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Real-Time Sample Analysis Using a Sampling Probe and Miniature Mass Spectrometer

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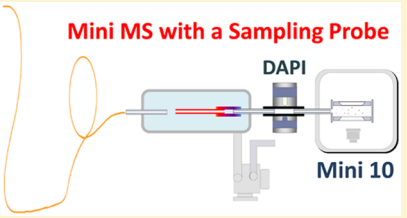
ABSTRACT: A miniature mass spectrometry system with a sampling probe has been developed for real-time analysis of chemicals from sample surfaces. The sampling probe is 1.5 m in length and is comprised of one channel for introducing the spray and the other channel for transferring the charged species back to the Mini MS. This system provides a solution to the problem of real-time mass spectrometry analysis of a three-dimensional object in the field and is successful with compounds including those in inks, agrochemicals, explosives, and animal tissues. This system can be implemented in the form of a backpack MS with a sampling probe for forensic analysis or in the form of a compact MS with an intrasurgical probe for tissue analysis.



On-site chemical analysis provides information promptly for decision making[1] and can support a wide range of applications, such as the screening of agrochemicals in foodstuffs,[2,3] monitoring of pollution in the environment, and checking the authority of the products. Recent development in mass spectrometry techniques also indicated a potential of intrasurgical analysis for supporting the surgeons' decisions during an operation.[4,5] The implementation of real-time chemical analysis, however, requires that complete analysis procedures be performed at the site of sample collection in a fast and simple fashion. Miniature devices have been developed for different analytical technologies, such as gas chromatography (GC),[6] ion mobility spectrometry (IMS),[7] and mass spectrometry (MS),[8] to enable real-time analysis in the field. MS provides highly specific molecular information for a broad range of compounds; its miniaturization, however, can be challenging due to the vacuum required for mass analysis. Miniaturization of the pumping system has been one of the most critical steps for developing small MS instruments, especially for analysis of nonvolatile compounds. Discontinuous atmospheric pressure interface (DAPI) was designed to sample ions from the atmospheric pressure environment with small pumping systems.[9] Ions are introduced with a short opening time (about 13 ms) through the DAPI and then trapped in an ion trap over a delay time of several hundred milliseconds, which is required to allow the elevated pressure to decrease back to millitorr level for mass analysis. A scan cycle as short as 300 ms was achieved with a 550 g turbo and 350 g scroll pump.[10] Various versions of integrated ion trap mass spectrometers have been developed with the DAPI interface and small pumping systems,[11−13] with the smallest one weighing only 4 kg.[12]

The significance of having an atmospheric pressure interface for miniature MS instruments lies in its enabling the coupling of ambient ionization methods[14−17] for direct analysis of nonvolatile compounds in complex samples. Ambient ionization allows direct analysis of samples in their native states.[18,19] Ion transfer over a long distance has also been combined with ambient ionization to develop sampling ionization probes that give easy access to the sample.[20−22] Nonvolatile analytes were ionized from the surfaces of the objects of interest and the charged species sent back to a mass spectrometer for MS analysis. It was found that the gas flow[23,24] could facilitate the efficient transfer of the ions over a long distance through a thin tube,[25] which can possibly be inserted in an endoscope for in vivo analysis during laparoscopic or endoscopic procedures. Real-time analysis of tissue samples was achieved by simply pushing a sealed sampling tip against the tissue, and lipid profiles were obtained with the desorbed, charged species transferred over 4 m with a 1.6 mm i.d. flexible tube. With proper flow of gas applied, no high voltage or organic solvent was required for the desorption ionization, which makes the method compatible for in vivo analysis. Auxiliary pumping was used to pull the gas for ion transfer, which altered the gas dynamics of the sampling area and minimized the destruction to the tissue surface.[25]

Portable systems with sampling probes have been explored for real-time, in-field chemical analysis. This concept was first demonstrated with backpack mass spectrometers. A low temperature plasma ionization source and a vacuum manifold containing the mass analyzer were separated from the main body of the instrument but connected via a tube.[26] This configuration was designed on the basis of the idea of bringing the mass analyzer closer to the sample. In a later study,[10]

