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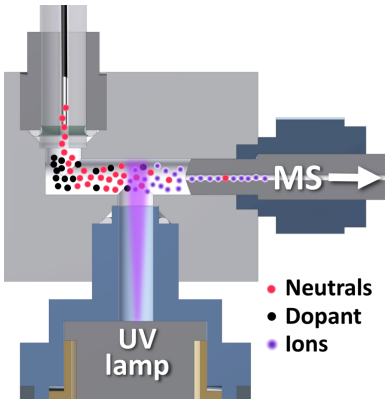
Abstract



A novel capillary ionization source based on atmospheric pressure photoionization (cAPPI) was developed and used for the direct interfacing between solid-phase microextraction (SPME) and mass spectrometry (MS). The efficiency of the source was evaluated for direct and dopant-assisted photoionization, analyzing both polar (e.g., triazines and organophosphorus pesticides) and nonpolar (polycyclic aromatic hydrocarbons, PAHs) compounds. The results show that the range of compound polarity which can be addressed by direct SPME-MS can be substantially extended by using cAPPI, compared to other sensitive techniques like direct analysis in real time (DART) and dielectric barrier discharge ionization (DBDI). The new source delivers a very high sensitivity, down to sub-parts-per-trillion (ppt), making it a viable alternative when compared to previously reported, and less comprehensive direct approaches.

Keywords: atmospheric pressure photoionization, APPI, capillary ionization, SPME, direct analysis, low polar compounds, PAHs, pesticides.

Introduction

Atmospheric pressure photoionization (APPI) is a soft ionization technique which relies on ultraviolet photons to ionize chemical compounds at ambient pressure. It was introduced as an ionization technique for liquid chromatography-mass spectrometry (LC-MS) by Robb et al.[1] and Syage et al.[2]. The first use of photoionization in combination with gas chromatography-mass spectrometry (GC-MS) was reported by Revelsky et al.[3] in 2003, followed by many others in the next years [4–14]. Like most ambient ionization techniques, APPI delivers soft ionization, meaning that the energy transferred to the analytes during the ionization process is relatively low, i.e., mainly radical molecular ions or protonated

quasimolecular ions are formed, with little to no fragmentation. The softness of the ionization is in most cases very useful, and makes atmospheric pressure ionization (API) techniques attractive compared to conventional electron ionization (EI) techniques, where electrons are usually accelerated at 70 eV, causing extensive fragmentation of the molecules of interest.

Two important parameters affecting the ionization in APPI are the type of UV lamp used and the use of dopants. Direct current (DC) and alternated current (AC) discharge lamps are normally used, the latter providing higher photon fluxes compared to DC lamps. Depending on the type of gas in the lamps, the resulting UV photons will have different energies, e.g., krypton (Kr) lamps emit photons with energies of 10.0 and 10.6 eV, while argon and xenon lamps generate 11.7 and 8.4 eV photons, respectively[13]. Choosing the right photon energy is very important, since only compounds having ionization energies lower than the UV photons can be ionized. Lamps emitting photons with higher energy allow to ionize a wider range of compounds, but this also generates higher background signals from interfering compounds (atmospheric gases and chromatographic solvents[14]), while lower energy photon lamps are more selective and deliver cleaner spectra. For this reason, Kr lamps are the most frequently used sources of UV photons, since most organic molecules have ionization energies below the lamp's energy[14], while using less energetic lamps might preclude the ionization of some compounds of interest.

Because of the relatively low photon density delivered by UV lamps, dopants can be used to enhance the ionization[1]. Dopants are UV-absorbing molecules having an ionization energy (I.E.) intermediate between the photon energy and the I.E. of the compounds of interest. They are introduced into the ionization source at a much higher concentration than the compounds of interest, such that they absorb most of the UV photons. Subsequently, the neutral analyte molecules are ionized by charge and/or proton transfer reactions[13], depending on the nature of the dopant.

Capillary APPI (cAPPI) is a variant of APPI and refers to an approach of ionizing molecules in a confined volume inside the source itself,[15,16] which improves the ionization efficiency and ion transmission to the MS. Haapala et al.[15] reported a capillary photoionization source (CPI) which consists of a heated capillary having a MgF_2 window through which UV photons are allowed to enter the source. The authors were able to ionize selected polar and nonpolar compounds, including hormones, with limits of detection down to 2-6 pg/mL in combination with GC. Kersten et al.[16] used a different approach, with a cAPPI source which does not require the use of windows for the introduction of UV photons. In that setup, a custom spark discharge lamp was embedded in the MS transfer capillary, with sensitivities down to the low

ppbv range, and the possibility to monitor extremely fast reactions thanks to a temporal resolution on the order of milliseconds.

In addition to photoionization-based approaches, Jorabchi et al.[17] proposed an approach based on a combination of DART and APPI, where the use of a UV lamp together with a dopant supply was able to increase the ion yield of positive ions from 3 to 5 times, compared to conventional DART. Cody and Dane[18] also reported the use of dopant-assisted DART as a way to extend the range of compounds that can be ionized, with an ionization mechanism similar to APPI. Although a systematic determination of the limits of detection for PAHs was not reported, signal could be detected for a 5 ppb sample of PAHs, spiked on a melting point tube and directly analyzed by DART[18].

