International Journal of Mass Spectrometry xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Mass Spectrometry

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

Short communication

Development of an on-line microextraction method for use in fiber-spray/mass spectrometry

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ARTICLE INFO

Article history:
Received 4 May 2017
Received in revised form 12 June 2017
Accepted 4 July 2017
Available online xxx

Keywords:
Fiber-spray/mass spectrometry
Hollow fiber liquid phase microextraction
3,4-Methylenedioxymethamphetamine

ABSTRACT

A novel fiber-spray/mass spectrometry method using a piece of a porous hollow fiber is described. An adapter, fabricated by a 3D-printer, was designed to connect the fiber and a standard ESI (electrospray ionization) needle, in which a Taylor cone was formed and the resulting ions were detected by a mass spectrometer. Since a porous hollow fiber is usually used for microextraction, the so-called hollow fiber liquid-phase microextraction (HF-LPME) method, a new methodology that involves coupling HF-LPME and fiber-spray, was developed for the first time. We report herein on the design and testing of a microextraction kit. The kit consists of a centrifuge tube (reservoir for the sample solution) and a piece of a porous hollow fiber (for sample extraction). The kit was placed between the mass inlet and the ESI needle. Using the kit, analytes can be extracted from a very dilute solution and then evaporate and escape from the fiber surface. When they make contact with the ESI plume, which arises from the ESI needle tip, the molecules are ionized and then detected by a mass spectrometer. Using the setup, it was possible to improve the limit of detection after microextraction by ~360-fold when 3,4-MDMA (3,4-methylenedioxymethamphetamine) was analyzed, and the limit of detection achieved was 2 ng/mL.

1. Introduction

A wide variety of ionization methods, including desorption electrospray ionization [1], easy ambient sonic spray ionization [2,3] and electrospray-assisted laser desorption ionization [4–6], have been developed in recent years. Direct analysis in real time was first reported in 2003 and was commercialized 2 years later. The methodology provides real time data by simply exposing samples of various shapes and states to the direct analysis in real time ion source without the need for sample preparation [7]. The development of paper spray-mass spectrometry (PS-MS) has opened new insights in the field of mass spectrometric analysis since its debut on 2010, because they are straightforward and permit high throughput MS analysis [8]. These methods, their ultimate goal is for point-of-care [9–14], are currently in widespread used, because they are quite simple and straightforward and also because they permit the speed of a mass-spectrum analysis to be increased. They clearly allow MS analysis to be faster, in-situ testing-possibly coupled with miniature MS. Furthermore, the most recent developments in new ionization sources for *in-vivo* sampling and direct electrospray, such as coated blade spray mass spectrometry [15], biocompatible solid-phase microextraction to atmospheric pressure ionization mass spectrometry (API-MS) [16], swab touch spray MS [17,18], and hydrogel sampling combined with MS have also been reported [19,20]. Swab touch spray mass spectrometry represents another example of the generating electrosprays from unconventional emitters (a swab made of rounded porous material) [17]. The measurements were made using a medical swab as both the sampling probe and means of ionization. Electrospray from suspended, dripping, and levitating droplets has also been reported. Although each of these above-mentioned methods has certain unique advantages and disadvantages with respect to sensitivity, precision, and simplicity of use, an on-line concentration technique combined with ambient ionization mass spectrometry has not yet been reported.

Hollow fiber liquid phase microextraction is a simple method for sample preparation [21–23] and is frequently used in gas chromatography-mass spectrometry [24], liquid chromatography-mass spectrometry [25], capillary electrophoresis [26,27] and even ambient ionization mass spectrometry [28,29]. HF-LPME has permitted numerous research cases to be successfully completed, including the screening and quantification of anticancer compounds [30], the determination of drugs that are abused, [31–35] non-steroidal anti-inflammatory drugs [36] and in pesticide analysis [37–40].

