

Enhancing sensitivity of ion mobility spectrometry determination of aldehydes by in situ gas phase derivatization with dibutylamine

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Abstract A simple and fast method for the detection of aldehydes by headspace solid-phase microextraction (HS-SPME) based on nanostructure polypyrrole film coupled to ion mobility spectrometry (IMS) is described. The detection of aldehydes (pentanal, hexanal and heptanal) has been successfully accomplished using in situ chemical derivatization with dibutylamine as the derivatization reagent and IMS. The simultaneous and rapid detection of aldehydes is important, since elevated level of aldehydes is considered as the biomarker of different diseases. The highlight of this method was that it involved an amine nucleophilic addition reaction (which was often considered as Mannich reaction) in gas phase for enhancing IMS sensitivity of aldehydes. Dibutylamine was used as the derivatization reagent driven into the cell by using a syringe pump. The calibration graphs were linear in the range of 2.0–50.0 $\mu\text{g mL}^{-1}$ with $R^2 \geq 0.99$ in aqueous solutions and limit of detections were determined $\leq 1.8 \mu\text{g mL}^{-1}$. The RSD% values of the aldehydes determination was $\leq 8 \%$. Here we have demonstrated that other amine types (butylamine and tributylamine) can derivatize aldehydes and significantly improve the IMS sensitivity of tagged analytes. However, IMS spectrum is complicated by presence of the different product ions in the process.

Keywords Enhancing sensitivity · Ion mobility spectrometry · Aldehyde · HS-SPME · Polypyrrole · Nanostructure

Introduction

Aldehydes receive an increasingly considerable concern due to their potential adverse health effects and environmental prevalence; various aldehydes can be recognized as biomarkers of cancer diseases [1]. The toxicity of low molecular aldehydes to humans and animals is well known as a result [2]. There are many possible aldehydes sources for humans, such as aldehydes of environmental or occupational concerns, dietary and formed endogenously aldehydes by intermediary metabolism, and drugs that are aldehydes or that form reactive aldehyde metabolites that cause side-effect toxicity [3]. The analysis of exhaled breath has been used to noninvasively obtain information about inflammatory processes within the lung. The exhaled breath contains a complex mixture of volatile organic compounds (VOCs), which can be detected using different methods. The development of highly sensitive and selective techniques with trace-level detection and unequivocal analyte identification capabilities is becoming increasingly desirable in analytical chemistry [4]. In recent years, a range of spectrometric techniques have been deployed to investigate human breath with studies being initiated into different diseases, infections, cancer and more general point of care and intensive care applications [5–12].

As a result, the analysis of aldehydes in biological samples (mainly blood) has obtained much attention due to their directly being related to the internal activities [1]. Many methods for the detection of aldehyde in samples have been reported, such as fluorometry, spectrophotometry, high-performance liquid chromatography (HPLC), gas chromatography, headspace-solid phase microextraction gas chromatography–mass spectrometry (HS-SPME- GC–MS) [2, 13–17] and ion mobility spectrometry (IMS) [18]. Rapid determination of different compounds by IMS devices has nowadays become a routine technique [19]. This fast and

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low-cost method has become an ideal technique for the fast and sensitive detection of trace quantities of volatile organic and inorganic compounds such as: explosives [20–22], drugs [23, 24], metal [25], biological compound [26–29], and volatile environmental pollutants [30–32], VOCs obtained from bronchoscopic sampling of breath [33]. Breath samples taken within the lung during bronchoscopy and to search for significant differences between signals arising from the tumor site compared to those from the collateral lung [33]. Two different types of IMS, such coupled to multi-capillary columns (MCC/IMS) [34–37] and differential mobility spectrometers [12, 38, 39] were reported.

Headspace solid phase microextraction (HS-SPME) with sampling from the headspace above the sample can especially offer a high potential in biomedical analysis, for producing neat spectra and protecting the fiber from irreversible damages by non-volatile concomitants present in the biological matrix [40].

In our study, we were able to extract aldehydes from headspace of solution by nanostructure polypyrrole as solid phase microextraction fiber and detected with IMS at atmospheric pressure after in situ chemical derivatization with dibutylamine as the derivatization reagent in gas phase. Dibutylamine was driven into the cell by using a syringe pump. Experimental conditions, like extraction temperature and time, solution pH, pump speed were optimized firstly.

