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Characterization of a capillary spray cell for easy analysis of extracts of biological samples

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ABSTRACT

We present a very simple electrospray unit, a capillary spray cell, for easy analysis of small (10–50 μL) sample aliquots. The sample, e.g., an unfiltered extract, is injected to a small sample cell, made of alumina and containing a short fused silica capillary mounted in its side. By the application of a 5 kV potential between the sample cell and the entrance orifice of a mass spectrometer with an atmospheric pressure interface, the sample is dragged out of the cell at a rate of a few μL/min and an electrospray is generated at the tip of the silica capillary. The capillary spray cell benefits from a high internal diameter (up to 250 μm) and very easy and inexpensive replacement of the capillary, which makes the sprayer well suited for analysis of unfiltered extracts. We demonstrate the direct analysis of extracts from plants and insects. In quantitative measurements using internal standards, a relatively high sensitivity (low ng/mL) is obtained together with good linearity (R^2 = 0.998) in the range of 10–1000 ng/mL. The capillary spray cell is also suited for use with field portable mass spectrometers, since no syringe pump or nebulizer gas is needed. Furthermore, the capillary spray cell is easily manufactured by most mechanical workshops.

1. Introduction

Since its breakthrough in the 1980s electrospray ionization mass spectrometry [1] and later nanoelectrospray ionization mass spectrometry [2] have played increasingly bigger roles in today's work with mass spectrometry since they are particular well suited for the polar compounds which are found in most biological samples [3,4]. The majority of mass spectrometers today are sold with Electrospray ion sources built to work in the hyphenation with an HPLC system, thus accommodating liquid flows of up to 1 mL per minute. These sources are typically fed with sample solution from either an HPLC or a syringe pump, and gasses are used to various extents to assist in the nebulisation of the sample solution and subsequent desolvation of the analyte droplets [5]. At lower flow rates the nebuliser gas is not needed as the charged droplets can be formed by the electrospray potential alone [6].

However, in most setups, even without nebuliser gas, a syringe pump is still needed to provide the necessary transport of sample solution to the spray. That changed with the introduction of the static nanospray source where the sample, typically 2–10 μL total volume, is injected into a glass tube which has been pulled in one end to obtain a tip with an orifice of 2–5 μm and coated with a gold film to enable electrical contact to the sample solution [2]. With this setup a forced flow is not needed as the applied electric field is able to generate a flow by itself, controlled by the diameter of the capillary tip. The technique provides a stable signal for a long time from just a few microlitres of sample, however with relatively high expenses in consumables.

Very simple ways to generate an electrospray from a droplet of sample solution have been demonstrated by Shiea et al., by deposition of a droplet on an object onto which high voltage is applied. This object has been of various materials and shapes such as a copper ring [7], a copper coil [8] or a gold coated optical fiber [9], providing simple ways to analyze tiny amounts of sample with low costs of consumables and no use of nebuliser gas or sample delivery pumps. A variation of this is the so-called probe electrospray by Hiraoka et al. [10] where a solid needle picks up a droplet of sample in a motorized fashion and moves it to the proximity of the MS inlet orifice. Ionization then occurs from the needle similarly to the techniques describes above. This technique was later implemented in a new ambient imaging technique where the needle systematically samples a whole area [11], similarly to other MS imaging techniques such as, e.g., DESI imaging [12].

An alternative solution is the microfabricated electrospray emitter presented by Sikanen et al. in 2008 which provides the options of free flow as well as forced flow electrospray [13]. Operated in free flow mode a sample amount of 20 μL will give a very stable signal for nearly 30 min. It was successfully applied for analysis of pharmaceuticals, peptides and proteins. However, the construction of these microfabricated emitters is quite complicated, as it requires

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the use of UV-lithography on silicon wafers, resulting in a relatively high production price and limited availability.

Recently, the paper spray method was presented by Cooks and co-workers [14,15]. Paper spray too enables the analysis of small amounts of solution without the use of syringe pump or nebulizer gas, as a small drop of sample is simply applied to a pointed piece of paper, and an applied high voltage generates charged droplets from the tip of the paper in a nanospray-like fashion. One of the qualities of paper spray ionization is the capability of fast analysis of dried blood spots by direct extraction and ionization of the compounds in the blood spot.