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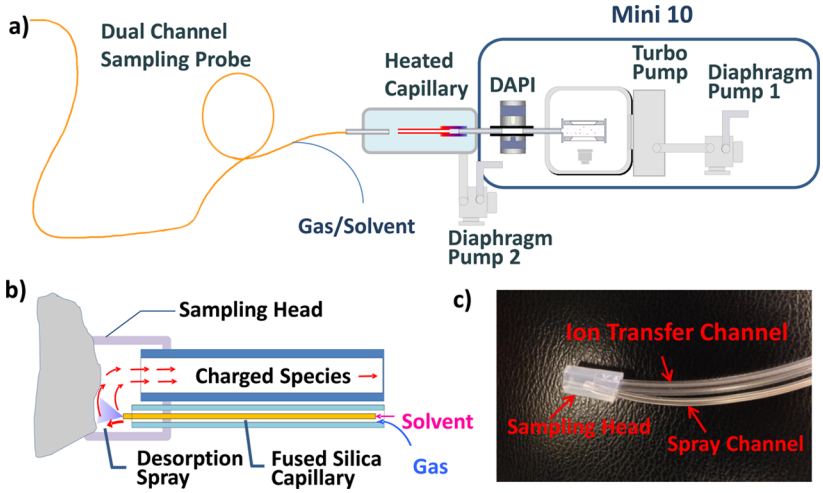

Figure 1. (a) Schematic of the miniature MS system with an integrated sampling probe. (b) Configuration of the sampling head of the probe. (c) Photo of the sampling end of the probe.

ultrasmall turbo pumps were used and incorporated into the hand-held sampling unit. In the current study, we attempt to couple a flexible thin-tube sampling probe with a hand-held mass spectrometer. The potential advantages of this configuration are the ease of operation with the lightweight and flexible probe and its compatibility with devices like medical endoscopes. The disadvantage, however, mainly is associated with the long distance transfer of the charged species and the potential significant loss in sensitivity for the analysis. An exploratory study was carried out to demonstrate this concept, with an integrated system built and tested for the analysis of chemicals from different sample surfaces.

INSTRUMENTATION

A home-built miniature ion trap mass spectrometer, Mini 10,[9,11] was modified for this study. It consisted of a DAPI interface, a rectilinear ion trap (RIT), a channel electron multiplier (DeTech 2300, Detector Technology Inc., Palmer, MA) with a conversion dynode, a Pirani gauge (series 925C, MKS Instrument Inc., Andover, MA), a Pfeiffer Hipace 10 turbo pump (10L/s, Pfeiffer Vacuum Inc., Nashua, NH), and a KnF N84.3 diaphragm pump (5 L/min, KNF Neuberger Inc., Trenton, NJ). The flow constraining capillary for DAPI was 10 cm long and of 1.6 mm o.d. and 0.5 mm i.d. Three rf frequencies (1238, 1038, and 760 kHz) were used for trapping and MS analysis of ions in three different mass ranges (m/z 55−460, m/z 78−660, and m/z 160−1300, respectively). The conversion dynode was operated at −3850 V for positive ion detection and +3850 V for negative ion detection.

The sampling probe of 1.5 m length was coupled to the modified Mini 10 as shown in Figure 1a. It had a dual-channel configuration, one channel for delivering the nebulizing gas and solvent for spray desorption and the other one for transferring the ions back to the mass spectrometer. The spray tube had a coaxial configuration with an outer tube (510 μm i.d., 1520 μm o.d.) for delivery of nitrogen gas and an inner fused silica capillary (50 μm i.d., 150 μm o.d.) for delivery of solvent. The ion transfer channel was 1.5 m long, 1.6 mm i.d., and 3.2 mm o.d. The sampling head has an opening of 3.2 mm. It was made of a soft material, silicone, so as to provide a seal on the surface. Once the seal is provided, the charged species desorbed from the sample surface by the charged droplets from the sprayer were guided back by the gas flow into the ion transfer channel (Figure 1b). An adapter was designed to provide connection between the probe and the Mini 10. An additional diaphragm pump (rough pump 2 in Figure 1a, KnF N84.3, KNF Neuberger Inc., Trenton, NJ) was connected to the adapter to pull the gas inside the ion transfer channel toward the MS. In a previous study,[25] it was shown that a vacuum seal could be produced at the sampling head with the additional pumping and the destruction to the soft samples, such as tissues, was minimized. A flow control meter was used to adjust the pumping flow rate. The nitrogen gas pressure used for desorption ionization was 230 psi, corresponding to a gas flow rate of 0.7 L/min.