Experimental

Chemicals and reagents

Pyrrole (Fluka, Switzerland) was distilled and stored in a refrigerator in dark prior to use. Sodium dodecylbenzenesulfonate (SDBS) was used as dopant from Aldrich. The stock solution of aldehydes and amines from Merck (Darmstadt, Germany) at a concentration of 1000 mgL^{-1} was prepared by dissolving appropriate amounts of each reagent in methanol (analytical grade). These standards were stored at $4 \text{ }^\circ\text{C}$ and were used for the preparation of working standard solutions. All other chemicals and reagents were of analytical grade purchased from Merck (Darmstadt, Germany).

Apparatus

The SPME holder for manual sampling was obtained from Azar Electrode (Ourumieh, Iran). A magnetic stirrer (Heidolph MR 3001 K) and a $2 \text{ mm} \times 5 \text{ mm}$ stirring bar were used to stir the solution. A laboratory made circulating cell was used to keep stable the temperature of solutions and SPME fiber, respectively. All pH measurements were performed at $25 \pm 0.1 \text{ }^\circ\text{C}$ by use of a pH meter (Metrohm 713, Switzerland) with a standard uncertainty of 0.1 mV. In all

experiments, amine solutions (in methanol) directly infused into the injection port of IMS using a syringe pump at a steady state pumping speed ($40 \text{ } \mu\text{Lmin}^{-1}$) high enough to meet optimum conditions. Electrochemical polymerization of pyrrole was carried out using Behpajuh potentiostat (BHP 2061-C model, Isfahan, Iran). Detection and quantification of aldehydes were carried out using an ion mobility spectrometer (IMS). The IMS (model 1000) used in this study was constructed in Isfahan University of Technology, Iran. The scanning electron micrographs of the fiber surface were obtained using a model S4160C Hitachi (Japan).

Fiber coating

Polypyrrole film doped with DBS (PPy-DBS) as solid phase was prepared electrochemically using a three-electrode system. PPy-DBS film was directly electrodeposited on the surface of a platinum wire (as working electrode) from an aqueous solution containing pyrrole (0.1 molL^{-1}) and SDDBS ($7 \times 10^{-3} \text{ molL}^{-1}$) by the application of a constant potential of +1.1 V versus Ag/AgCl electrode for 300 s. Prior to electropolymerization, the solution was deoxygenated by purging with N_2 for 10 min, and the platinum wire surface was cleaned in acetone and methanol using ultrasonic bath for 10 min and was subsequently washed with distilled water.

Results and discussion

Sampling and spectral behavior of aldehydes

The surface characteristics of the polymer film were investigated by scanning electron microscopy (SEM). Figure 1 shows the micrographs of the PPy-DBS fiber at 35000 fold

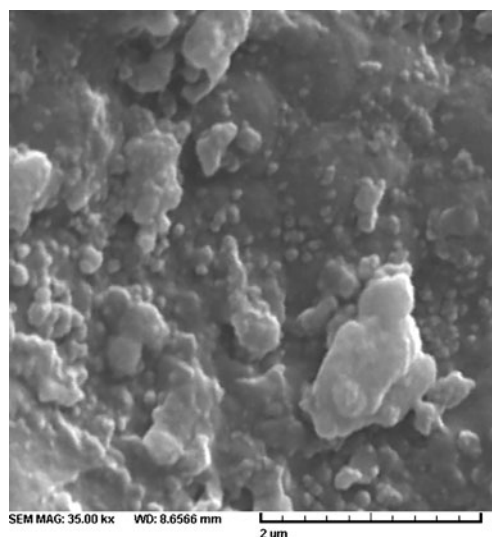


Fig. 1 The SEM of the PPy-DBS fiber at 35000 fold magnification

magnification. One clearly observes that the deposited polymers containing the spherical shape with particle size between 90 to 350 nm.

Figure 2 shows IMS spectra of aldehydes sampling by PPy-DBS fiber from the headspace above the sample solution. In the IMS spectral analysis of aldehydes, the instability of protonated aldehyd groups can pose significant problems in IMS analysis, affording a large number of pseudomolecular ions having different drift time values, resulting in highly complex spectra and decreased sensitivity (Fig. 2).