We present here a capillary spray cell, a simplified version of the electrospray emitter mentioned above [13]. In comparison, the silicon wafer has been replaced by a small block of aluminum and the microchannels simply consist of a small piece of fused silica capillary mounted in a piece of Teflon tubing. In contrast to the microfabricated emitters, the capillary spray cell can be manufactured with relatively little effort by most mechanical workshops.

2. Experimental

2.1. Chemicals

Water was prepared with a Millipore Direct-Q3 UV system providing a resistivity of 18.2 MΩ/cm. Methanol was purchased from VWR and all other chemicals were purchased from Sigma–Aldrich. Unless otherwise stated, all solutions were made in a 50:50 mixture of methanol and water.

2.2. Construction of the capillary spray cell

A photo of the capillary spray cell is seen in Fig. 1(a). It is in its simplest design a 10 mm × 15 mm × 30 mm aluminum block with a 3 mm deep Ø 5 mm hole serving as sample cell. The sample cell is connected to the end side of the block with a Ø 1/16 in. hole positioned such that the center of that hole is aligned with the bottom of the sample cell. A 9 mm piece of 1/16 in. Teflon tubing (Upchurch Scientific, Oak Harbor, WA) is plugging the hole and in that piece of Teflon tubing an 18 mm piece of fused silica capillary (SGE, Austin, TX) is mounted, connecting the sample cell to the atmospheric interface of a mass spectrometer. The exact lengths of the Teflon tubing and the silica capillary are not crucial. Fused silica tubing of inner diameter (ID)/outer diameter (OD) 25/150 μm, 50/150 μm, 110/170 μm, 150/220 μm and 250/350 μm were used, and the Teflon tubing was selected with an ID that would fit the OD of the capillary that was used. An additional hole was drilled at the rear end of the aluminum block, facilitating the application of high voltage by an alligator clip.

For analysis of several samples and comparison across different capillary dimensions a second block of similar design but with four sample cells was manufactured (Fig. 1(b)) having 5 mm long and 3 mm wide cells of 3 mm depth.

2.3. Mass spectrometry analysis

The capillary spray cell was used with a Thermo LTQ XL mass spectrometer (Thermo Scientific, San Jose, CA). In its most primitive – but fully functional – setup the capillary spray cell was mounted on a lab stand positioned in front of the mass spectrometer inlet as seen in Fig. 1(a). For convenience, all the results presented here were obtained with the capillary spray cell mounted in a modified nanospray source (Proxeon, Odense, Denmark) whereby accurate positioning of the spray cell was easily achieved (Fig. 1(b)). The capillary spray cell was operated with a high voltage of 5 kV from the high voltage power supply of the mass spectrometer, applied directly to the aluminum block. The mass spectrometer was operated in full scan mode, unless otherwise stated.

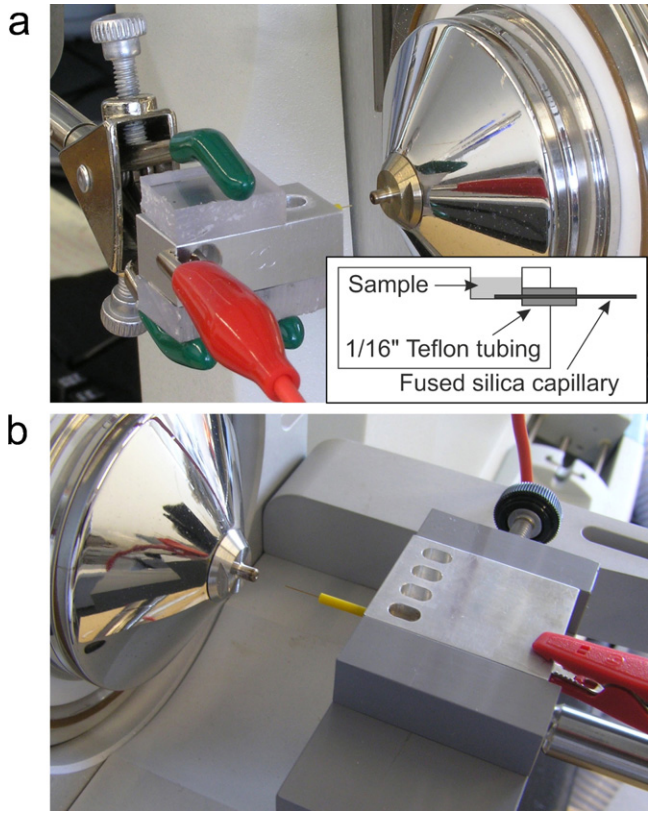

Fig. 1. (a) The capillary spray cell in its simplest design, mounted on a laboratory stand. The inserted drawing shows a side view of the cell. (b) The multi-cell capillary spray cell mounted on a modified Proxeon nanospray source.