EXPERIMENTAL SECTION

Experiments were performed to study the design of the sampling probe, its interface with the miniature mass spectrometer, and the operation condition for the chemical analysis. The optimum material for the transfer line and the number of ion injections through DAPI as well as the requirement of heating for desolvation were determined. Analyses of a variety of samples were performed to characterize the integrated system and to demonstrate its versatility for in-field chemical analysis.

E. coli polar lipid extracts were purchased from Avanti Polar Lipids, Inc. (Alabaster, AL). A sonic spray source[27] was built for ionizing the polar lipid extracts in experiments for optimizing the conditions of the interface between the sampling probe and DAPI. Methanol solutions of agrochemical PCP (2,3,4,5,6-pentachlorophenol) and DNP (2,4-dinitrophenol) were both prepared with an analyte concentration of 100 ppm. A blue ballpoint pen (Pilot BPS-GP, Pilot Corp., Jacksonville, FL) was used to write on the print paper (Business 4200, Xerox Corp., Norwalk, CT) to create the ink samples. For the study of the aging of the ink samples, another blue ballpoint pen (S.K.B. SB-1000 0.5 mm, Kaohsiung, Taiwan) was used to write on the print papers to prepare the ink sample, some of which were then exposed to a 100 W incandescent lamp for different lengths of time periods to simulate the aging of ink samples under lights. Pure methanol (Mallinckrodt Backer Inc., Phillipsburg, NJ) was used as the spray solvent for the analysis of PCP, DNP, and ink. Tissue sections of rat brain, liver, lung,

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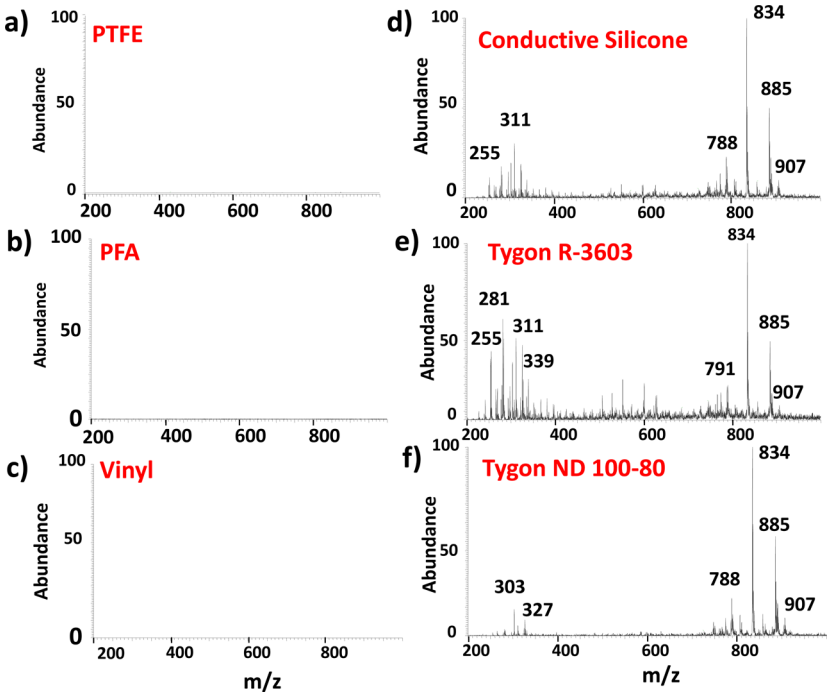

Figure 2. Mass spectra recorded for analysis of rat brain tissue sections using ion transfer tubes made of (a) PTFE, (b) PFA, (c) vinyl, (d) conductive silicone, (e) Tygon R-3603, and (f) Tygon ND 100-80. Tube lengths of 1 m, 1.6 mm i.d., LTQ in negative ion mode.

and intestine were prepared at thicknesses between 10 and 30 μm using a cryostat microtome and mounted on the glass slides. Pure water (D.I. water from Milli-pore Milli Q system) was used as the spray solvent for tissue analysis, and solvent flow rate of 8 μL/min was controlled using a syringe pump. No high voltage was used for the desorption spray in any analysis.

