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Development of A Miniature Mass Spectrometer with Continuous Atmospheric Pressure Interface

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Abstract

The demand for on-the-spot analysis is met by a miniature mass spectrometer which is preferred to be robust, stable, as small as possible and capable of analyzing different samples by coupling with various ionization methods. However, largely constrained by the atmospheric pressure interface (API), these aspects are difficult to be realized in one system. Herein, we describe the development of a new miniature mass spectrometer with balanced performance. The miniature mass spectrometer is small in size (30×30×18 cm) but has a continuous API, which was achieved by high-pressure ion trap operation and maximized ion transfer efficiency with the utilization of a differential pumping system. The miniature mass spectrometer was characterized and optimized in terms of stability, sensitivity, mass range, mass resolution and scan speed. Rapid analysis of mixtures was demonstrated by coupling the miniature mass spectrometer with the ambient ionization technique of paper spray. This is the smallest miniature mass spectrometer to date, which has a continuous API.

1. Introduction

With the capabilities of measuring the mass-to-charge (m/z) ratio of ions and thereby determine molecule weight and elucidating molecular structure, mass spectrometry (MS) has been widely used in many applications either alone or coupled with chromatography techniques.[1-5] The development of miniature (or portable) mass spectrometers over the past decade[6-13] has further expanded the applications of MS into different areas, such as homeland security[14-16], environment monitoring[17-20], personal healthcare[21,22], space exploration[23-25] and etc., which require on-site chemical analysis in real time.

The efforts of developing miniature mass spectrometers started with the miniaturization of mass analyzers. Researchers have fabricated smaller or even micro-meter sized quadrupole ion traps and quadrupole rods using techniques such as micro-electromechanical systems (MEMS), advanced laser fabrication techniques.[26-29] However, a vacuum system (or the pumping system) is typically the major parts of a MS system, which consumes a large portion of system power and volume. Therefore, miniaturization of a mass analyzer (or even together with the ionization system[30]) has very limited impacts towards the miniaturization of a MS system on a system level. Testing of these miniaturized mass analyzers was usually performed in a large vacuum system, which might be still bulky and consume kilowatts energy.[31]

Generally speaking, two types of miniature mass spectrometers have been developed on a system level up to now: 1) miniature mass spectrometers with continuous gas inlets and internal ionization sources,[32-37] which could only analyze

gas or volatile samples. In order to hold a vacuum environment with very limited pumping powers, the continuous gas inlets used in this type of miniature instrument, typically membranes[36,38-43] or capillaries with extremely low gas flow rate[32,44], does not allow the transfer of ions from atmosphere to vacuum, thus preventing the analyses of non-volatile samples. Although ion transfer could be achieved by increasing the gas flow rate and by utilizing much larger and powerful vacuum pumps, the size and power consumption of the MS instrument will suffer correspondingly.[45,46]

2) Miniature mass spectrometers with a discontinuous atmospheric pressure interface (DAPI),[47-49] which can work with ionization sources in ambient environment. In a DAPI setup, high gas flow rate and efficient ion transfer are realized by mechanically opening the API for a very short duration (on the scale of milli-seconds).[47,48] DAPI has enabled the use of miniature mass spectrometers for the analyses of liquid and even solid samples, especially when coupled with ambient ionization sources.[50-53] In spite of these advantages, the use of a mechanical switch to control vacuum pressure and ion introduction duration lowers the scan speed,[13,47] stability, robustness of the system, especially when used in some on-site applications involving harsh environments. Of course, a mass spectrometer with a discontinuous inlet could also work with internal ionization sources to lower the vacuum load.[33,54] In summary, having a miniature mass spectrometer with a continuous API (with ion transfer capability) is technically challenging but attractive in terms of practical applications.

In this work, a new miniature mass spectrometer with a continuous API was developed, which was enabled by high pressure ion trap operation and the design of a

differential pumping system with maximized gas flow rate and ion transfer efficiency. The total dimensions of the instrument are around 30×30×18 cm, and the system weight is ~ 6 kg including electronics, power supply, etc.. After optimization, good stability (signal relative standard deviation, RSD < 7%), reasonable sensitivity (limit of detection, LOD 1 ug/mL; linear of quantitation, LOQ 1-100 ug/mL), better than unit mass resolution, broad mass range (from 200 Da to 2500 Da), and high scan speed (5 Hz) were achieved for the miniature mass spectrometer.