The presence of dibutylamine as derivatization reagent resulted in improvement in ion intensity and the substantial spectral simplification possibly by weakening of ion interactions and the subsequent stability of analyte ions in IMS cell. The detection of aldehydes (pentanal, hexanal and heptanal) has been successfully accomplished using in situ chemical derivatization with dibutylamine. Dibutylamine was used as the derivatization reagent driven into the cell by using a syringe pump. The enhancement sensitivity of IMS in positive ion mode toward compounds including nitrogen functional groups is due to high proton affinity of these groups. One of simple reaction that can be useful for aldehyde derivatization is amine nucleophilic addition reactions. Most reactions of aldehydes involve the carbonyl oxygen and are, in the first instance, addition reactions. Primary and secondary amines are especially suited to the study of the addition reactions of aldehydes, since they contain easily detachable (“active”) hydrogen atoms. In most cases the first recognizable step is addition of the amine to the carbonyl group of the aldehyde, in the sense

of the first phase of the amine nucleophilic addition reactions to aldehydes (1):



In the majority of cases, the hydroxy amine reacts further, in one of several ways. It may, for example, lose water, to give an imine (Schiff base); this corresponds to the “crotonaldehyde stage” of the Mannich condensation (2):



Alternately, the hydroxy amine may react further with one or the other of the reagents or with itself; or the Schiff base may be involved in the various subsequent reactions which are encountered, and which often lead to the formation of complex reaction products. The nature of the amine is the determining factor, even more frequently than the experimental conditions, for example tertiary amines bear no “active” hydrogen; they seldom enter into reaction with aldehydes [41].

The mobility of an ion in electric fields in IMS drift tubes depends on the inverse of both its collision cross section and the square root of its reduced mass. Eiceman et al. reported that mobility resolution of ions in IMS and IMS/MS experiments can be enhanced through chemical modification of the supporting gas atmosphere [42, 43]. For example, protonated ammonia and hydrazines form complexes with ketones and the differences in masses and mobilities of the resulting ions are sufficient for separation in an ion mobility spectrometer at ambient pressure. Morrison and Howard also reported, that a protonated hydrazone is observed under chemical ionization conditions in a drift tube attached to a mass spectrometer in the reaction of protonated hydrazone with aldehydes and ketones [44].

The effect of butylamine (primary amine) as derivatization reagent on the sensitivity and spectra simplification of selected aldehydes was also studied. The results showed that sensitivities were practically constant at the same experimental conditions with dibutylamine, whereas IMS spectra complicated due to the formation of unwanted side products. Clear, sensitive and simplified spectra were generated by using dibutylamine as derivatization reagent.

The concentration dibutylamine in IMS cell are directly proportional to the derivatization solution flow rate. By increasing the pumping speed, the concentration of protonated amine in the IMS is increased until proton exchange reaction between reactant ions and analyte reach to equilibrium in the ionization source at a steady state condition under a constant temperature. At high pump speeds may lead to blackout corona in the ionization chamber. So we obtained $40 \mu\text{L}\cdot\text{min}^{-1}$ as the optimized flow rate of dibutylamine (Fig. 3A). At this flow rate aldehyd-amine have

