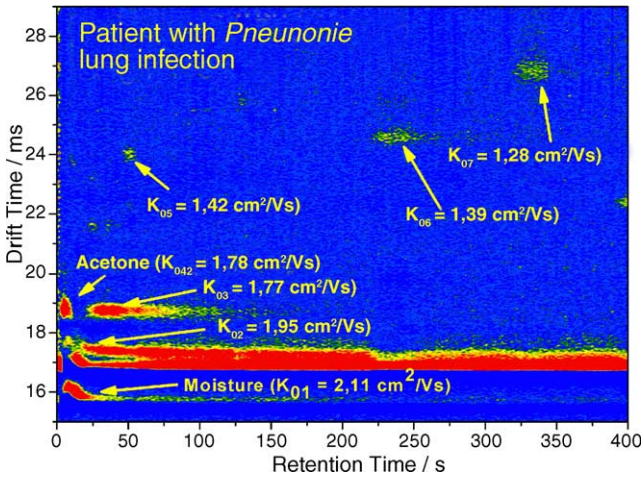

Fig. 5. IMS-topographic plot from the breath of a patient suffering lung infection.

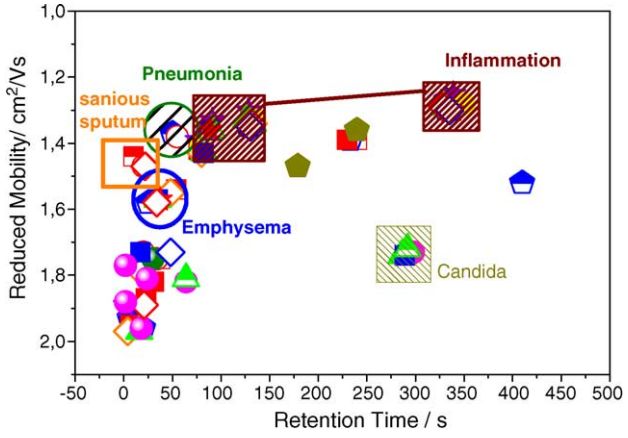

Fig. 6. Pattern of the peaks found exclusively at patients with pulmonary diseases. Peaks of airways inflammations detected on higher frequency are marked with brown boxes, of emphysema with blue circle, of fungal *Candida* infections with green box, of bacterial *Pneumonie* infections with green circle and of sanious sputum with orange box.

air of the healthy person acetone was identified based on its reduced mobility (K_{02} = 1.78 cm^2/V s). Acetone has a similar retention time like water, but it possesses a stronger proton affinity ($PA_{acetone}$ = 812 kJ/mol, PA_{water} = 691 kJ/mol), which is enough to be ionised in ion-molecule reactions. For other molecules, which have lower proton affinity or build instable ions, the sensitivity of IMS can be especially affected by water.

Comparing the two IMS-chromatograms the differences are conspicuous; in the case of the ill patient the 2D-plot shows diverse additional peaks. Two peaks coming at the retention times 28 s (K_{02} = 1.95 cm^2/V s) and 36 s (K_{03} = 1.77 cm^2/V s) are probably degradation products of antibiotics or other drugs, because they were also found in the breath of several persons who had treated with antibiotics. The peak at the position of 50 s and K_{05} = 1.42 cm^2/V s was also detected in the exhaled air of other patients suffering from *Pneumonie* infection. Two other bigger substances with lower mobility values (K_{06} = 1.39 cm^2/V s and K_{07} = 1.28 cm^2/V s) and longer retention times (t_{ret6} = 244 s, t_{ret7} = 330 s) were often found in case of patients with bacterial infections and airway inflammations.

Fig. 6 gives a summary from the breath pattern of the 22 patients examined suffering from different pulmonary lung diseases. Peaks found also in the exhaled air of healthy persons are not displayed in this plot.

Peaks summarized with the brown box were detected in the breath of patient with airways and pulmonary inflammations. Inflammations occur normally as secondary disease at persons with weak immune system, so these peaks could be found with big frequency in case of these patients. The blue circle shows the peaks detected at persons suffering from a very often diagnosed lung airflow limitation disease—emphysema. In the green box the potential markers of fungal *Candida* infection are displayed. Peaks summarized with the green circle were found in the case of patients with bacterial *Pneumonie* infections.

To verify the characteristic peaks detected, further measurements will be investigated including a larger number of patients and healthy persons. Data will be processed using statistical methods to clear the assignment between the diseases and the characteristic pattern of the IMS-topographic plots. In the near future, the results should be confirmed by comparatively analysis using mass spectrometry. Quantification of the compounds identified will be intended.

4. Conclusions

The system constructed by coupling of IMS to MCC exhibits sufficient high sensitivity for detecting organic metabolites. The MCC–IMS can be well applied to detect mixtures of analytes like exhaled air. The main benefit of the technique developed is the possibility of on-site and rapid analysis, which allows the direct application of the system in hospitals. Moreover, the possibility of the system's further miniaturisation may support the commercialisation of the device. Using MCC–IMS directly in the clinical diagnostic will provide new additional information within some minutes and facilitate building databases for several illnesses.

Acknowledgements

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