3. Results and discussion

3.1. The capillary spray cell in operation

Before use, and periodically during use, the aluminum block was ultrasonically cleaned in methanol. Given the low costs in consumables and easy change of capillaries (a capillary can be cut and mounted in about a minute), the Teflon piece and the fused silica was frequently changed, such that in general new pieces were used with every change of sample in order to eliminate carryover. The fused silica capillary was cut in the traditional way, i.e., by scratching it on the side with a cleaving stone, thereby penetrating the polyimide coating, and subsequently pulling it horizontally. With the fused silica capillary properly mounted in the aluminium block the capillary spray cell was positioned in front of the MS inlet and the high voltage (5 kV) was applied. A typical amount of 30 μL of sample solution was injected using an Eppendorf pipette, and the electrospray would typically be up running within the next 10 s, sometimes after some adjustments of the position of the capillary spray cell relative to the MS inlet. As the sample cell of the capillary spray cell was easily accessible during use, the sample solution could be refilled or exchanged (using an Eppendorf pipette) while the analysis was running. In this way, for example, a 7-point calibration curve was generated in 12 min. We also found that a sample change could be made from one compound to another with just one rinse of methanol in between: 30 μL of a 500 ng/mL solution of diphenhydramine was injected and a good signal at m/z 256 was readily obtained. Then the remains of the diphenhydramine solution were removed and 30 μL of methanol was injected and 30 s

later removed. Finally, 30 μL of a 500 ng/mL solution of methadone was injected, resulting in a clear signal at *m*/*z* 310 from methadone while the signal at *m*/*z* 256 had disappeared completely.

The multi-cell capillary spray cell in Fig. 1(b) was tested with four different samples simultaneously. When the capillary spray cell was positioned optimally for one sample cell, no signal was observed from the samples in the other three sample cells (whose capillaries were further away from the MS inlet) and no drainage of liquid from those cells was observed either. Thus by moving the capillary spray cell horizontally, the desired sample cell could be chosen for analysis. In this way, spectra of four different samples were recorded in less than a minute.

As stated, methanol and water in a 50:50 mixture was the standard solvent used for the results presented here. The capillary spray cell was tested with solutions of 1 μg/mL methadone in a variety of solvents in and found to work with mixtures of methanol and water containing at least 30% of methanol (pure water did not work as solvent) and with pure methanol. Likewise, good spectra were obtained with 100% acetonitrile as well as with a 50:50 mixture of acetonitrile and water. Good spectra of methadone in dichloromethane were obtained upon a liquid–liquid extraction of methadone from a basic aqueous solution into dichloromethane. Dichloromethane thus works well as a solvent for the capillary spray cell, while the similar experiment with the more non-polar hexane as solvent did not turn out successfully. This is in good agreement with previous studies of solvent effects in electrospray ionization [16,17]. For the molecules used in this study, the addition of acid (e.g., formic acid) was found not to be necessary and did not improve the stability of the signal or the sensitivity.

3.2. Spray profiles for different capillary diameters

The capillary spray cell was tested with fused silica capillaries with internal diameters of 25–250 μm. They were all able to provide a strong and relatively stable signal, however, the capillary with 110 μm ID turned out to be the most reliable one with respect to the ease with which the electrospray was initiated. For some of the other diameters the electrospray would not always start immediately, typically due to bubbles of air inside the capillary. The electrospray could then be helped to start, e.g., by varying the spray-inlet distance (thus modifying the electric field), turning off and on the high voltage or removing and refilling the sample solution. It appeared to be the capillary forces in combination with the electric field of the electrospray rather than the gravitational force on the sample liquid that drove the liquid flow through the capillary. The liquid level in the sample cell did not have any impact on the spray as long as the capillary was fully covered by sample solution.