Direct interfacing of SPME to MS is an approach which has been developing rapidly in recent years[19]. Although several applications in food[20], environmental[21] and clinical[22] analysis have been reported, it still represents a niche application used in very specific cases, mostly targeted analysis. The reasons for that include the presence of more pronounced matrix effects and the fact that geometric parameters have to be carefully controlled during the entire analysis. The most successful direct coupling approaches are based on ambient ionization techniques like DART[23], DESI[24], or spray ionization[25–27], although several non-ambient methods have been reported, including the ones based on EI[28], ICP[29,30], LDI[31] and MALDI[32]. We recently proposed a new approach for the direct coupling of SPME to MS, based on dielectric barrier discharge ionization (DBDI) and thermal desorption[33], which reduced matrix suppression effects by decoupling the desorption of the analytes from their ionization, and which is not affected by geometric parameters of the SPME device.

A major limitation of direct coupling approaches based on ambient ionization is the limited range of compound polarity which can be investigated. Because most of the API sources used rely on proton transfer reactions as the main ionization pathway, nonpolar molecules cannot be efficiently ionized in most cases, with only few exceptions[34–37], which limits the potential of direct coupling approaches and confines them to the analysis of polar molecules. An ionization source based on APPI is therefore beneficial to extend the accessible molecule polarity range, and to fully exploit the advantage of direct couplings to MS.

In this work, we describe the design of a novel cAPPI source which was used to direct interfacing SPME to MS. A more conventional GC-cAPPI-MS hyphenation was also used to evaluate the performance of the source. The construction is simplified compared to previous approaches, and allows for more flexibility for direct (non-chromatographic) analysis of samples. The source was used to analyze several compounds belonging to different chemical

classes, from very polar ones like atrazine pesticides to nonpolar ones like polycyclic aromatic hydrocarbons (PAHs).

Experimental section

Materials. HPLC-grade acetonitrile, water, hexafluorobenzene (99%) and chlorobenzene (99.9%), iodobenzene (>99%) and fluorobenzene (>99.5%) were obtained from Sigma-Aldrich (Buchs, Switzerland), and toluene (99.85%) and acetone (99.9%) from Acros Organics (Geel, Belgium). Analytical-grade pesticide and drug standards were purchased from Sigma-Aldrich, and were: ametryn, atrazine, prometon, prometryn, propazine, simazine, terbutryn, disulfoton, famphur, parathion, parathion-methyl, phorate, sulfotep, thionazin, triethyl thiophosphate, dimethoate, metolachlor, pyrimethanil, malathion, cyprodinil, flusilazole, cyproconazole, trifloxystrobin, quinoxyfen, tebuconazole, pyriproxyfen, pyridaben, difenoconazole, azoxystrobin, diazepam, cocaine, methadone, desipramine, imipramine, MDMA, ketamine, lidocaine and fentanyl. Phenanthrene-d_{10}, pyrene-d_{10}, and a polycyclic aromatic hydrocarbon mix (CRM 47930) were purchased from Sigma-Aldrich.

Sample preparation. Individual pesticide standard stock solutions were prepared at a concentration of 5 mg/mL in acetonitrile (ACN), and stored at -20°C. A mix of the pesticides at 100 μg/mL in acetonitrile was prepared from the stock solutions. Drug solutions were used as received, at a concentration of 1 mg/mL or 0.1 mg/mL in methanol. Diluted pesticide, drug and PAH mix solutions were prepared in ACN, and stored at a temperature of 4 °C while not in use. Water solutions used for SPME extractions were prepared by spiking PAH, pesticide and drug ACN solutions in HPLC water, maintaining a H_2O/ACN ratio of 99:1 (v/v).

Gas Chromatography. A Shimadzu GC-2014 was equipped with a split/splitless injector and a SLB-5ms 30 m, 0.25 mm, 0.25 μm column (Supelco). The carrier gas was helium (99.999%), maintained at a constant linear velocity of 40 cm/s. The injector temperature was 270 °C and 2 μL aliquots of sample were injected with an AOC-20i autosampler, in splitless mode for 1.1 minutes.

The GC oven temperature program was 55 °C for 1.1 min, ramped at 25 °C/min to 150 °C, followed by 10 °C/min to 280 °C, and by 20 °C/min to 315 °C, held for 8 min. For the SPME-GC experiments, the temperature programs were the same, with the exception of the

initial hold time, which was equal to the SPME desorption time and set to 1.4 minutes (in splitless mode). For liquid injection and SPME experiments, 4 mm and 0.75 mm I.D. liners were used, respectively.

The interface with MS was done by inserting the GC capillary column directly into the ionization source, enclosed in a transfer line kept at 300 °C. The column was placed at a horizontal distance of 5 mm from the center of the UV lamp, to minimize possible sample adsorption on the transfer line walls.

Mass spectrometry. Detection and quantification of selected pesticides was performed by a high resolution LTQ Orbitrap mass spectrometer (Thermo Scientific, San José, CA, USA). The total gas flow entering the source was constant and dictated by the inlet of the mass spectrometer, i.e., the metal transfer capillary dimensions, having an inner diameter of 0.6 mm, resulting in gas flow rates of 1.0 L/min. The LTQ interface parameters were as follows: capillary voltage, 0 V; tube lens voltage, 60 V; capillary temperature, 250 °C. The acquisition was performed with a mass window of 50 to 1000 *m/z*, with 1 micro scan, and with a maximum injection time of 100 ms. Automatic gain control (AGC) was used.

Quantification. Quantification by SPME-GC-cAPPI-MS and SPME-cAPPI-MS analyses was performed according to the extraction procedure reported below (section: SPME extractions). All analyses were performed in triplicate, and the calibration range investigated was between 0.01 pg/mL and 3000 pg/mL.