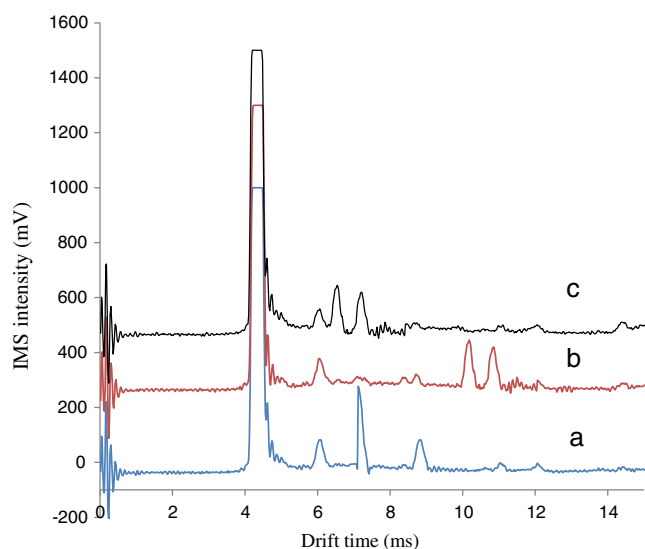
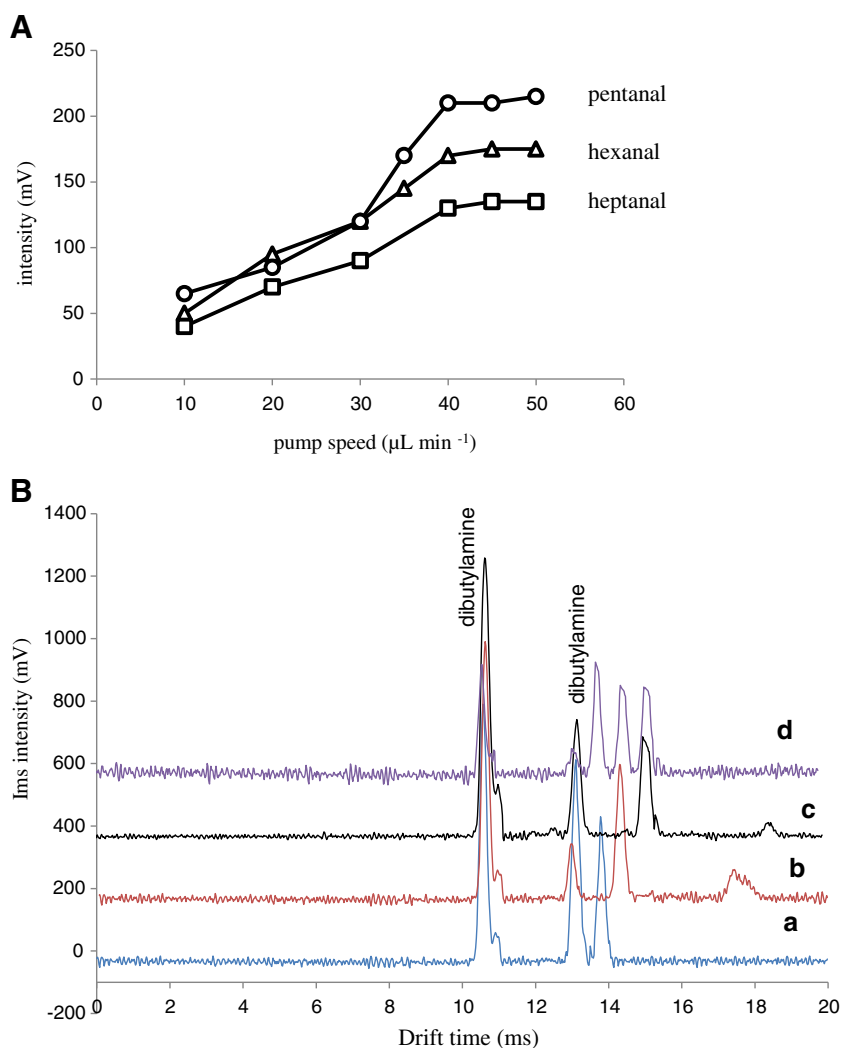


Fig. 2 IMS spectra of pentanal (a), hexanal (b) and heptanal (c) sampling by PPy-DBS fiber from the headspace of $10 \mu\text{g}\cdot\text{mL}^{-1}$ the aldehyde solution in water

Fig. 3 **A** Effect of pump speed on the HS-SPME for $2 \mu\text{g mL}^{-1}$ aldehyde IMS peak height after in situ chemical derivatization with dibutylamine in gas phase; sample volume: 5 mL, stirring rate: 300 rpm, extraction time: 20 min, extraction temperature: 40°C , NaCl: 2.0 mol L^{-1} , dibutylamine concentration: $150 \mu\text{g mL}^{-1}$ in methanol, pump speed $40: \mu\text{L min}^{-1}$, pentanal-amine (\circ), hexanal-amine (Δ) and heptanal-amine (\square). **B** The ion mobility spectrum obtained by HS-SPME using a PPy-DBS film from headspace of $2 \mu\text{g mL}^{-1}$ of pentanal (a), hexanal(b), heptanal (c) and mixed solution (d) after in situ chemical derivatization with dibutylamine in gas phase



maximum intensities. Ion mobility spectrum of different aldehyd-amine products is shown in Fig. 3B.

For identification purposes, reduced mobility (K_0) is often used instead of drift time. Reduced mobilities are calculated for positive ion mode using ammonium as the calibrant. The reduced mobility is normalized to a standard pressure (760 Torr) and temperature (273 K). Reduced mobility can be calculated using Eq. (3), where K_0 is the reduced mobility with the units of ($\text{cm}^2 \text{V}^{-1} \text{s}^{-1}$), and t_d is the drift time. The regression equation of the mass-to-mobility correlation curve for corona discharge IMS was shown in Eq. (4):

$$K_0(\text{unknown}) = K_0(\text{standard}) \times t_d(\text{standard})/t_d(\text{unknown}) \quad (3)$$

$$\text{Log } m = -0.52 K_0 + 2.95 \quad (4)$$

The peaks observed in the corona discharge IMS spectra can be assigned to ions formed by hydrogen abstraction and clustering with water [45, 46]. Therefore, in Eq. (4) m is the mass of product ions. The optimized instrumental conditions for obtaining the IMS spectra of the aldehydes and its

products are listed in Table 1. The drift times and reduced mobility ions together with their corresponding mass-to-mobility are given in Table 2.

