Talanta 191 (2019) 141–148

Contents lists available at ScienceDirect

Talanta

journal homepage: www.elsevier.com/locate/talanta

Hyphenation of a MEMS based pre-concentrator and GC-IMS

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ARTICLE INFO

Keywords:
Ion mobility spectrometry
Gas chromatography
Adsorption
Thermal desorption
In-line pre-concentration
Diphosphonate cavitand

ABSTRACT

A **m**icro-**e**lectro-**m**echanical **s**ystem (MEMS) based pre-concentrator filled with a standard Tenax TA adsorbent as well as with a synthetic receptor designed to adsorb 3-hydroxy-3-methylhexanoic acid (3H3MHA), a particular metabolite only available from human beings, was adapted to a custom made ion mobility spectrometer with gas-chromatographic pre-separation (GC-IMS). This combination was compared to a traditional sample loop GC-IMS. The application of a pre-concentrator is highly beneficial for the GC-IMS as analysing technique. By variation of the adsorbed sample volume, the system can be adapted to changing sample concentration ranges easily, thus increasing sensitivity significantly. Detection limits of few hundred ppq_V could be obtained in this work for eucalyptol and 3 human metabolites (benzaldehyde, 2-ethyl-1-hexanol and decanal) as exemplary analytes. Moreover, the appropriate choice of selective pre-concentration phases in the pre-concentrator enables an adaptation of sampling to the composition of the mixture. Relevant compounds in very low concentrations can be amplified by using specially designed cavitands while interfering substances could be suppressed. This was successfully demonstrated by detecting 3H3MHA, a compound exclusively available in human sweat, which can be used to locate trapped or hidden individuals.

1. Introduction

Gas Chromatography - Ion mobility spectrometry (GC-IMS) is a highly sensitive and selective combination of two techniques, detecting volatile compounds in the ppb_V down to the upper ppt_V-range. GC-IMS have already been applied for many applications such as process control [1,2], bio-marker research [3], drug detection, [4] medical diagnosis by breath analysis [5] or even in medical animal models [6]. Its use even below such low concentrations [7] requires accurate sampling, which generally rules out the in-line sampling mode. Typically, off-line pre-concentration steps using solid phase micro extraction (SPME) [8] or sampling tubes filled with adsorbents such as Tenax TA [9] are applied. This entails elaborate auto-sampling devices or even manual transfer of the SPME fibre or sampling tube to the desorption unit of the analytical device.

When gas-chromatographic pre-separation [5] is coupled to any detection step, a continuous sample introduction is no longer possible. Therefore, sampling must be adapted to the situation by a sequential sample introduction. This could be drawing and storage of the sample volume for later analysis, as the GC technique relies on a focussed sample injection. With regard to IMS as detector, the most common solution is the application of a sample loop with a particular volume. However, this requires the injection of the sample into the loop for a particular time to ensure it contains only the sample, which is at least an exponential process. When injecting the sample into the analytical system by a carrier gas, corresponding to an exponential dilution, not the complete original sample will be introduced into the GC column at one time, thus leading to smaller signals with significant tailing compared to a sudden complete sample introduction.

Another disadvantage of the traditional sampling is related to the analysis of extremely complex and humid samples such as human breath or environmental air. Quite often humidity or interfering species have negative influence on the identification and quantification of the

Abbreviations: 3H3MHA, 3-hydroxy-3-methylhexanoic acid; GC, gas-chromatography; IMS, ion mobility spectrometry; MEMS, micro-electro-mechanical system; MPC, MEMS based pre-concentrator; PTFE, polytetrafluoroethylene; RIP, reactant ion peak; SPME, solid phase micro extraction; VOC, volatile organic compounds

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https://doi.org/10.1016/j.talanta.2018.07.057
Received 29 March 2018; Received in revised form 17 July 2018; Accepted 18 July 2018
Available online 19 July 2018
0039-9140/

compounds of interest for a particular application. Therefore, a rapid and selective sampling would be a significant improvement when coupled to a GC-IMS. The use of in-line pre-concentration was already demonstrated with a different setup for differential mobility spectrometry [10].

Here we report an innovative approach to increase sensitivity and robustness for the lower ppt_V-range in IMS analyses, by introducing an innovative MEMS (**m**icro-**e**lectro-**m**echanical **s**ystem) based pre-concentration device [11]. This device was implemented in-line in the sampling module to enable an automated sampling and analysis without any transfer of the adsorbed sample to the desorption unit. The analytical performance of the hyphenated instrument was tested with eucalyptol, a "Signs of Life" mixture and 3-hydroxy-3-methylhexanoic acid (**3H3MHA**) as specific marker of human sweat [12]. In this last case, the detection of extremely low concentrations of the analyte was made possible by the presence of a pre-concentration phase operating via molecular recognition [13], while for eucalyptol a LDL as low as 300 ppq_V was demonstrated.