The quantification was based on positive ionization full scan mode with centroid acquisition, at a resolution of 30'000 (FWHM at 400 *m/z*). For each compound, the ion signal was integrated with a mass window of 2 ppm. In all cases, a 1/x weight was used for the calibration. Because of the high resolution used, background noise was not always observed in the extracted ion chromatograms within the 2 ppm mass tolerance window around the exact mass of the considered compounds. Therefore, the classical approach based on the evaluation of signal-to-noise ratio was not applicable, but limits of detection (LODs) and quantification (LOQs) were evaluated by analyzing samples at decreasing concentration.

Ionization source. A novel capillary APPI source was developed and built in-house. To allow high operating temperatures and minimize adsorption of analytes, the source was realized in stainless steel. The source assembly consists of three main parts: source core, desorption chamber and UV lamp assembly (Fig. 1).

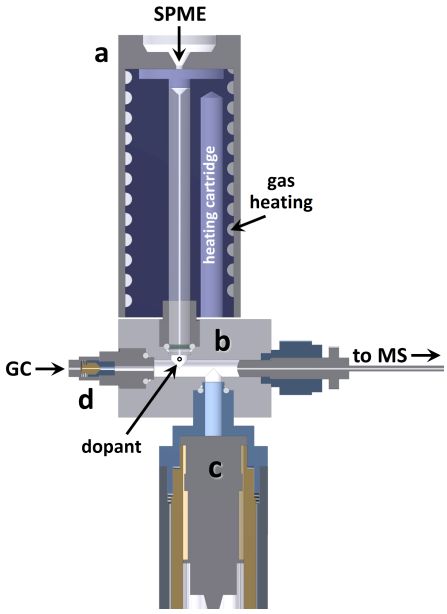


Fig. 1. Schematic of the capillary APPI source developed for this study. a) desorption chamber, b) source core, c) UV lamp assembly, d) capillary column connection.

The ionization chamber itself was connected directly to the mass spectrometer by means of a Swagelok connector. Since this is a capillary source, the amount of gas passing through it and entering the mass spectrometer is determined by the vacuum in the MS itself. By using a 0.6 mm inner diameter metal transfer line in the LTQ, the gas flow rate entering the MS was measured to be 1.0 L/min. This gas flow was delivered by a thermal desorption chamber directly connected to the ionization chamber. The desorption chamber allowed to desorb the SPME fibers, as well as pre-heat the nitrogen gas entering the source. A precise temperature control (± 0.1 °C) of the desorption chamber and the source core was achieved by using PID controllers. Adsorption of the compounds inside the desorption unit was minimized by using a glass liner which was passivated by silanization.

Ionization was achieved by using a DC-excited kripton discharge lamp (Heraeus Noblelight UK, model PKS106) emitting UV photons at 10.6 and 10.0 eV. The lamp was operated through a lab-built high voltage power supply, at a current of 0.38 mA. A lamp housing was built using stainless steel and PEEK, and the lamp assembly was also connected to the ionization chamber.

The dopant was introduced into the ionization chamber by means of a fused silica capillary, and it was evaporated directly inside the camber without additional gas. A precise control of the dopant flow rate was achieved by using a pressure-assisted liquid introduction system: a dopant reservoir was kept under pressure and contained one end of the fused silica capillary. The desired flow rate was then achieved by adjusting the operating pressure in the dopant

reservoir, and the capillary inner diameter and length, and determined by using Poiseuille's formula, assuming laminar flow[38].

All the different parts of the source were connected and sealed together by using high-temperature o-rings. A good seal was important to avoid sensitivity losses due to ambient air entering the ionization source.

Once generated, the ions were guided into the MS using vacuum only. No ion optics were used, since the ionization region was only a few millimeters away from the MS entrance capillary.

The newly constructed source was compared to a well-characterized low temperature plasma source based on DBDI developed by our research group (details reported elsewhere[33,38–40]). The DBDI source was operated with an AC voltage (1.6 kV_{p-p}, 6 kHz frequency) applied to two concentric ring-shaped electrodes, separated by a dielectric quartz capillary connected to the MS-inlet. Since the ionization mechanism of this source is mainly based on hydronium cluster formation and proton transfer, the low temperature plasma mostly yields $[M+H]^+$ ions, with little to no fragmentation. In our setup, the softness of the ionization was also due to the very short residence time of the compounds inside the reactive plasma. In our experiments, nitrogen was used to ignite the plasma, although regular air or CO_2 have also been shown to be suitable gases for this source[41].

In particular, nitrogen was used as gas in both cAPPI and DBDI to avoid interference from room air contaminants (e.g., plasticizers) and to prevent oxidation of the SPME fibers at high temperatures. While in DBDI an increase in the ionization efficiency was achieved when the N_2 was humidified to 90% (R.H. at 25 ºC), in cAPPI the opposite was true, therefore dry nitrogen was used.

Both ionization sources are based on a capillary sampling, and the use of a thermal desorption step prior to ionization allowed us to decouple the desorption event from the ionization, minimizing matrix suppression phenomena. The neutral analytes coming from the SPME or GC were drawn into the extended inlet capillary of the MS, and ionized during their transfer into the vacuum. This differs from other atmospheric pressure ionization sources, as the ionization happens in a confined volume inside the source itself, and not in an open environment. In this way, the robustness and ion transmission into the MS are greatly increased. Another important advantage of our SPME-MS setup is that it is not affected by geometric parameters like angles and distances between the SPME device and the MS, which are crucial in other systems like DART, DESI or spray techniques.