For each of the capillary sizes a spray profile was recorded, by injecting 30 μL of a 1 μg/mL solution of diphenhydramine and methadone (two compounds were used in order to confirm that their mutual intensity ratios remained constant throughout the experiment, which indeed they did). Fig. 2 shows the spray stabilities of different capillary sizes, based on the *m*/*z* 310 signal of methadone. Not surprisingly, the 30 μL of sample solution is used up faster with higher capillary IDs. With the 25 μm capillary the 30 μL of sample provide signal for more than half an hour (Fig. 2(a)) whereas they only last a couple of minutes with the larger capillaries (Fig. 2(e) and (f)). Just as for the static nanospray probe, the flow rate is governed by the dimensions involved. For the capillary spray cell the ID of the capillary defines both the size of the channel through which the sample is transported as well as the size of the tip from which the Taylor cone of the electrospray is generated, due to the square cut that results from cutting fused silica capillary with a cleave stone. The 110 μm capillary seems to perform well in both aspects and functions with a very high reliability at a flow rate of about 3 μL/min.

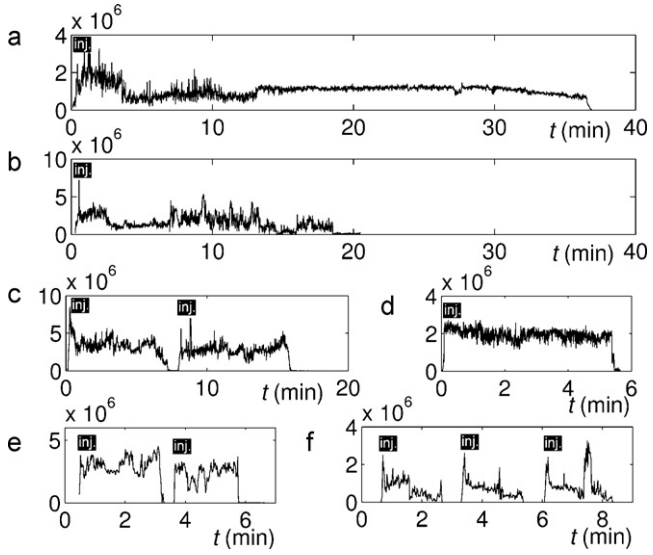

Fig. 2. The signal of the *m*/*z* 310 peak of methadone for different capillary internal diameters. 30 μL of a 1 μg/mL solution was injected as marked in the graphs: (a) 25 μm, (b) 50 μm, (c) 110 μm; (d) The 110 μm capillary pulled over a flame: (e) 150 μm, (f) 250 μm.

The spray profiles in Fig. 2 show that the signal of the capillary spray cell does not have the stability known from the static nanospray probe or the microfabricated electrospray emitters. This is not surprising since the spray tip results from the easy, but primitive cutting with the cleave stone. In order to see if this could be improved in a relatively simple fashion while maintaining the simplicity of the capillary spray cell, the 110 μm ID/170 μm OD capillary was pulled over a flame resulting in a tip with a relatively sharp apex in contrast to the square cut obtained with the cleave stone. As seen in Fig. 2(d) the stability of the spray improves when the tip is pulled over a flame. The inconvenience of the pulled tip, besides of course the time it takes to make it when a large number of tips is needed, is that the tip becomes fragile to handle once the polyimide coating has been burnt off. However, the simple cleave stone cut capillaries work well for most purposes as they provide clean spectra and good sensitivities which is also why this was the method of choice for the results presented here. The fluctuations in absolute intensities observed in the spray profiles did not influence the relative abundances of the peaks in a mass spectrum which were very stable.

For capillary diameters of 110 μm ID and above, a nicely shaped Taylor cone was visible by the naked eye.

For all capillary sizes the onset voltage was 3–3.5 kV and the optimal spray voltage around 5 kV, in contrast to the 1.5–2 kV in nanospray, but in good accordance with the 4.5 kV of paperspray. The microfabricated electrospray emitter lies somewhere in between with an optimal spray voltage of 2.5 kV, which is reasonable as the size of its spraying orifice is in between that of a nanospray tip and the capillary spray cell.

The optimal spraying distance of the capillary spray cell is quite flexible as it functions well at distances from 3 mm to beyond 1 cm, with a tendency that capillaries with large diameters work better at longer distances, which again is in good accordance with the tendency seen in going from standard non-pneumatically assisted ESI to nanospray.