2. Theory and Instrumentation

Design of the continuous API miniature mass spectrometer needs to have comprehensive consideration of the vacuum system, ion transfer devices and the mass analyzer, an ion trap in this case. There are tradeoffs among pumping speed of the vacuum system, gas flow rate and ion transfer efficiency through the API, operating pressure of the ion trap, total dimensions and power consumption of the system. A balance needs to be achieved between the pumping speed and power consumption of the vacuum system, so that acceptable ion transfer efficiency and ion trap operating pressure could be achieved, which largely determines sensitivity and mass resolution of the system.

2.1 Theoretical Design of the Vacuum System

The key of vacuum design is that the pressure of the vacuum chamber needs to be low enough to operate the ion trap (below ~10 mTorr), as well as the electron multiplier (EM). Selection of vacuum pumps is restricted by their size and power consumption, which results in a vacuum system with very limited pumping speed. In order to maintain a suitable working pressure inside the ion trap, a two-stage vacuum chamber was designed as shown in Figure 1a. In this design, the ion trap and the EM were placed in the second vacuum stage. The first vacuum stage was connected to the atmospheric pressure environment by a stainless steel capillary, and a pinhole was implemented between the first and the second vacuum stages. The combination of a turbo pump and a diaphragm pump was applied to maintain the pressures inside these two vacuum stages.

Gas dynamic analyses were then performed to determine appropriate dimensions of the capillary and the pinhole, as well as determine the pumping speed of the vacuum system. With the continuous gas inlet, gas throughput through the capillary (Q^1_{in} or amount of gas flow into the first vacuum stage in unit time) equals to that passing through the diaphragm pump (Q^1_{out}).

$$Q^1_{in} = C_1(P_0 - P_1)$$

$$C_1 = \frac{\pi d_1^4}{128\eta L}\frac{P_0 + P_1}{2}$$

$$Q^1_{out} = P_1 S_1 \quad (1)$$

where C_1 is the conductance of the capillary at 20℃ (viscous flow model),[55] P_0 is atmospheric pressure, P_1 is the pressure in the first vacuum stage, d_1 is the inner diameter (ID) of the capillary, L is the length of the capillary, η is the viscosity of air, S_1 is the pumping speed of the diaphragm pump at pressure P_1. After selection of the diaphragm pump and the capillary dimensions, the pressure in the first vacuum stage could be calculated from Equation 1.

An ion trap typically works at a pressure below 10 mTorr, and the pressure in the first vacuum stage is expected to be within the Torr range. Therefore, gas flow from the first vacuum stage to the second vacuum stage is assumed to be within the transition flow region, which requires,[55]

$$0.02 < \frac{P_1 + P_2}{2} \cdot d_2 < 0.67 \quad Pa \cdot m \quad (2)$$

where P_2 is the pressure in the second vacuum stage and d_2 is the diameter of the pinhole. Similarly, gas throughput through the pinhole (Q^2_{in}) equals that through the turbo pump (Q^2_{out}),

$$Q_{in}^2 = C_2(P_1 - P_2)$$

$$C_2 = 1341\frac{{d_2}^4}{L_2}\frac{P_1+P_2}{2} + 121\frac{{d_2}^3}{L_2}\frac{1+189d_2\frac{P_1+P_2}{2}}{1+234d_2\frac{P_1+P_2}{2}}$$

$$Q_{out}^2 = P_2 S_2 \quad (3)$$

where the pinhole is treated as a short tube and C_2 is the conductance of the pinhole at 20℃ (transition flow model),[55] L_2 is the length of the pinhole. S_2 is the pumping speed of the turbo pump at pressure P_2. Pressure in the second vacuum stage can be obtained after selecting a turbo pump and knowing the pinhole dimensions.

With the consideration of both pumping speeds, dimensions and power consumptions, a turbo pump Hipace 10 (Pfeiffer vacuum, Germany) and a diaphragm pump SVF-E0-50 (Scroll Tech, USA) were selected. Using Equation 1 and 3, pressures within the vacuum chamber were calculated theoretically for capillaries and pinholes with different parameters, as presented in Table 1. As shown in Table 1, almost all combinations of capillaries and pinholes selected could maintain a low enough pressure (< 10 mTorr) in the second vacuum stage. Capillaries and pinholes with smaller IDs would lead to lower vacuum pressures; however, smaller IDs would also lower ion transfer efficiencies through these ion transfer devices.[56] Based on these considerations, a 1 mm long pinhole with a 0.3 mm ID was implemented as shown in Figure 1b, and capillaries with different IDs (0.12, 0.18 and 0.25 mm) were tested.