SPME extractions. The SPME fibers used were 100 μm PDMS (CTC Analytics AG, Switzerland). They were used with a short pre-equilibrium extraction time (2 min). Extractions were performed at room temperature (25 °C) with a stirring of 1500 rpm. The extraction volume was 20 mL, from 99:1 H_2O/ACN solutions, and a PAL RTC autosampler (CTC Analytics) was used to fully automate the analytical workflow. PDMS fibers were used since they have high affinity for nonpolar analytes, as well as a moderate affinity for most of the pesticides and drugs used in this study. Since a wide range of compound classes was investigated at the same time, we preferred to use the same extraction device type. For more targeted analysis, specific SPME devices can be used, according to the analyte affinity to the extracting phase.

Results and discussion

The cAPPI source was developed for high-throughput direct SPME-MS analyses. Most literature data concerning ambient sources like DART, DBDI and spray techniques deal with polar analytes, with little data reported for nonpolar compounds analysis. Therefore, this work will mainly focus on direct analysis of nonpolar compound.

Chromatographic analysis

To evaluate the performance of cAPPI compared to existing approaches, the source was first coupled to GC. The reported GC-cAPPI showed a higher background signal in the mass spectrum when compared to GC-DBDI[40], mainly determined by the dopant ions signal and few plasticizers. Figs. 2 and 3 show the overlay of the extracted ion chromatograms (EICs) for each of the PAHs and drugs, analyzed by SPME-GC-cAPPI at a concentration of 10 pg/mL and 100 pg/mL, respectively, with a short extraction time of only 2 minutes. The amount of PAHs (expressed in mol/mL) subjected to SPME extraction are also reported in Fig.2. Although the number of moles of PAHs present in the sample decrease with their increase in molecular weight (MW), signal intensity is often higher for high MW compounds, because of the higher extraction efficiency of the SPME fiber and the increased ionization efficiency. In Figs. 2 and 3, the overlaid TICs were plotted instead of the total ion current (TIC) for a better visualization of the chromatographic peaks: the LTQ Orbitrap was operated in full scan mode (50-1000 *m/z*) for a broader untargeted approach, and the main contribution to the TIC was determined by the background signal, when analytes were present at low concentration levels.

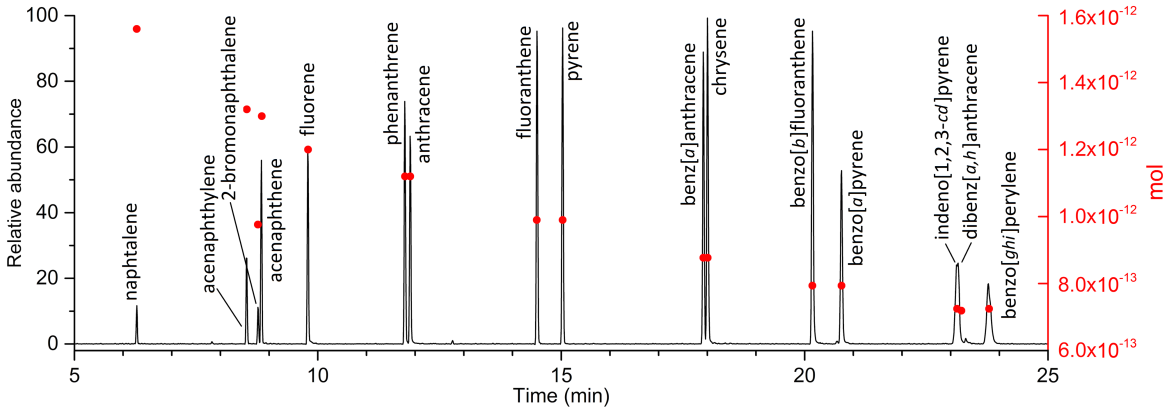


Fig. 2. SPME-GC-cAPPI-MS chromatogram showing the overlaid extracted ion chromatograms of a PAH mix (at a concentration of 10 pg/mL) with a 2 ppm mass window. SPME extractions were performed from 20 mL aqueous solutions by using a PDMS 100 µm fiber. The extraction time was 2 minutes. The amount of PAHs subjected to SPME extraction, expressed in mol (per 20 mL) is also reported. NL = 3.87 E7.

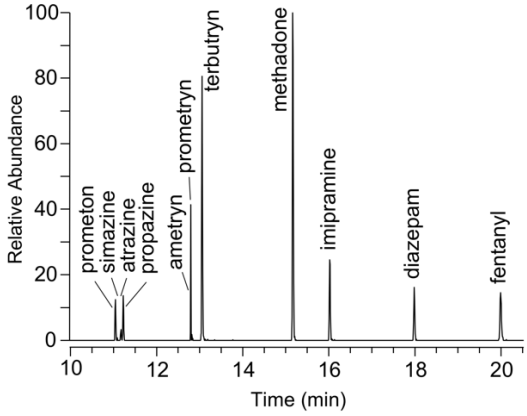


Fig. 3. SPME-GC-cAPPI-MS chromatogram showing the overlaid extracted ion chromatograms of triazine pesticides and drugs at a concentration of 100 pg/mL with a 2 ppm mass window. SPME extractions were performed from an aqueous solution by using a PDMS 100 µm fiber. The extraction time was 2 minutes. NL = 1.30 E7.

The intra-day RSDs of the SPME-GC-cAPPI approach ranged from an average of 5% and 8% for pesticides, drugs and PAHs without the use of dopant and with PhCl as dopant, respectively (Table S1).