3.3. Calibration curves with internal standards

As for the nanospray and paperspray methods the exact geometry of the setup is hard to reproduce accurately upon a sample change, and an internal standard is therefore useful for quanti-

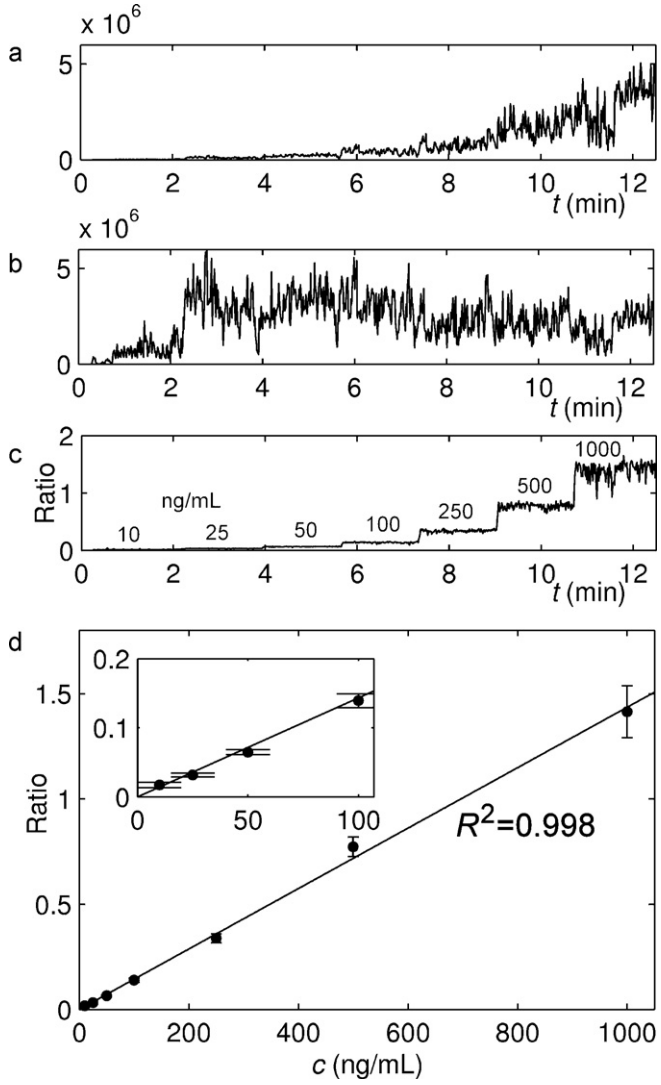

Fig. 3. The generation of a calibration curve for diphenhydramine using diphenhydramine-d_5 as internal standard. (a) The m/z 256 signal of diphenhydramine. (b) The m/z 261 signal of the internal standard. (c) The ratio of the m/z 256 and the m/z 261 signal. (d) The calibration curve obtained by plotting the ratio vs. concentration. The error bars show the standard deviations of the ratios.

tation. In order to examine the quantitative performance of the capillary spray cell, a calibration curve was made for diphenhydramine (m/z 256) in concentrations from 10 ng/mL to 1000 ng/mL, using deuterated diphenhydramine (m/z 261) at 500 ng/mL as internal standard. The calibration curve was made using the same piece of capillary for all concentrations, with the samples injected in the order of increasing concentrations and no rinsing in between sample changes. The extracted ion chromatograms for m/z 256 and m/z 261 are seen in Fig. 3(a) and (b), respectively. It is obvious from Fig. 3(a) that calibration cannot be made by the m/z 256 signal alone. This is also seen in Fig. 3(b) which should ideally show a quite constant signal since the concentration of the internal standard was the same in all solutions. However, when the analyte signal at m/z 256 is related to the signal of the internal standard as in Fig. 3(c) where their ratios are plotted, then results suitable for calibration are obtained. The resulting calibration curve (Fig. 3(d)) has a correlation of $R^2 = 0.998$ in the entire range of 10–1000 ng/mL. Based on the slope and the standard deviation of the ratio at low concentration, an LOD of 8.2 ng/mL and an LOQ of 27.5 ng/mL were calculated. In order to examine how critical the choice of internal standard is, a similar calibration curve was made for nortriptyline (m/z 264), using amitriptyline (m/z 278) as internal standard. The calibration curve, which is found in the supplementary material, has a correlation $R^2 = 0.9997$ in the range of 10–500 ng/mL, LOD = 2.7 ng/mL and LOQ = 9.1 ng/mL. For both calibration curves the standard deviations were in the order of 5–8%. It is thus clear that the capillary spray cell is not dependent on deuterated internal standards for quantitative use.