Optimization of HS-SPME conditions for aldehydes determination

To optimize the method all the extractions were performed from the headspace of 5 mL water solution spiked with

Table 1 The optimized experimental IMS conditions for aldehydes

Parameter	Value
Corona discharge voltage (V)	3000
Drift field voltage (V)	6000
Drift gas flow, N_2 (mL min^{-1})	380
Carrier gas flow, N_2 (mL min^{-1})	120
Drift tube temperature ($^\circ\text{C}$)	150
Injection temperature ($^\circ\text{C}$)	180
Drift tube length (cm)	11
Shutter grid pulse (μs)	250

Table 2 The drift times and reduced mobility ions together with their corresponding mass-to-mobility

Ion products (Mass) ^a	drift time (ms)	K_0 (cm ² V ⁻¹ s ⁻¹)	Mass-to-mobility (a.m.u)
Butylamine (73)	8.0 ^b , 10.6, 13.0	2.00 ^c , 1.50, 1.22	81 ^d
Dibutylamine (129)	10.5, 13.1	1.52, 1.16	144
Butylamine-Pentanal (141)	10.7, 13.2, 13.7	1.49, 1.21, 1.16	141
Butylamine-Hexanal (151)	11.4, 12.8, 17.3	1.40, 1.24, 0.92	156
Butylamine-Heptanal (196)	12.2, 15.2	1.31, 1.05	170
Dibutylamine-Pentanal (197)	13.7	1.11	220
Dibutylamine-Hexanal (211)	14.3	1.12	231
Dibutylamine-Heptanal (225)	15.0	1.06	248

^a Mass (a.m.u)^b Corresponding drift time of monomer^c Corresponding reduced mobility ion^d Calculated from Eq. (4) with relative errors < 5 %

appropriate amount of standard aldehydes solution (2 $\mu\text{g mL}^{-1}$). The effects of the main extraction parameters, such as

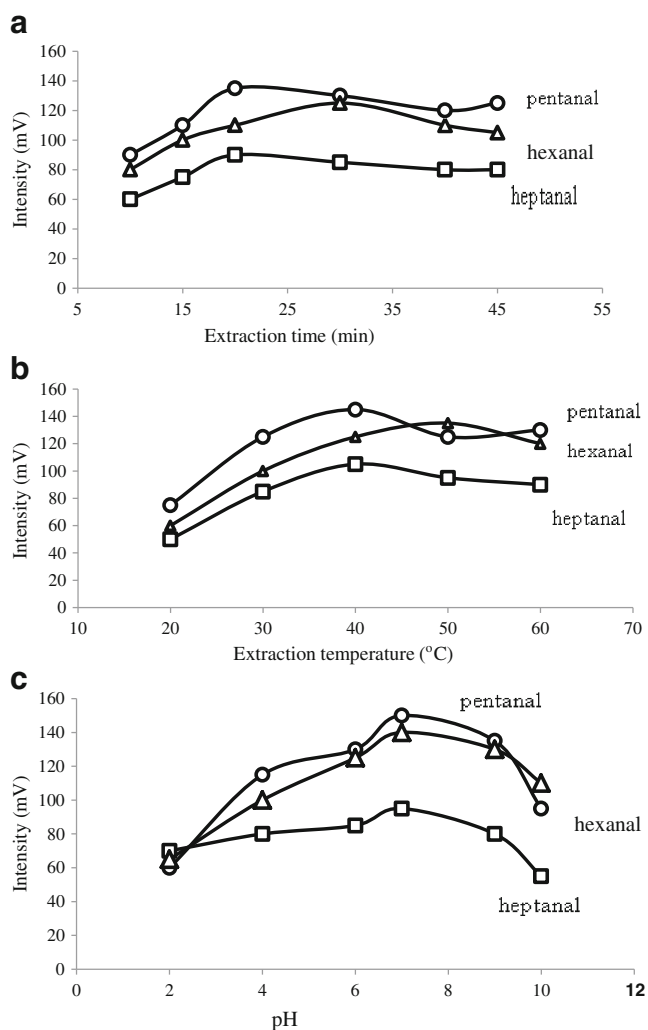


Fig. 4 Effect of extraction time (a), extraction temperature (b) and sample pH (c) on the HS-SPME-IMS for 2 $\mu\text{g mL}^{-1}$ of pentanal (\circ), hexanal (Δ) and heptanal (\square) after in situ chemical derivatization with dibutylamine in gas phase; sample volume: 5 mL; stirring rate: 300 rpm, extraction temperatures: 40 $^{\circ}\text{C}$ (in a, c), extraction time: 20 min (in b, c), extraction pH: 7 (in a, b) NaCl: 2 mol L^{-1} (a, b, c)