2. Materials and methods

2.1. GC ion mobility spectrometry (GC-IMS)

A custom-made ion mobility spectrometer coupled to a multi-capillary gas-chromatographic column (GC-IMS, ISAS, Dortmund, Germany) was used for the present study. The details are described elsewhere [5]. The IMS consists of an ionisation region equipped with a 500 MBq Tritium ß-radiation source, a Bradbury-Nielsen grid for ion introduction into the 12 cm drift region operated at 330 V/cm and a Faraday-plate for detection. The drift time of the particular ions is measured and after normalising its reciprocal value to drift length, electric field strength and to temperature and pressure, the so-called reduced ion-mobility is obtained (Eq. (1)), which is a general measure for the identification of the compounds detected. Using ß-radiation ionisation, the present drift gas is ionised resulting in protonated water clusters, the so-called reactant ions (RIP). The ionisation of analytes in the sample occurs by proton transfer from the reactant ions.

$$K_0 = \frac{L_D}{E \cdot t_D} \cdot \frac{p}{p_0} \cdot \frac{T_0}{T} \quad (1)$$

With K_0: reduced ion mobility in $cm^2\ V^{-1}\ s^{-1}$
E: electric field strength in V/cm
L_D: drift path length in cm
t_D: drift time in s
p: pressure in hPa, $p_0 = 1013.2$ hPa
T: temperature in K, $T_0 = 273.2$ K

Clustering of the different analyte ions among each other and with water molecules takes place when analysing complex, humid gas samples, thus making their identification difficult or even impossible. Therefore, an additional separation is required by using gas-chromatographic columns before the sample is introduced in to the IMS. For the present study, a multi-capillary column (OC-5, 20 cm, 150 mL/min, 40 °C, Sibertech, Novosibirsk, Russia) was applied for rapid GC separation.

Using a GC-IMS for gas-phase analysis, the sample cannot be introduced into the analytical system continuously. Therefore, commonly a sample volume is used. This volume – usually 1–10 mL – is flushed with the sample and by switching a 6-way-valve it is introduced into the analytical system. In general, the entire sampling and analysis process is divided into 8 steps:

1. Flushing of the sample volume
2. Injection of the sample volume into the GC column
3. Gas-chromatographic separation in the GC column
4. Introduction into the IMS
5. Ionisation of the sample compounds
6. Introduction of the ions into the drift region by the Bradbury-Nielson grid
7. Ion mobility separation in the drift tube
8. Detection by the Faraday-plate

With typical settings (e.g. 10 mL sample loop, 150 mL/min carrier gas and sample flow) drawing a sample into the loop requires ~25 s to provide a sample concentration of > 99,9% in the sample loop. Vice versa, it also takes ~25 s to inject > 99,9% of the sample into the analytical system. Although the injection process is often cut off after e.g. 10 s to avoid tailing when already ~95% of the sample is injected, the procedure of sampling and sample introduction takes in the range of 20 – 60 s, depending on sample flow and volume, thus avoiding rapid and targeted sampling, in particular when the available sample volume is limited.

2.2. Data interpretation

For data interpretation, the software IONysos (ION-GAS GmbH, Dortmund, Germany) was used. It enables data treatment in a first step, including baseline correction, smoothing and normalisation of signal intensity to the reactant ion peak (RIP).

Retention time deviations – due to small temperature or flow deviations – were aligned linearly to the absolute retention time of a known compound as described in detail in [14]. The drift velocity of the ions obtained from the drift time measurement could be normalised to electric field, drift length, pressure and temperature. However, alternatively we align the ion mobility to the position of the RIP with a known reduced ion mobility with even better reproducibility [15].

In the next step, the particular peaks detected in the 3-dimensional plot (signal intensity vs. ion mobility and retention time) are indicated and can be assigned to particular compounds by comparison with a substance database. In general, the inverse drift time is used as x-axes as it is proportional to the measured drift time, the retention time is the y-axes and the signal intensity is colour coded. (see Fig. 3 as an example). The signal intensity can be converted into a concentration after a calibration carried out earlier. Finally, the concentrations from different GC-IMS analysis data can be compared automatically.

For visualisation, in general, the reactant ion signal (RIP) is subtracted from the data. Thus, even small signals in the shoulder of the RIP can be made visible.

2.3. MEMS based pre-concentrator (MPC)

Using Silicon micromachining technology, a set of small-sized purge &trap pre-concentration cartridges was prototyped at CNR-IMM, Bologna. Two versions sized 25 mm x 7 mm and 25 mm x 14 mm were fabricated, consisting of silicon/borosilicate chips with integrated thin-film platinum metallisations implementing Joule heating and temperature sensing capabilities. Details on the fabrication process are reported in [11]. Fig. 1(a) and (b) show the mask layouts and photographs for the two versions, while Fig. 1(d) shows a simplified cross-section of a MPC chip.

The chips feature two holes on the top borosilicate wafer as in- and outlets, and implement a micro-chamber which can be filled with a mesh of sorbents by applying vacuum to the pre-concentrator output and slowly dripping the sorbent phase into the inlet. Integrated filter structures at the outlet side of the micro-chamber avoid leakage of the mesh during the filling procedure. During purge&trap operation, the flow direction is inverted between the sampling and the desorption phases, therefore a suitable filter mesh must be installed at the inlet side of the chips. Fig. 1(c) shows a photograph of two MPC chips filled with different sorbents. Cavitand ABii was custom made at the University of Parma, Italy and Tenax© TA (mesh 80/100), a porous polymer