This differential pumping design could maximize the use of these two pumps and achieve higher gas flow rates, thereby obtaining higher ion transfer efficiency through

the API. Gas flow rate into this differential pumping system is about 6.2×10^{-3} L/s at a base pressure of 2.2 mTorr. By using the same pumps but having a single stage vacuum chamber (still at a base pressure of 2.2 mTorr), the gas flow rate would only be about 2.9×10^{-5} L/s. In other words, this differential pumping system design could increase the gas flow rate by more than 200 times than a one-stage pumping system.

2.2 Instrumentation

Based on this two-stage vacuum system design, a continuous API miniature mass spectrometer was constructed as shown in Figure 1b. A linear ion trap (LIT) with hyperbolic electrodes and dimensions of 4×4 mm (center to electrode distance), and 40 mm (length) was used as the mass analyzer. An electronic control system was built in-house. This electronic system could generate a single-phase radio frequency (RF) signal (~1.053 MHz, ~3 kV_{0-p} maximum), an AC signal with stored waveform inverse Fourier transform function (SWIFT), two low direct current (DC) voltages (-200 V~ 200 V) and a high DC voltage (-2 kV~0 V). All these signals could be synchronized and controlled by a laptop computer. Ionization sources, including atmospheric pressure chemical ionization (APCI), nano-electrospray ionization (nanoESI) and paper spray, have been used to characterize the performance of the continuous API miniature-MS.

A typical scan function of the continuous API miniature-MS is shown in Figure 1c. Different from a conventional miniature-mass spectrometer with a DAPI interface,[57] the EM was turned on all the time during MS detection in this MS, and ion introduction was controlled by the DC voltage applied on the endcap of the LIT,

which was facing the pinhole (Endcap 1). Dipolar resonance ejection (369 kHz, 1-2 $V_{0\text{-}p}$, otherwise specified) was used to mass-selectively eject ions out of the ion trap for MS analysis, unless otherwise specified.

2.3 Samples

Polyethylene glycol (PEG) 600 and PEG 1500, GPRP, MRFA, reserpine, rhodamine B, DEET and cytochrome C were all purchased from Sigma Aldrich (St. Louis, MO, USA). All samples were diluted in methanol/water (1:1 v/v), except cytochrome C which was diluted in methanol/water (1:1 v/v) with the addition of 1% acetic acid by volume.

3. Results and Discussion

A miniature mass spectrometer with a continuous API is expected to have the following features: environmentally robust, stable with high repeatability, fast in MS analysis, capable of coupling with different ionization techniques in the ambient environment, as well as acceptable MS resolution and sensitivity. These features would enable broad usage of miniature mass spectrometers in different in situ chemical analysis applications. Performance of the miniature mass spectrometer developed in this work was optimized and characterized.

Optimization of the capillary. The capillary connecting atmosphere and the first vacuum stage has two important functions: first, limiting the gas flow, thus keeping the vacuum inside the chamber; second, allowing efficient ion transfer from atmosphere to vacuum. All three capillaries (ID 0.12, 0.18 and 0.25 mm) could hold a low enough pressure inside the chamber as shown in Table 2. The differences between theoretical analysis and measured pressures could be due to the fact that supersonic gas expansion occurs between the capillary and the pinhole,[58,59] which causes a pressure distribution within the first vacuum stage. Capillaries with smaller IDs lead to lower pressures, which are more favorable for MS analysis in terms of MS resolution. However, capillaries with smaller IDs also result in lower ion transfer efficiency.[56] Experiments were also carried out to test the ion transfer capabilities of these capillaries using peptide MRFA (1000 μg/mL, nanoESI). However, no spectrum could be recorded when using the 0.12 or 0.18 mm ID capillaries, which indicates that the ion transfer efficiencies through these capillaries are not high enough for the

miniature mass spectrometer setup in this study. After balancing vacuum pressure and ion transfer efficiency, the capillary with 0.25 mm ID was finally selected. In addition, distance between the end of the capillary and the pinhole would affect ion transfer efficiency from the first vacuum stage to the second vacuum stage, as well as the pressure inside the second vacuum stage. After optimization, a distance of 15 mm was selected. As a result, the final pressures inside the first and second vacuum stages are 6.6 Torr and 6.6 mTorr, respectively.