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http://dx.doi.org/10.1016/j.ijms.2017.07.001
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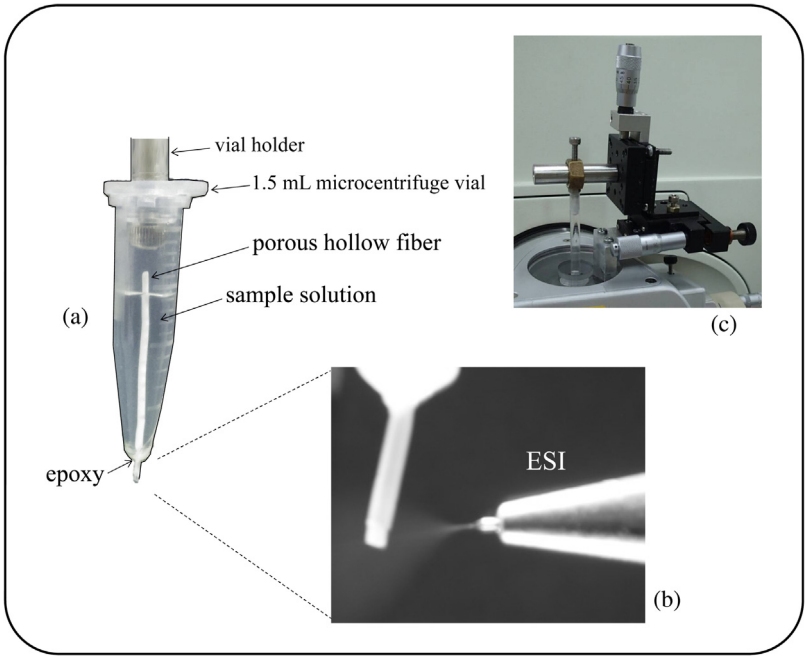

Fig. 1. Three photos of the micro-extraction kit (photo, a), Taylor cone observed when the kit was used for ESI (photo, b) and the actual size of the 3D-stage (X-Y-Z translation stage, photo-c).

In this study, we report on the development of a novel methodology for fiber-spray/mass spectrometry. The procedure involves combining an on-line concentration technique with ambient ionization mass spectrometry. A commercially available porous-polypropylene hollow fiber was used; 3,4-MDMA was used as test sample, as reported in our previous studies. Details of the procedures for on-line microextraction and the improvement in the limit of detection are reported.

2. Experimental

2.1. Reagents

Porous polypropylene hollow fibers (I.D., 0.6 mm; wall thickness, 0.2 mm; average pore size; 200 nm) were acquired from Membrana (Model, PPQ3/1; Wuppertal, Germany). Acetonitrile, methanol and acetone were purchased from Merck (Darmstadt, Germany). Analytical grade *n*-dodecane was obtained from ALFA Aesar (Heysham, England). Caffeine was purchased from HPC (Osaka, Japan). The 3,4-MDMA standard and a clandestine tablet which contains 3,4-MDMA and ketamine were previously donated by the Command of the Army Force of Military Police, Forensic Science Center, Taiwan.

2.2. Apparatus

A mass spectrometer (Finnigan LCQ Deca XP Plus) was used in the study. The mass signal was recorded under the full scan mode (*m/z*, 150–300) and an Xcalibur data system was used for data collection, and the data were converted to ASCII text files. A syringe pump (KDS100) was used for providing auxiliary liquid (methanol). A pH meter (Horiba NaVi F-52) was used to adjust the pH of the sample solution. The 3D-printer, which was purchased from GoHOT (Model, UP! Plus), was used to prepare an adapter for the hollow fiber.

2.3. Kit construction

Photo (a) in Fig. 1 shows the construction of the microextraction kit. It consists of a centrifuge tube (1.5 mL) and a piece of hollow, porous polypropylene fiber (3.5 cm in length). A hole (1 mm in diameter) was drilled at the bottom of the centrifuge tube and the porous hollow fiber was inserted into the hole, leading to the construction of the microextraction kit; epoxy was used to seal the assembly. As a result, the porous hollow fiber was inserted inside the centrifuge tube and was used for sample extraction. The end of the portion that projected outside the centrifuge tube was sealed using needle-nose pliers. Photo (b) shows a Taylor cone observed when it was used for ESI; photo (c) shows a X-Y-Z translation stage (3D stage) that was used to hold the kit to adjust the arrangement at an optimal location, when the ESI experiment was performed.

2.4. Extraction steps

To start the procedure, a medical syringe was used to inject *n*-dodecane into the hollow fiber. After several seconds, when the *n*-dodecane was immersed in and then absorbed by the fiber wall, the remaining, unabsorbed *n*-dodecane (inside the fiber) was removed by blowing air through the interior of the fiber. In this step, *n*-dodecane was used to form a liquid membrane during the liquid–liquid extraction process. After this, 15 μL of acetonitrile (extraction solvent) was injected into the lumen of the fiber, and a 1.0 mL aliquot of sample solution was poured into the centrifuge tube for extraction.