RESULTS AND DISCUSSION

In a previous study, it was found that the survival of the ions or the charged species during a transfer in gas flow was dependent on their reactivity.[20,23,28] In this current study, we observed that the types of the materials used for the ion transfer tube had a significant impact on the ion transfer. For an investigation for selection of the transfer tube, six common types of plastic tubes (all 1 m long, 1.6 mm i.d.) were used to construct the sampling probes of 1 m. Each of them was coupled to a LTQ (Thermo Scientific Inc., San Jose, CA) and tested for analysis of a rat brain tissue section. Negative ion mode was set for MS analysis. As shown in Figure 2, strong signals were obtained for fatty acids and lipids with transfer tubes of conductive silicone, Tygon R-3603, and Tygon ND 100-80, but not for polytetrafluoroethylene (PTFE), perfluoroalkoxy alkane (PFA), or vinyl chloride (Vinyl). In the previous study[23] when using tubes of a larger internal diameter, 4.3 mm, ion transfer was achieved using PTFE, although not as well as Tygon. When thinner tubes were used in these studies, the material effect was much more significant and not even chemical noise was observed with PTFE, PFA, or vinyl tubes. These three materials have a common characteristic: they are known to be easily negatively charged on their surfaces.[29] In a separate test involving transfer of positive ions using PTFE, the signal was also found to be low. In contrast, the charges on the surface of the conductive silicone could be drained, so they will not be accumulated to create a high electric potential. Tygon tubes were designed to have high resistance to the accumulation of chemical residues, which presumably helps to minimize the charging on their surfaces. Among the tested materials, Tygon ND 100-80 is certified for medical applications. We used it for the rest of the experiments reported in this manuscript.

The experiments testing the tube material were done in parallel with the optimization of other features of the integrated system to improve the sensitivity for direct sampling chemical analysis. Loss of ions was inevitable over a long-distance transfer. Accumulation of ions in the ion trap analyzer could be one of the solutions. For each ion introduction event, the DAPI open time was limited, since the manifold pressure would otherwise be raised too high and ions could not be effectively trapped. Therefore, multiple ion introductions[30] were used for each MS analysis cycle, as shown in Figure 3a,b. The variation of manifold pressure for a scan cycle with ten ion introduction events is shown in Figure 3a. For each ion introduction, 13 ms DAPI open time was used and the manifold pressure rose up to about 100 mTorr. A delay time of 500 ms followed each ion introduction, during which the pressure dropped below 10 mTorr. To test this analysis procedure, a lipid extract sample (100 μg/mL in 90/10 water/methanol) was ionized using a sonic spray source and a 30 cm long tube of 1.6 mm i.d. was used to transfer the ions to the DAPI of the Mini 10. Mass spectra were recorded for direct analysis of lipid extracts, with the number of ion introduction events being varied. The signal-to-noise ratios (S/N) of plasma-PE (38:6) at m/z 748 were calculated for each mass spectrum and are plotted as a function of number of ion introduction events in Figure 3b.

Another parameter that was optimized using the same setup for improving the sensitivity was the temperature of the heated capillary. The sampling probe was originally coupled to the DAPI without a heated capillary, and it was found that the signal intensity was extremely low. In previous studies, it was observed that ions from spray sources could survive much better than low temperature probe or atmospheric pressure chemical ionization sources.[23,28,31] It was proposed that the