the temperature, sample pH, extraction time and ionic strength of sample were studied and optimized. The maximum of peak height of analyte was used as the IMS response to evaluate the extraction efficiency under different conditions. The optimum extraction time was determined by varying the exposure time of the fiber in the headspace of 2 $\mu\text{g mL}^{-1}$ aldehydes in aqueous solution from 10 to 45 min. It is generally accepted that the reduction of the diffusion layer is essential in order to reach equilibrium faster, which is easily achieved by sample agitation. Therefore, magnetic stirring was applied during the extraction step; Fig. 4a illustrates the extraction time profile.

In HS-SPME approach temperature has a profound effect on extraction efficiency. It influences the rates of mass transfer and the partition coefficients of the analyte by increasing the Henry's constant and vapor pressure of analyte. Consequently, the concentration of analyte in the headspace and fiber coating would be increased. But temperature has two effect, one of them is increase concentration of sample in head space and another decies adsorption of sample in high temperature because of adsorption is exothermic processes, then we should optimized it in point that first phenomenon's be in high and second be in low amount. The extraction ability enhances with increasing temperature (Fig. 4b). Thus, the sample temperature was held at 40 $^{\circ}\text{C}$ for subsequent analysis.

To consider the effect of pH on the extraction, the PPy-DBS fiber was exposed to the headspace over the stirring liquid samples for 20 min with the same concentration in the 2 $\mu\text{g mL}^{-1}$ level at different pH values (2.0–10.0). Observed

Table 3 Analytical results for determination of aldehydes in water sample by HS-SPME and in situ chemical derivatization with dibutylamine and IMS determination

Aldehyde-dibutylamine	DLR ($\mu\text{g mL}^{-1}$)	Correlation coefficient (R^2)	RSD% ($n=3$)	LOD ($\mu\text{g mL}^{-1}$)
Pentanal	2–50	0.990	7.0	1.3
Hexanal	2–50	0.992	5.5	1.6
Heptanal	2–40	0.993	8.0	1.8

values in Fig. 4c have revealed that sample pH has an important influence on the form of the extracted analyte on the PPy-DBS fiber, and have the best extraction efficiency in pH7. SPME methods can be optimized by altering the ionic strength of the matrix. Typically, analyte solubility decreases as ionic strength increases (salting-out effect). A decrease in analyte solubility improve sensitivity by promote analyte partitioning into the fiber. The influence of ionic strength of the sample solution on the HS-SPME effectiveness was evaluated in the range of 0–4 molL⁻¹ of NaCl concentration. The best results obtained for an aqueous sample containing 2 molL⁻¹ NaCl, therefore, all further extractions were conducted with 2 molL⁻¹ NaCl added.

The spiked water sample was employed to investigate the linearity, repeatability and limit of detection under the optima experimentally conditions. Main figures of merit were established under optimized conditions for HS-SPME of aldehydes in water samples. Best analytical characteristics were obtained with pH7, extraction time of 20 min and sample containing 2 molL⁻¹ of NaCl at temperature of 40 °C, respectively. In order to assess the repeatability, peak height of three replicate analysis for 2 µg mL⁻¹ aldehydes were used and expressed as relative standard deviation (RSD%). The RSD% for aldehyde determination was ≤ 8 %. The calibration graphs was linear in the range of 2–50 µg mL⁻¹ with $R^2 \geq 0.99$ in aqueous solution. The limit of detections was determined ≤ 1.8 µg mL⁻¹ at a signal-to-noise ratio (S/N) of 3. Result of HS-SPME-IMS analysis for spiked water samples is displayed in Table 3.

Conclusion

In this work, a new method for the analysis of aldehydes was proposed using dibutylamine as the derivatization reagent for simultaneous determination of pentanal, hexanal and heptanal by HS-SPME-IMS. This method represents several advantages such as, in situ chemical derivatization in gas phase, enhancing sensitivity and successfully simplified IMS spectra. Regarding sensitivity, repeatability, time of analysis among other characteristics, the proposed method was shown to be adequate to evaluate aldehyde levels in water samples without any further pre-treatment.

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