Since analytes having different polarities were analyzed, experiments were made to determine a suitable dopant. A mix of PAHs, pesticides and illicit drugs in ACN was determined by GC-cAPPI-MS using 2 µL injections. Fig. 4 shows the effect of different dopants on the ionization efficiency for both polar (triazines) and nonpolar (PAHs) compounds. Fluorobenzene (I.E.= 9.20 eV), chlorobenzene (I.E.= 9.07 eV), bromobenzene (I.E.= 9.00 eV), iodobenzene (I.E.= 8.72 eV), hexafluorobenzene (I.E.= 9.90 eV), acetone

(I.E.= 9.7 eV), toluene (I.E.= 8.83 eV) and anisole (I.E.= 8.20 eV) were testes as dopants (I.E. values obtained from www.nist.gov), each introduced in the ionization source at a flow rate of 5 µL/min via a solvent-assisted liquid introduction system.

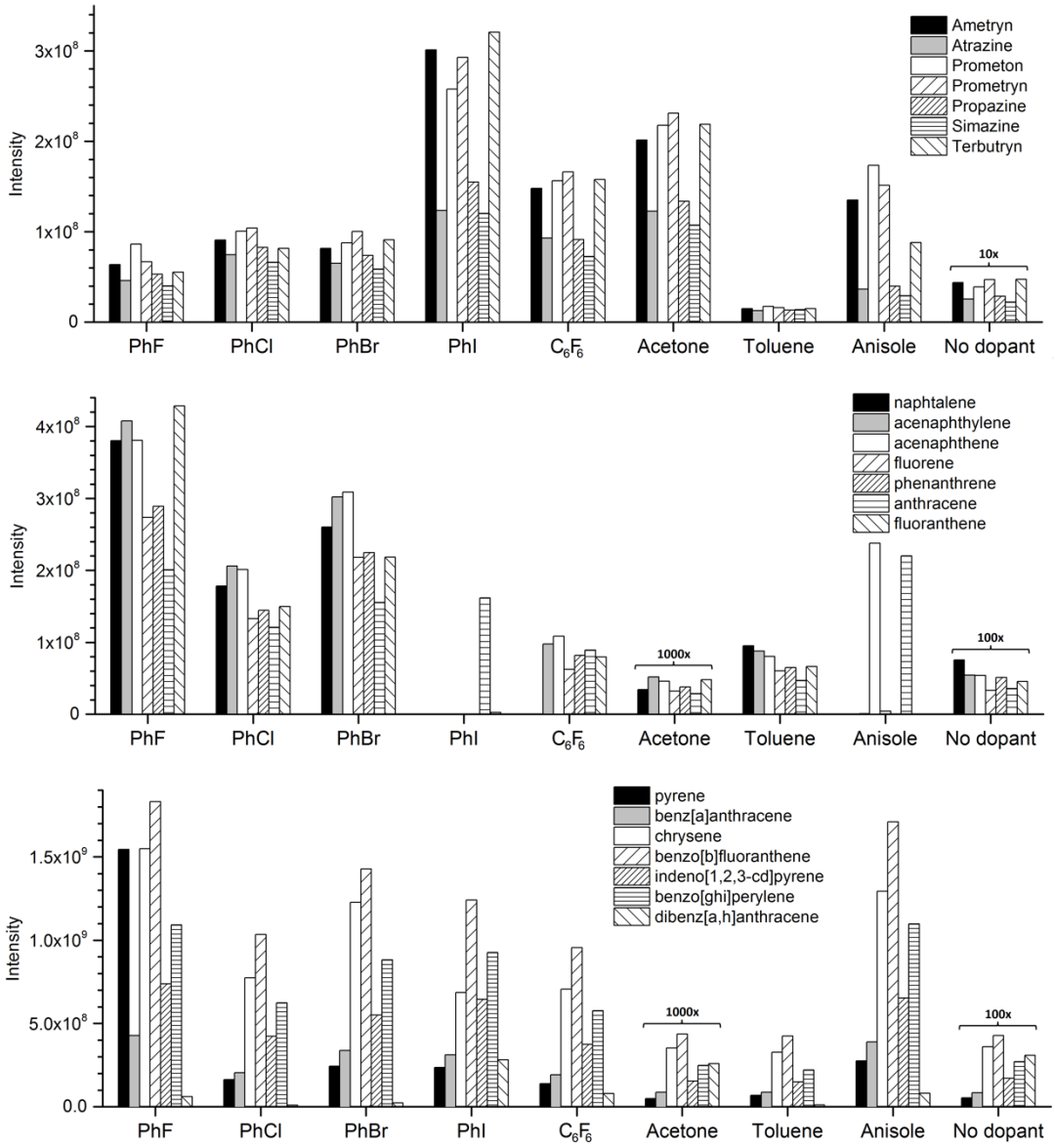


Fig. 4. Effect of different dopants on the ionization efficiency of polar and nonpolar compounds in GC-cAPPI-MS. A sample containing a mix of triazine pesticides and PAHs at 200 ng/mL in ACN was injected in the GC (2 µL aliquots). Dopant flow rate was 5 µL/min for each dopant. The estimated error is below 10% for most data points, and no larger than 20% in all cases where an RSD value was determined.

Based on these results, PhCl and PhF were used for all analyses, since they delivered more consistent results over a wide range of compound polarity, while other dopants were well suited for polar analyses (e.g., acetone and PhI) but poorly performed for nonpolar analyses.