3.4. Mass spectra of plant extracts

An advantage of the large orifice of the capillary spray cell compared to that of a nanospray tip is that it does not clog easily. It is thus possible to use the capillary spray cell for rapid analysis of extracts that would otherwise have to be centrifuged or filtered prior to analysis. In order to demonstrate this application, extracts were made of a fresh opium poppy capsule (*Papaver somniferum*) and dried coca leaves. The opium poppy extract was made by putting half of a very small capsule in a vial with 600 μL of methanol, shaking it on a vortex mixer for 5 min and then adding 600 μL of water. Finally, stock solution of diphenhydramine was added as internal standard to a concentration of 1 μg/mL. 30 μL of the extract was taken directly from the vial (still containing the capsule with seeds, etc.) to the capillary spray cell, mounted with the 250 μm ID capillary, and the spectrum in Fig. 4(a) was readily obtained. The total analysis time, including extraction, was 10 min. The spectrum reveals several of the alkaloids known from the opium poppy [18]. As expected, the concentrations of the alkaloids are quite high, as evidenced by the small peak at m/z 256, representing the 1 μg/mL of added diphenhydramine.

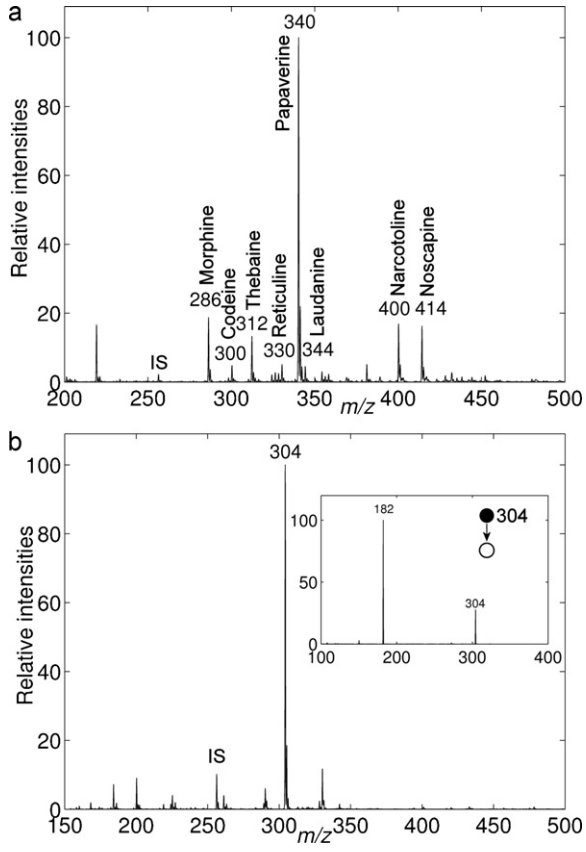

Fig. 4. (a) The mass spectrum of the extract of an opium poppy capsule, showing the presence of a large number of alkaloids. (b) The mass spectrum of an extract of 3 mg of dried coca leaves. The presence of cocaine was confirmed by MS/MS (insert). The IS label in both spectra refers to the internal standard (1 μg/mL of diphenhydramine).

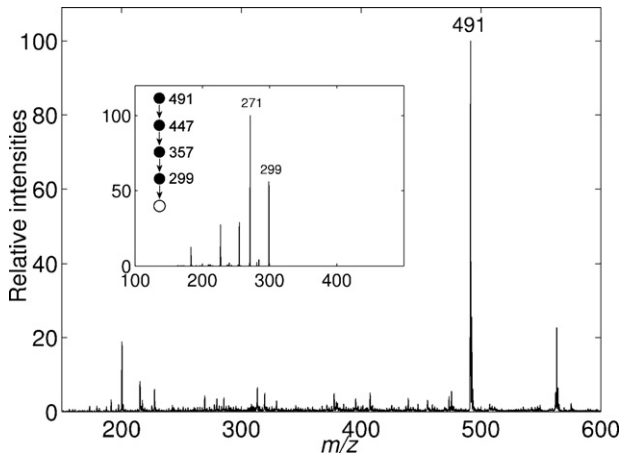

Fig. 5. The mass spectrum (negative ion mode) of an extract of the Cochineal insect, showing a high occurrence of carminic acid, as confirmed by MS^5 (insert).