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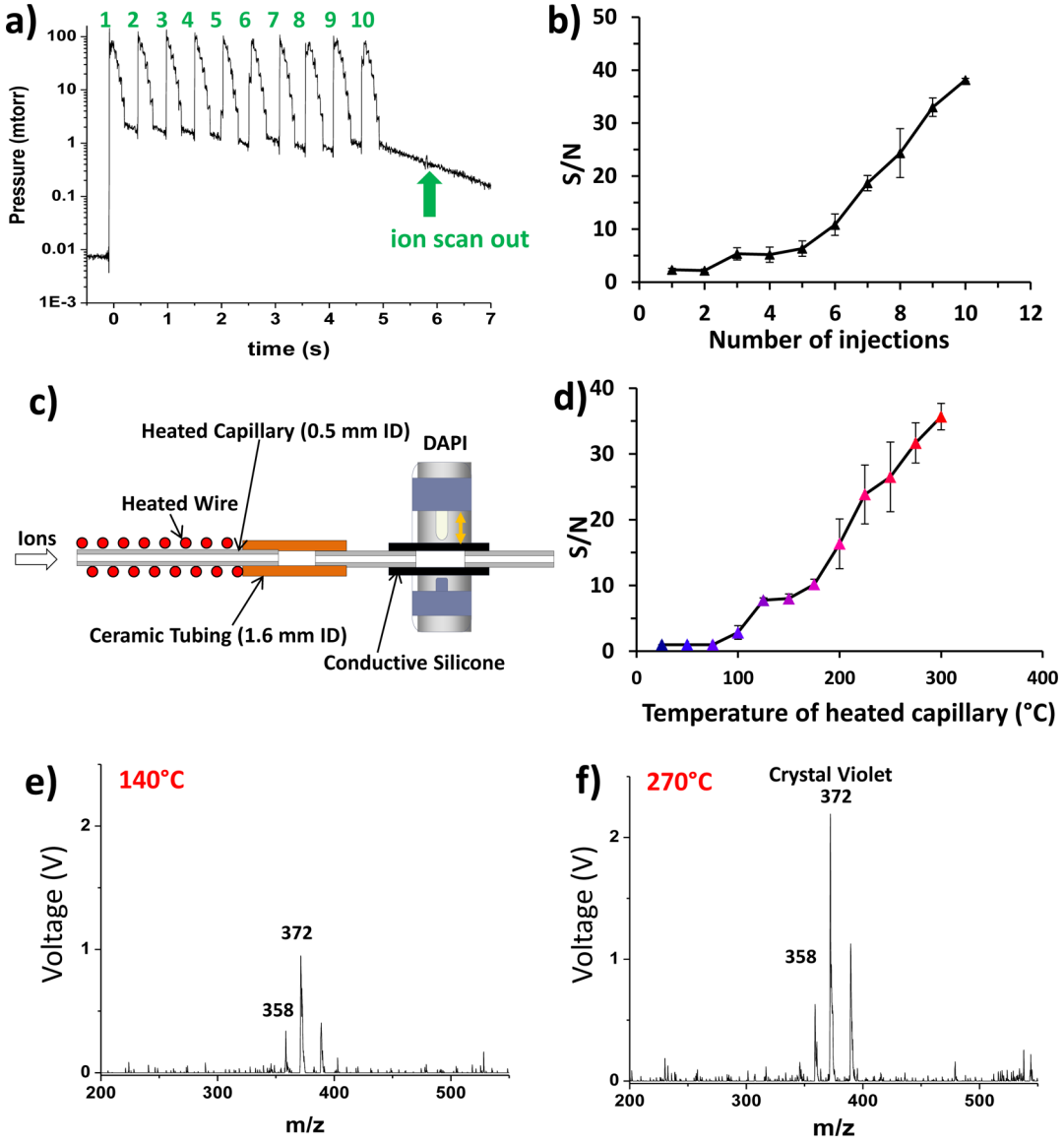

Figure 3. (a) Variation of the manifold pressure during a scan with ion introduction, DAPI open time of 13 ms. (b) S/N of peak m/z 748 for plasma-PE (38:6) as a function of the number of ion introduction events for each scan, mass spectra recorded using a sonic spray ionization source for analysis of lipid extracts, ion transfer tube of 30 cm length and 1.6 mm i.d., heated capillary temperature of 270 °C. (c) Configuration for coupling of the heated capillary with the DAPI. (d) S/N of peak m/z 748 for plasma-PE (38:6) as a function of the temperature of the heated capillary, 10 ion injections for each scan. (e) Direct analysis of ink on paper using the 1.5 m long dual-channel sampling probe with desorption ionization function, 10 ion introduction events per scan at 140 °C and (f) at 270 °C.