With all dopant tested, all PAHs were detected as $M^{\bullet}$ as the most abundant species. When using dopants, benzo[*a*]pyrene, indeno[1,2,3-*cd*]pyrene, benzo[*ghi*]perylene and dibenz[*a,h*]anthracene could also be detected as $[M+H]^+$, being protonated inside the source because of their higher proton affinities.

The effect of dopant flow rate on the ionization efficiency was evaluated for PhCl and PhF, and the results showed that the ionization efficiency remains relatively constant over a dopant flow rate between 1 and 5 µL/min. For this reason, a flow rate of 5 µL/min was chosen for all analyses. This flow rate was also chosen because of the higher amount of compounds entering the source during direct SPME analyses, requiring a higher number of reactive dopant species.

Direct coupling of SPME to MS

The direct SPME-cAPPI-MS approach was then used to directly analyze a wide range of substances with different polarities and molecular structures (Fig. 5). The major goal was to analyze both polar and nonpolar compounds at the same time, and since no chromatography was performed in this part of the study and all analytes are ionized simultaneously, high resolution mass spectrometry is needed to assign molecular formulae based on accurate mass.

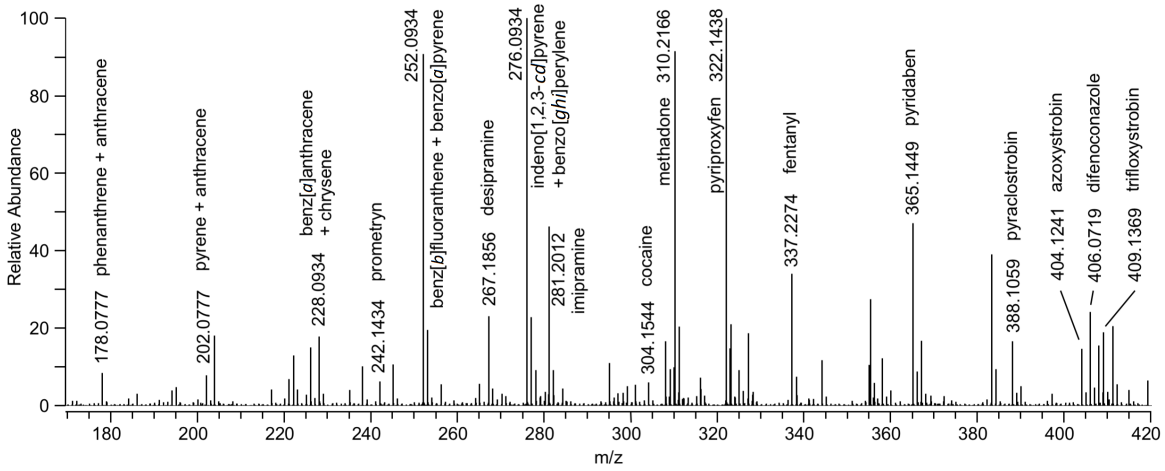


Fig. 5. Direct SPME-cAPPI full scan MS of a mix of pesticides, drugs, and PAHs at 1 ng/mL in an aqueous solution (H_2O/ACN 99:1 v/v), extracted for 2 minutes, showing the simultaneous ionization of polar and nonpolar compounds. PhF was used as dopant, at a flow rate of 5 µL/min. NL = 1.03 E7.

Calibration curves for PAHs were obtained for both SPME-GC-cAPPI and direct SPME-cAPPI by high resolution MS (Fig. 6). In both cases, a linear dynamic range (LDR) of 2 to 3 orders of magnitude was achieved.