3. Results and discussions

3.1. Fiber spray/mass spectrometry

Fig. 2 shows the Taylor cone when a piece of porous hollow fiber (3.5 cm in length; rinsed with methanol) was used. The upper photo shows the actual size of the set up. The applied voltage on the ESI needle was +4500 V. We were very surprised to find that a cut flat end on a porous hollow fiber caused the production of a Taylor cone. It should be noted that the electrospray is usually formed from a sharp tip, such as a needle, pipette tip or triangular shaped chromatography paper tip, where the opposing forces of surface tension and electric field produce the cusp

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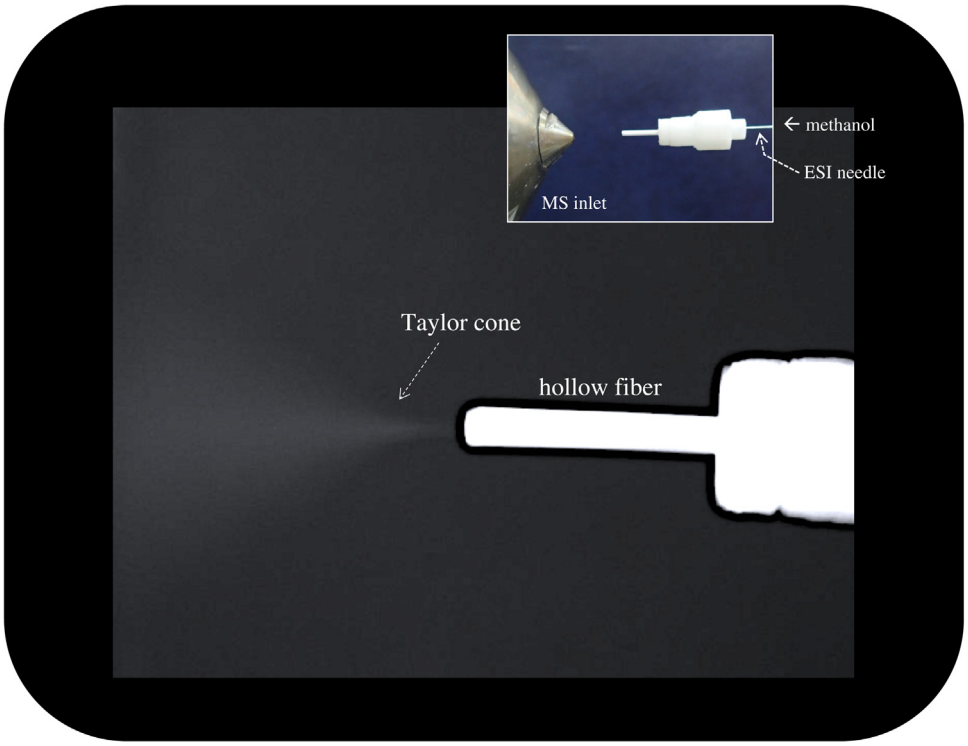

Fig. 2. A Taylor cone was observed during the electrospray ionization process, when a high voltage (+ 4.5 kV) was applied to the porous hollow fiber. Upper photo, actual size of the fiber and its holder used in this study.

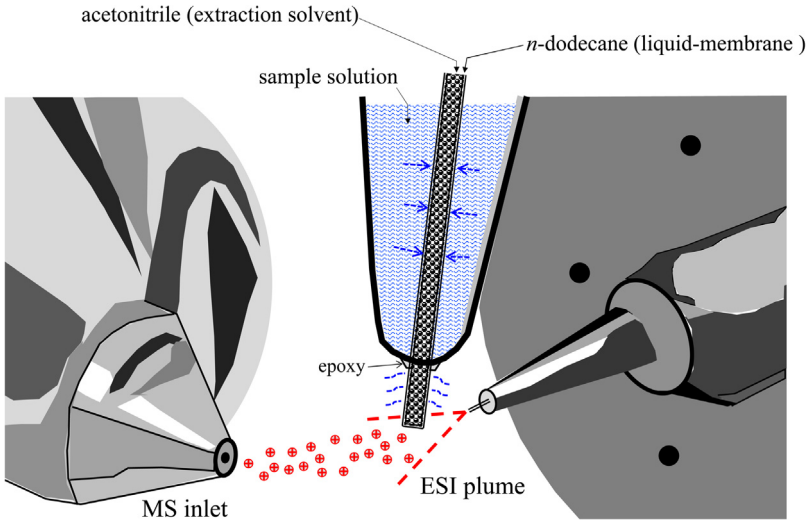

Fig. 3. Schematic diagram of the on-line micro-extraction fiber-spray/mass spectrometry developed in this study.

shaped Taylor cone. When it was discovered that a porous hollow fiber can be used for an ESI material, many applications become possible, such as the use of frit, porous material, or even sponge.