ions surviving the transfer process might have been in droplets or as solvent clusters during the transfer and that they became fully desolvated at the inlet of the mass spectrometer. The solvent molecules surrounding the ions could actually protect the ions from loss through reactions. Addition of a heated capillary to the DAPI was expected to improve desolvation significantly. A stainless steel capillary of 10 cm length, 0.5 mm i.d, and 1.6 mm o.d. was connected to the front capillary of the DAPI through a ceramic tube (1.6 mm i.d. and 3 mm o.d.) as a heat insulator. The capillary was wrapped with a braided fiberglass sleeve for electrical insulation, then coiled with a resistive heating wire (6.75 Ω/ft, part number 30BNC, Consolidated Electronic Wire & Cable, Franklin Park, IL), and coated with alumina adhesive (930HP, Cotronics Corp., Brooklyn, NY) for fixing the wire and heat insulation. Spectra were recorded, with 10 ion introduction events for each scan, for the lipid extracts at different temperatures of the heated capillary, and the S/N of plasma-PE (38:6) at m/z 748 was calculated and plotted as a function of the temperature as shown in Figure 3d. It was observed that the S/N started to increase significantly once the capillary temperature was raised above 80 °C and continued to increase linearly with the temperature of the heated capillary. The 1.5 m long sample probe was then coupled with the Mini 10 through this heated capillary and tested by analysis of ink on print paper made using a blue ballpoint pen (Pilot BPS-GP). The signal of crystal violet (m/z 372) appeared when the capillary was heated to 140 °C (Figure 3e). The S/N was improved by a factor of 2 when the temperature increased to 270 °C (Figure 3f).

The miniature MS system with the 1.5 m long sampling probe was then tested in a series of applications, such as analysis of agrochemicals, detection of explosives, and signature

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authentication based on the aging of the ink. Ten ion introductions prior to each mass scan and heating of the capillary to 270 °C were implemented. Pentachlorophenol (PCP) is an agrochemical that has been used as fungicide, insecticide, herbicide, and algaecide. Nowadays, it has been banned in ten countries due to its slow biodegradation rate and high toxicity.[32] To demonstrate the idea of quick, on-site analysis, 300 ng of PCP was deposited on a glass slide, and the mass spectrum was obtained immediately after the sampling tip of the probe reached to the point of deposit (Figure 4a). The spectrum recorded clearly showed the isotope distribution of $[M - H]^-$ with m/z 263, 265, 267, and 269.

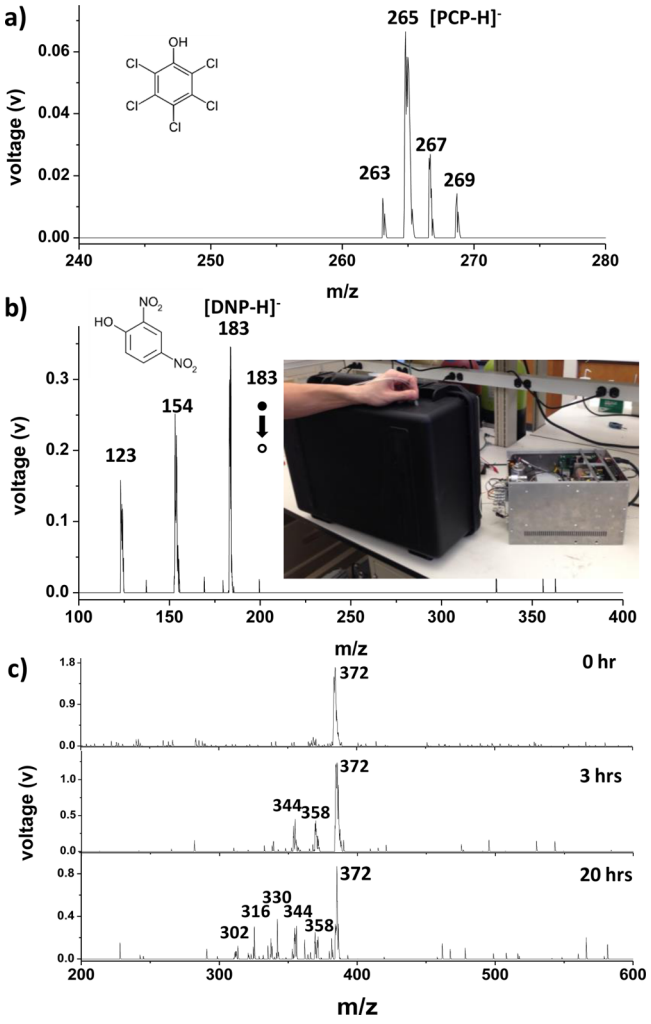

Figure 4. Real-time analysis of chemical compounds from the surface using the integrated miniature MS system with a 1.5 m long sampling probe. (a) Mass spectrum for detection of 300 ng of PCP on a glass slide. (b) Product ion mass spectrum for 300 ng of DNP from the outer surface of a Pelican case. (c) Mass spectra of the blue ballpoint pen ink on print paper after exposure to the light from a 100 W incandescent lamp for 0, 3, and 20 h.