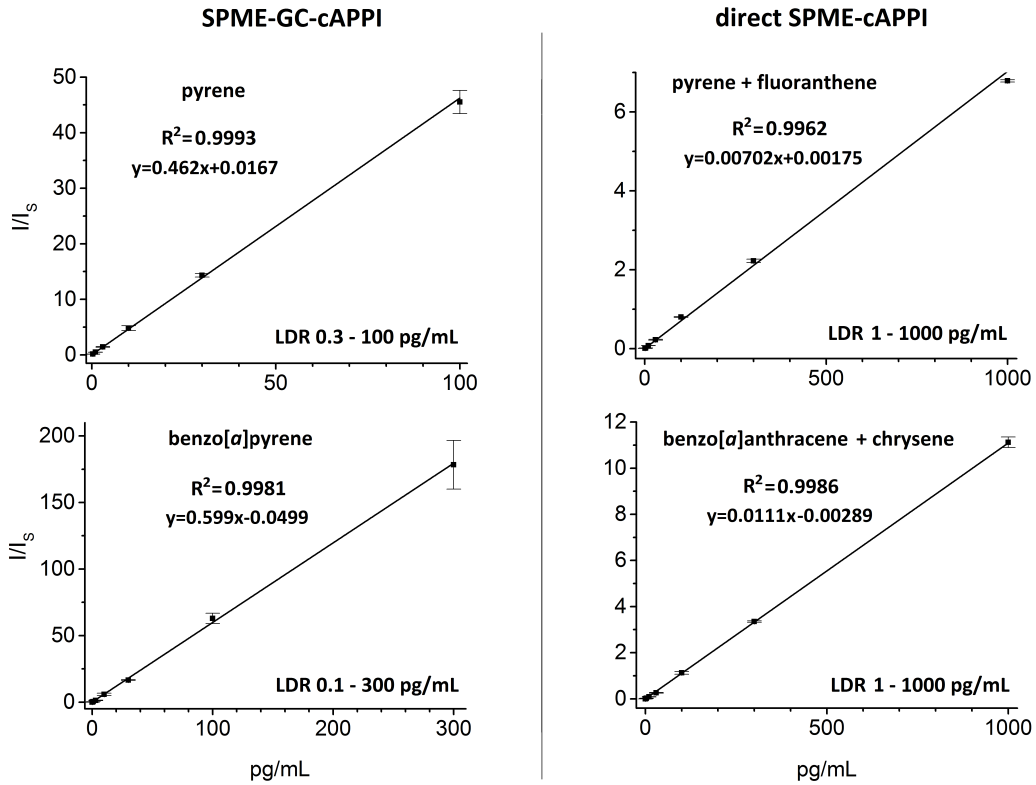


Fig. 6. Quantification of selected PAHs in water by SPME-GC-cAPPI-MS (left) and direct SPME-cAPPI-MS (right). For the direct approach, phenanthrene-d_{10} was used as internal standard (I_S) at a concentration of 50 pg/mL. For the GC calibrations, pyrene-d_{10} at 2 pg/mL and phenanthrene-d_{10} at 2 pg/mL were used as I_S for pyrene and benzo[*a*]pyrene, respectively.

When compared to the GC approach, the direct method showed slightly higher LODs. It is important to notice that, while PAH isomers could be resolved by GC, with a direct approach the ionization of all compounds is simultaneous, and the resulting calibration curves accounts for the sum of isomeric species. Both the GC and direct SPME approaches showed good repeatability (Table 1). For each approach, a newly conditioned 100 µm PDMS fiber was used.

	SPME-GC		Direct SPME	
pg/mL	10	1000	10	1000
naphtalene	3.7	6.2	24	20
acenaphthene	15	2.7	11	16
acenaphthylene	13	4.3	7.0	14
fluorene	10	5.4	0.2	14
phenanthrene	10	4.8	3.5	2.5
anthracene	8.8	1.5		
fluoranthene	7.5	6.6	3.0	1.4
pyrene	4.8	3.2		
benz[*a*]anthracene	2.4	4.9	1.0	14
chrysene	2.5	4.0		
benzo[*b*]fluoranthene	4.2	5.7	3.1	0.4
benzo[*a*]pyrene	1.7	3.4		
indeno[1,2,3-*cd*]pyrene	12	5.1	3.0	16
benzo[*ghi*]perylene	6.3	3.6		
dibenz[*a,h*]anthracene	3.4	12	7.8	2.9

Table 1. Intra-day RSD for the considered PAHs (n=3), evaluated at 10 and 1000 pg/mL concentration levels. Both SPME-GC-cAPPI and direct SPME-cAPPI measurements were considered. PhF was used as dopant at 5 µL/min. For each approach, a new conditioned 100 µm PDMS fiber was used.

The

cAPPI source delivered a much higher sensitivity for nonpolar compounds like PAHs when compared to ambient sources like DBDI, with average LODs for the SPME-GC-cAPPI approach of 0.1 pg/mL for PAHs (2 minute SPME extraction, 5 μL/min PhF as dopant). These values are also better when compared to dopant-assisted DART[18], where PAHs spiked on a melting point tube directly analyzed were detected at concentrations down to 5 ppb, with a signal to noise ratio ≥ 10. In this case, however, the sample introduction approach was different, making a one-to-one comparison difficult.

The sensitivity for pesticides and drugs was more variable. Pesticides like terbutryn, quinoxyfen, flusilazole, trifloxystrobin and azoxystrobin had an LOD of 1 pg/mL, with an average LOD of 3 pg/mL for pesticides. For drugs, the average LOD was 30 pg/mL with, e.g., diazepam and methadone showing LODs of 10 and 3 pg/mL, respectively. The sensitivity was significantly higher than that obtained with dopant-assisted DART, where LODs for PAHs were at the low ng/mL level[18]. Also, to the best of our knowledge, no other direct interfacing approaches of SPME to MS aimed at sensitive quantification of PAHs were reported so far. The reason for this is that the ionization mechanism of the sources usually employed for SPME-MS, like DART or spray-based sources, rely mainly on proton transfer, and therefore do not allow for a sensitive ionization of nonpolar compounds.

It is important to mention that all these sensitivity values were determined for 100 μm PDMS fibers, and that better results for polar analytes can be obtained with different fibers, e.g, PDMS/DVB. Moreover, the use of acetone as dopant can improve the sensitivity even more for polar analytes yielding protonated ions, as can be seen from Figs 4 and 7. On the other hand, the use of acetone as dopant reduced the ionization efficiency of nonpolar molecules *via* a charge-transfer mechanism (Figs 4 and 7).

For direct SPME-cAPPI, the sensitivity was generally slightly lower (by a factor of 2-4), because of the absence of chromatographic separation and, more importantly, due to the release of polymers during direct SPME desorption, causing in-source ion suppression.

Comparison between cAPPI and DBDI

While the higher sensitivity observed in cAPPI for nonpolar analytes was expected due to the different ionization mechanism, it was important to evaluate the sensitivity of the source for more polar compounds as well, to check whether or not this source could represent a more universal alternative to other ambient sources for direct coupling of SPME to MS. For this reason, a comparison was done between cAPPI and a DBDI source we used in previous studies, which was shown to be very sensitive for polar and mid-polar compounds. For this

purpose, the cAPPI and DBDI sources were coupled to GC, and a mix of polar pesticides and drugs at 200 ng/mL was analyzed. The comparison results are shown in Fig. 7. DBDI was chosen for a direct comparison since it showed a sensitivity comparable or even higher than DART, with one of the major advantages being its reduced size and the fairly low chemical background noise [23,33]. Also, the sensitivity of DBDI for polar compounds was comparable to the one obtained with coated blade spray (CBS) ionization[27,33], which also allow to achieve low pg/mL or sub-pg/mL sensitivity for illicit drugs. However, CBS cannot provide high sensitivity for nonpolar compounds, since the ionization mechanism is ESI-based.