An extract of dried coca leaves was made by shaking 3 mg of dried coca leaves with 200 μL of methanol for 5 min, then adding 200 μL of water, and again spiking with diphenhydramine to a concentration of 1 μg/mL. Again, the extract was taken directly to the capillary spray cell, and the spectrum in Fig. 4(b) was obtained, including an MS/MS spectrum confirming the presence of cocaine at the *m*/*z* 304 peak.

3.5. Negative mode ionization

The capillary spray cell was found to work in negative mode too (applied spray voltage −5 kV), however with a severe decrease in sensitivity. Solutions were made in methanol and water of ibuprofen and naphtol, and both compounds were detected but with extremely low sensitivities compared to how the same solutions worked with standard pneumatically assisted electrospray ionization.

An extract was made of a dried specimen of the Cochineal insect (*Dactylopius coccus*) which is known to contain an amount of carminic acid of up to 22% of the dry weight of the insect [19]. The dry insect was shaken with 600 μL of methanol for 5 min and added 600 μL of water. The extract was analyzed with the capillary spray cell fitted with a 250 μm ID capillary, and the spectrum in Fig. 5 was obtained. Given its extraordinary high concentration in the cochineal, an intense peak from carminic acid (*m*/*z* 491) was observed, even allowing an MS^5 identification of the compound as seen in the insert of the figure.

The difficulty in working in negative ion mode compared to positive ion mode was also observed for the paper spray method [15]. It was then ascribed to a difference of the onset voltage of the electrospray in positive and negative mode, making the electrospray in negative mode more vulnerable to electrical discharges. The paper spray would not work with methanol/water (1:1) as solvent, but using pure methanol as the solvent instead would remedy for this, and spectra could be recorded also in negative mode.

Cech and Enke report in a review about ESI [20] that care should be taken in choosing the proper solvents for negative mode electrospray. They state that water and methanol, as we used here, in general yield poorer detection limits in negative ion mode ESI than in positive ion mode. It is thus likely that some performance could be gained in negative ion mode with the capillary spray cell by experimenting further with the choice of solvent, but it is still clear, as for paper spray, that the relative loss in sensitivity in going from positive to negative ion mode is much larger than what is known from nanospray and pneumatically assisted electrospray.

3.6. Analysis of peptides and proteins

The capabilities of peptide and protein analysis with the capillary spray cell were also tested, using the 110 μm ID capillary. Solutions of bradykinin (*M* = 1059 Da) and myoglobin (*M* = 17 kDa) were made qualitatively, estimated concentrations being in the order of 100 μg/mL or less, in a 50:50 mixture of methanol and water with 1% of formic acid. The spectra, which are found in the supplementary material, show the usual feature of multiply charged ions known from all variants of electrospray ionization [21].

3.7. Operation of other mass spectrometers

The capillary spray cell was initially developed and operated on an Agilent 1100 LC/MSD Trap where it, due the design of that instrument, was operated in reverse polarity, i.e., with high voltage on the MS inlet (−5 kV in positive ion mode) and the capillary spray cell grounded.

4. Conclusion

The capillary spray cell represents a very simple implementation of electrospray ionization which does not require the use of either syringe pump or nebulizer gas. It is particular well suited for the direct analysis of extracts from biological material, features that also make the capillary spray cell interesting in connection with field analysis using miniaturized mass spectrometers. The risk of carryover is eliminated by a quick change of capillary and a rinse of the sample cell, and the sample cell can be easily filled and refilled during operation, using a standard Eppendorf pipette.

The capillary spray cell has, despite its simplicity, a good quantitative performance, showing good sensitivities and linearity with an internal standard which need not be a deuterated compound. The signal can be further stabilized by pulling the capillaries over a flame and, for that matter, etching the tips in hydrofluoric acid, but that takes away some of the simplicity of the construction.

It can be readily implemented on any API mass spectrometer at very low cost, e.g., as an alternative to a Nanospray source where only occasional expected use might make it expensive to purchase, or where high consumption of spray needles, e.g., for teaching, makes it expensive in consumables. The dimensions (capillary size, sample cell volume and number of sample cells) can be selected according to the needs for a specific purpose, as a new capillary spray cell can be machined in less than an hour.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijms.2010.10.032.

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