As a demonstration of detection of hazardous substances, DNP, a agrochemical compound that can also be used for making explosives, was detected from a Pelican case (Pelican Storm Case iM2620, 54 × 41 × 27 cm, Pelican Products Inc., South Deerfield, MA) (Figure 4b). DNP (300 ng) in 3 μL of methanol was deposited in an area of 9 mm^2 on a Pelican case and let dry to form a dried spot. For detection, the Mini 10 was set for MS/MS with $[DNP - H]^-$ m/z 183 as the precursor ion. Ten ion introduction events were used for each mass scan. The sampling head of the probe moved across the surface of the Pelican case. When it covered the area of the DNP dried spot, the mass spectrum shown in Figure 4b was obtained, with characteristic peaks of DNP fragment ions at m/z 123 and 125. The use of a flexible probe certainly makes it convenient for checking different surfaces on a large object.

Direct analysis of the document ink, as a means for authentication, has recently been performed using ambient ionization mass spectrometry.[33,34] The photodegradation products of the ink can be observed and used to assess the age of the ink. In this study, ink samples on print papers, prepared using a SKB blue ballpoint pen, were exposed to the light from a 100 W incandescent lamp for 0, 3, and 20 h before they were examined using the miniature MS system with the sampling probe. The mass spectra recorded are shown in Figure 4c. The major component in the ink, crystal violet (m/z 372), was observed before the photodegradation and two degradation products at m/z 358 and 344 were observed after a 3 h exposure to the light, while three additional products m/z 330, 316, and 302 were observed after a 20 h exposure. The mass differences, each of 14 Da, were due to a series of demethylations. The use of a sampling probe for this type of analysis does not damage a document while specific chemical information becomes available for authentication or forensic purposes.

One of the goals for developing a thin and flexible sampling probe for MS analysis was intrasurgical MS specifically in vivo tissue analysis for use during a surgical or endoscopic procedure.[25] Some recent studies have shown the potential of using real-time MS analysis to provide rich molecular information on tissue to assist in surgical decision making.[5,35,36] The use of a miniature MS system, instead of a lab-scale mass spectrometer, would certainly make the implementation of real-time MS analysis much more convenient in a surgical room. We tested the integrated miniature MS system with a 1.5 m long sampling probe using tissue samples from rat brain, liver, lung, and intestine (Figure 5). The Mini 10 was operated in negative ion mode with ten ion introductions for each scan, at 270 °C heated capillary temperature and recording an extended mass range of m/z 160 to 1300 for analysis of lipids. In order to make sampling compatible with the medical procedure, no high voltage was applied to the spray and pure water was used as the spray solvent for the desorption ionization. The sampling head was pushed against each of the tissue sections on glass slides, and the mass spectra recorded are shown in Figure 5a–d. Different profiles of phospholipids were obtained for the rat organs, and bile acids were also observed from the intestine. The total time taken to record each mass spectrum was about 6 s. In this study, two separate tubes of 1.5 mm o.d. and 3.2 mm o.d. were used for the proof-of-concept experiment. For future implementation in endoscopic procedures, a dual-channel (1.6 mm i.d. and 0.5 mm i.d.) single tube fitted into the operating channel of an endoscope (<3.7 mm i.d.) or a laparoscope (<5 mm i.d.) can be easily manufactured by an extrusion process.