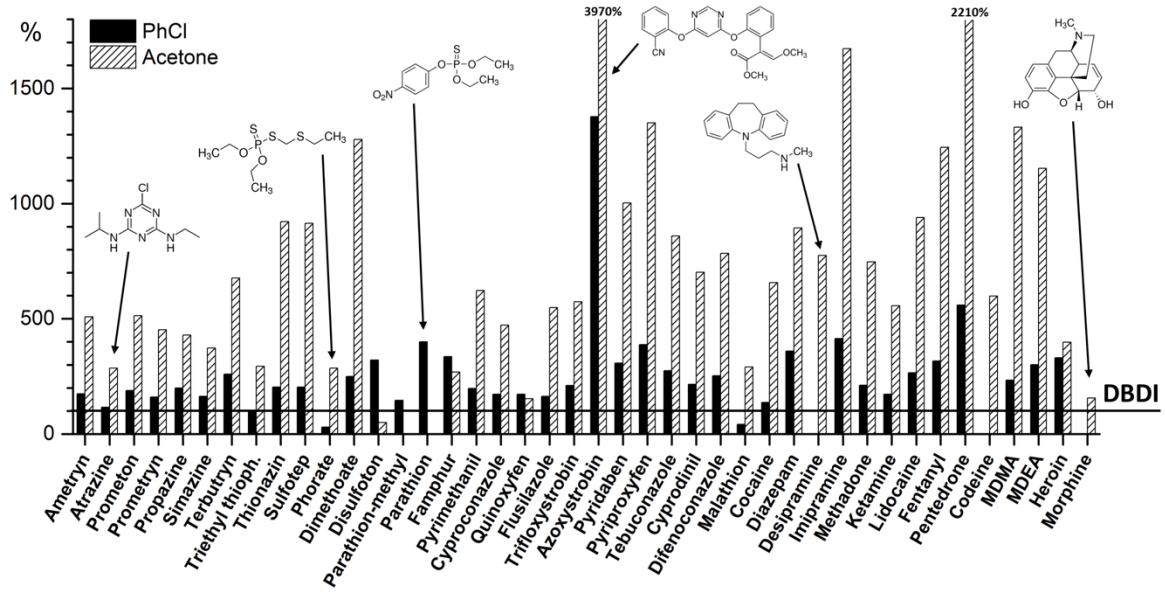


Fig. 7. Comparison of the ionization efficiency GC-cAPPI-MS and GC-DBDI-MS for the analysis of polar semi-polar compounds. The MS signal intensities for each compound were normalized to 100%, corresponding to the DBDI signal intensity. 2 µL of an ACN mix of all compounds at 200 ng/mL was injected in the GC. PhCl was used as dopant, at a flow rate of 5 µL/min. The estimated error is below 10% for most data points, and no larger than 20% in all cases where an RSD value was determined.

Most of the pesticides and drugs investigated were detected more efficiently by cAPPI, especially when containing aromatic moieties. For example, with acetone as dopant all triazines were detected more efficiently with cAPPI by a factor of 3 to 7, and compounds like azoxystrobin, pyriproxyfen, imipramine and pentedrone showed a much higher sensitivity with photoionization than in DBDI (up to 40 times higher signal intensity). At the concentration used, drugs like codeine and morphine were detected only when using acetone as dopant, while parathion and parathion-methyl were detected only using PhCl. In general, sensitivity was higher with capillary photoionization for most polar and semi-polar compounds even when using PhCl as dopant, although with acetone a higher ion yield was

observed. This was expected since all analytes are predominantly observed in the $[M+H]^+$ form, and acetone's behavior as dopant is based on proton transfer, rather than charge transfer in the case of PhCl. The $[M+H]^+$ ions observed when using PhCl as dopant are probably due to residual humidity in the nitrogen used, plasticizers in the source, or to minor contaminants in the dopant itself.

Conclusions

A novel capillary APPI source was built and used for the direct analysis of polar and nonpolar compounds. By using suitable dopants, limits of detection in the low-pg/mL to sub-pg/mL range were achieved for pesticides, drugs and PAHs, by extracting samples with SPME for only 2 minutes, allowing for untargeted, high-throughput analysis.

We showed the simultaneous and analysis of polar and nonpolar compounds by direct SPME-MS, previously limited to polar compounds analysis mainly by DART and spray ionization techniques. The breadth of ionization achieved was superior to other direct SPME-MS approaches based on ambient ionization sources like DBDI, already shown to be a very sensitive approach.

The sensitivity was in most cases comparable or superior to the previously mentioned approaches for polar compounds, with the advantage to be also extremely sensitive for nonpolar compounds, which so far could not be efficiently quantified with a direct SPME approach by ambient mass spectrometry. The key factors for this high sensitivity were the capillary nature of the source, as well as the solvent-free approach which minimized signal suppression.

The comprehensive coverage of compounds of cAPPI could certainly provide a solution to the lack of sensitivity for nonpolar compounds observed with other SPME-MS approaches, allowing fast and automated sample preparation/enrichment with SPME to be used without chromatography even for those samples containing polar and nonpolar analytes.

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