During the time when the ESI process is operational, it is necessary to continuously rinse the hollow fiber with the auxiliary liquid (methanol), a process that requires an adapter. As described in our previous study, the adapter was fabricated by a 3D-printer [41]. It consisted of a seal cap, fixed cover, solvent cell (inside the body; capacity, 0.1 mL) and the body itself. All of these parts are then combined to produce a kit that can be used in evaporation and ionization. Using this method, the limit of detection was similar to that obtained by regular paper-spray mass spectrometry when 3,4-MDMA was used as the test sample [42]. However, this can be improved when the online microextraction method was applied, as described below.

3.2. HF-LPME/ESI mass spectrometry

Fig. 3 shows a schematic diagram of the on-line microextraction fiber-spray/mass spectrometry developed in this study. The microextraction kit was located between the mass inlet and the ESI needle. Analytes can be extracted from a very dilute solution using the so-called hollow fiber liquid phase microextraction process, and the resulting extract then moves to the outside portion of the fiber by diffusion. Following this, the concentrated analytes were evaporated and escape, along with acetonitrile through the porous surface. Meanwhile, the electro-sprayed/charged droplets

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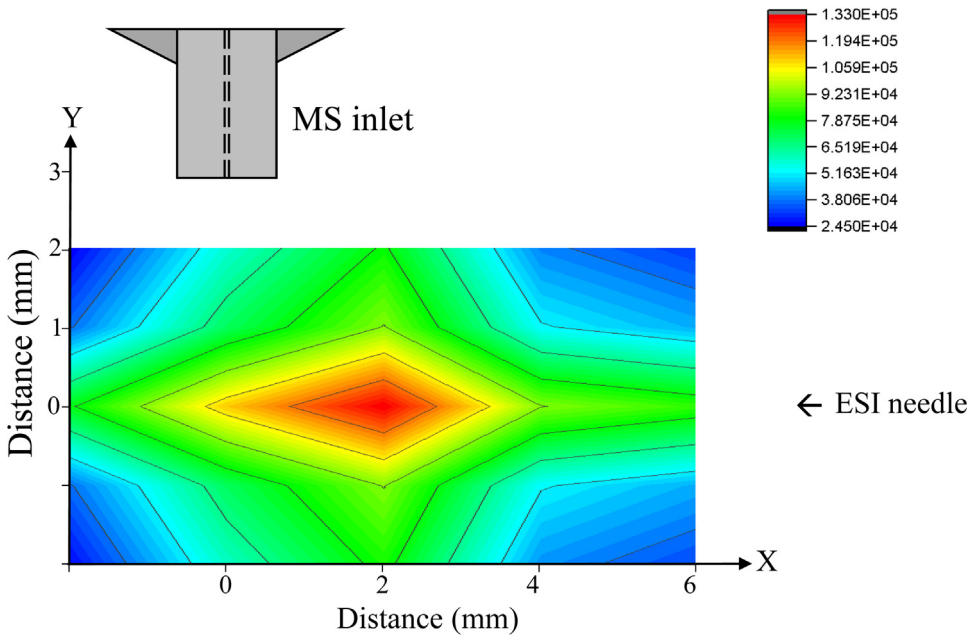

Fig. 4. Relationship between ion intensities and the positions where the fiber was located. It is clear that the position, indicated in red, is the optimized location. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

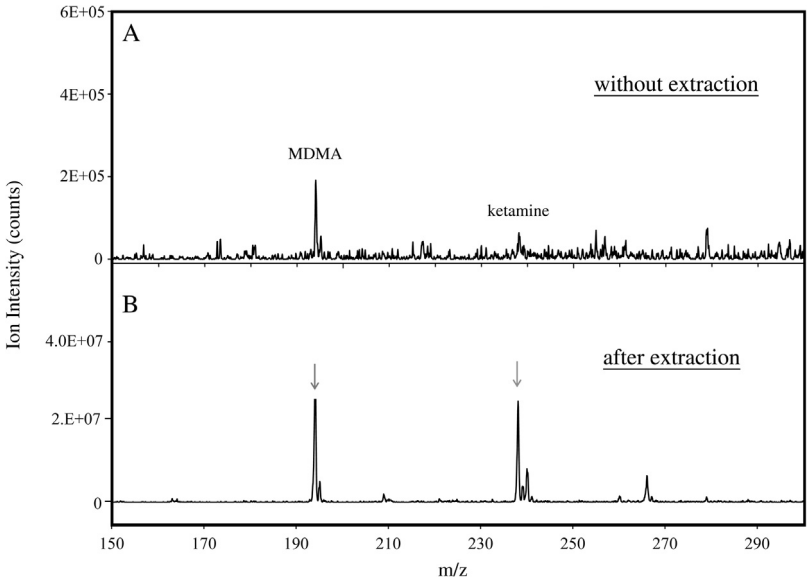

Fig. 5. Typical mass spectra obtained using on-line micro extraction fiber-spray/mass spectrometry. Frames A and B show the difference in peak intensity when the extraction process was used and not used (frame A, without extraction; frame B, after extraction); concentration levels of frames A and B are 10 μg/mL.