CONCLUSIONS

In previous work done by multiple research groups, sampling probes and miniature MS have been proposed and demonstrated independently. The combination of them is of great interest for future development of integrated MS systems for in-field, real time chemical and biological analysis. In this proof-

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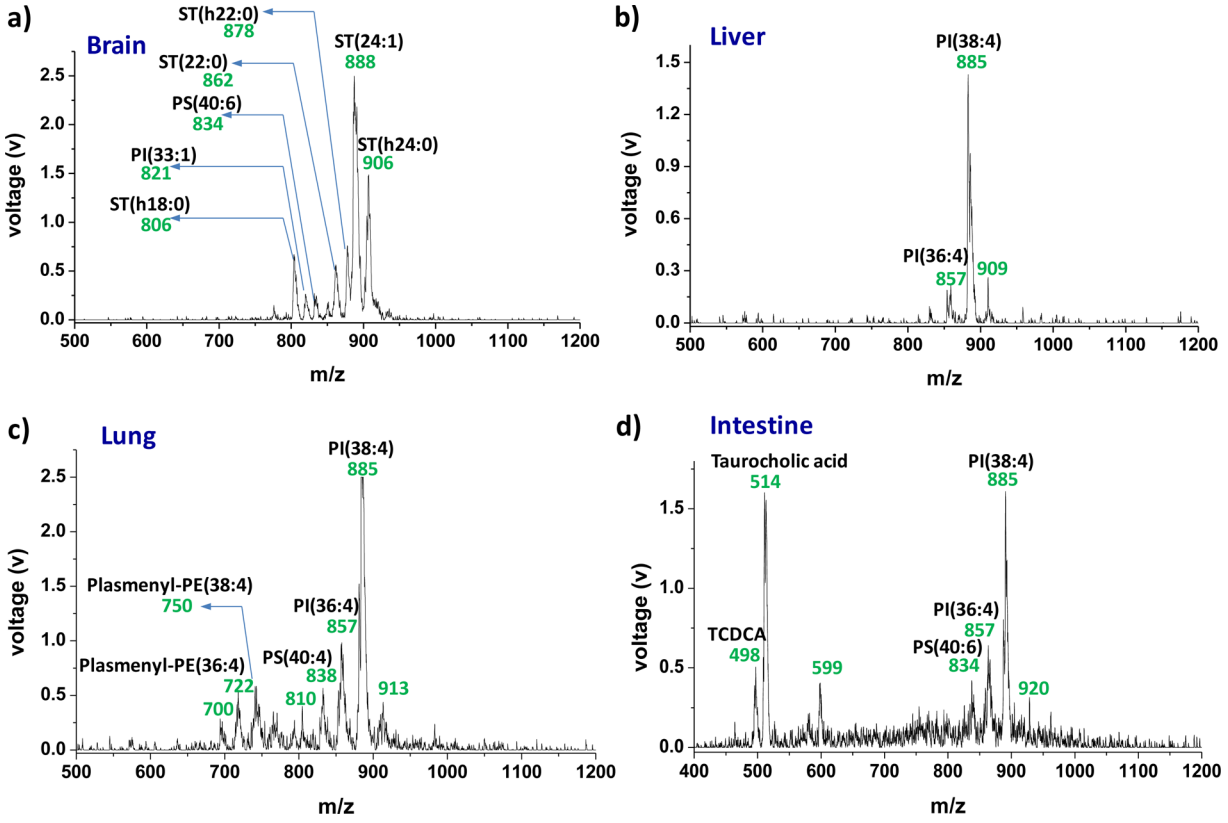

Figure 5. Mass spectra of tissue sections of rat (a) brain, (b) liver, (c) lung, and (d) intestine, direct analysis using the miniature MS system with a 1.5 m long sampling probe, 10 ion introduction events per scan, 270 °C heated capillary, no high voltage or organic solvent applied for the desorption spray; pure water was used as the spray solvent.

of-concept study, we investigated the feasibility of combining a thin sampling probe with a miniature ion trap instrument for direct analysis of semivolatile (e.g., crystal violet, PCP, DNP) as well as nonvolatile (e.g., lipids) compounds. The selection of the materials for the sampling probe will be dependent on the efficiency of ion transfer as well as the compatibility to other requirements in the application. Consistent with previous work using charged droplets for desorption ionization, high efficiency has been obtained for long distance transfer of the solvated ions; however, efficient desolvation through the interface to the mass spectrometer would also be critical for the MS analysis.

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Notes

The authors declare the following competing financial interest(s): Zheng Ouyang is the founder of PURSPEC Technologies Inc.

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