are produced from a regular ESI stainless needle. Once the evaporated materials from the surface of the hollow fiber (mostly neutral) meet the electrospray plume, ionization occurs under ambient conditions. This is similar to electrospray-assisted laser desorption ionization [5,6], in which a laser beam is used to generate analytes (gas phase). Since the position of the outside-fiber is very important in acquiring sufficient ions for detection, ionization efficiencies were investigated when the kit was placed in various positions. To determine the optimal position, a special 3D-stage was constructed. The glass, used for an observation window in the mass spectrometer, was replaced with an acrylic plate. The 3D-stage was set on the acrylic plate and a hole (diameter, 1 inch) was prepared to allow the kit pass through and move. Fig. 4 shows the relationship between ion intensities and the location of the fiber. In this case, caffeine was used as the test sample (concentration, 10 μg/mL) and the ESI voltage was +4.5 kV. It is clear that the position, indicated by a red color, i.e. from view of the mass inlet in vertical and horizontal distances by ~3 mm and 2 mm, respectively, is the optimized spot. Hence, this position was used in the following experiments.

3.3. Applications

Fig. 5 shows typical mass spectra obtained using the fiber-spray/mass spectrometry technique. Frames A and B show the difference between when microextraction was used or not (frame A, without extraction; frame B, after extraction). In order to compare with the efficiency of extraction, 0.2 g of NaCl was also added to the sample solution. NaCl was used to improve extraction efficiency due to the phenomenon of salting out. Following this, the pH value was adjusted to 11.0 using a 1 M NaOH solution. Finally, the

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concentration of the active components of the clandestine tablet was estimated to be 10 μg/1.0 mL of solution. Frame A shows the mass spectrum obtained from the clandestine tablet solution by fiber spray/mass spectrometry. The ion intensities for 3,4-MDMA (m/z = 194) and ketamine (m/z = 238) were 1.8×10^5 and 6.4×10^4, respectively. In contrast to this, frame B shows a mass spectrum obtained using the HF-LPME/evaporation/ESI mass spectrometry technique. The ion intensities of 3,4-MDMA and ketamine were found to be 3.0×10^7 and 2.3×10^7, respectively. We therefore conclude that, in this case, the ion intensity can be improved to ~360-fold by using on-line microextraction. To 3,4-MDMA, the limit of detection was about 2 ng/mL (S/N = 3). It should be noted that the types of extraction solvents, pH values of the sample solution and extraction times are all important variables and all of these parameters should be optimized. We found that when the pH values were adjusted from 9 to 13, it became clear that an alkaline solution was better. The pK_a values for 3,4-MDMA and ketamine are 7.8 and 10.14, respectively. This explains why the extraction efficiency for ketamine was better in an alkaline solution (pH, 11). The extraction time was investigated from 10 to 100 min at intervals of 10 min, and the findings show that 70 min was an appropriate time. We also found that when a stirring bar was placed inside the centrifuge tube, the extraction time could be shortened to 15 min.

4. Conclusion

The development of novel methods, including fiber-spray/mass spectrometry and HF-LPME/ESI mass spectrometry (an on-line concentration technique) are described. A fiber-spray ionization source that involves the use of a hollow liquid-phase micro-extraction fiber with a regular electrospray source was developed and tested. By using a commercial 3D-printer and a centrifuge tube, an economical and disposable hollow fiber kit was successfully designed and developed. The methodology is simple and economical, and is suitable for use in low-level drug screening. While the results show that the methodology is feasible, extensive work needs to be done to verify that the method can be effectively used for drug screening in biofluids. In fact, by using this new ESI method, determination of pesticide (such as glyphosate), traditional Chinese medicine (such as berberine, coptisine and palmatine) and fexofenadine have succeeded. Further applications are currently being explored.

Acknowledgment

This work was supported by grants from the Ministry of Science and Technology of R.O.C under Contract 103-2113-M-003-001-MY3.

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