Instrument stability. Stability and robustness are important figures of merits for a MS instrument, especially for a miniature instrument, which is intended to be used on site not in the laboratory. Instead of using mechanical switches to control vacuum and ion introduction, the miniature mass spectrometer developed here adopts a continuous API, which enables a suitable vacuum environment with a stable pressure. Furthermore, ion introduction duration could be precisely controlled by the electric voltage applied on Endcap 1. To test the stability of the instrument, the ion current of DEET dimer (m/z 383 Da) ionized using an APCI source and protonated MRFA (m/z 524 Da, 100 ug/mL) ionized using a nanoESI source were recorded. As shown in Figure 2, the ion current is stable with a RSD of < 7% for both DEET and MRFA ions.

Sensitivity. The gas flow rate and ion transfer efficiency of the miniature mass spectrometer are lower than those of a typical lab-scale ion trap MS or a mini-mass spectrometer with a DAPI. However, since the ion introduction duration is no longer limited by the mechanical opening duration and maximum allowable pressure inside

the vacuum chamber, the number of ions introduced into the LIT could be increased by increasing the ion introduction duration.[47] Before the LIT was saturated, a linear relationship was obtained between the ion count in the LIT and the ion introduction duration. Figure 3a and 3b plot the ion intensities of DEET (using APCI) and GPRP (100 ug/mL, nanoESI) with respect to the ion introduction duration. Good linearities were obtained ($R^2 > 0.99$) in both cases within the time range of 50-1000 ms. By increasing the ion introduction duration, sensitivity of the instrument could be improved as shown in Figure 3c. As the ion introduction duration increased from 50 to 1400 ms, the limit of detection (LOD) could be lowered from 25 to 1 ug/mL for GPRP using nanoESI. Without applying any automatic gain control (AGC) method, a good linear of quantitation (LOD) range (1-100 ug/mL, $R^2 = 0.9936$) could also be achieved for GPRP as shown in Figure 3d.

MS resolution. Typically the buffer gas pressure in a quadruple ion trap is kept below or around 1 mTorr. In the mini-MS developed in this work, the pressure in the second vacuum stage, where the LIT was placed, is relatively high (6.6 mTorr). The presence of buffer gas (air in this case) could help cool ions towards center of the ion trap, but at the same time, higher buffer gas pressures would broaden mass peaks in a mass spectrum, which will cause degradation of MS resolution.[60-62] As a result, MS resolution (FWHM) of the mass spectrometer was ~4.6 Da for GPRP (m/z 426, 50 ug/mL) with an MS scan rate of 19000 Da/s. Nevertheless, MS resolution could be improved by decreasing the MS scan rate. As plotted in Figure 4, unit resolution (FWHM = 1 Da) could be achieved when MS scan rate was decreased to 3000 Da/s,

and a FWHM of 0.5 Da was obtained with a MS scan rate of 1590 Da/s., In practice, MS resolution of the miniature-MS could be adjusted and optimized to meet practical requirements in different applications, with the price of slower MS scan speed.

Mass range. With the capability of coupling with various ionization techniques in the atmosphere environment, the continuous mini-MS should have a mass range that could match those appropriate to different ionization sources. The mass range of an ion trap mass spectrometer depends on many factors, including the geometric dimensions of the ion trap, RF frequency, maximum RF amplitude, and the *q* value used for resonance ejection.[63-65] In typical operations of the continuous API miniature mass spectrometer (dipolar resonance AC, 369 kHz), a mass range from 200 – 1000 Da was obtained, as shown in Figure 5a for PEG 600 (nanoESI, 100 ug/mL). The mass range could be extended for larger molecules by lowering the frequency of the dipolar AC excitation signal. Figure 5b shows the mass spectrum collected for cytochrome C (nanoESI, 100 ug/mL) by lowering the AC frequency to 345 kHz (5 $V_{0\text{-}p}$). The mass range could be further extended to 2500 Da/charge by lowering the AC frequency to 149 kHz (5 $V_{0\text{-}p}$). As a demonstration, the mass spectrum of PEG 1500 (nanoESI, 1000 ug/mL) was recorded and is shown in Figure 5c, in which the singly- and doubly-charged PEG 1500 ions could be observed well. Many factors, such as rf electronic stability, space charge effects in the ion trap, etc., would all affect mass accuracy of a MS instrument. Mass accuracy of the mini-MS is about 10^{-3}, which means the m/z reading is accurate to unit within a mass range of 100-1000 Da.

Coupling with an ambient ionization technique for rapid sample analysis.

With minimum sample preparation, ambient ionization techniques enable sample analysis in real time,[66-68] which is a perfect match with the continuous API miniature mass spectrometer for on-site chemical analysis. To study and determine the chemical compositions of a sample, both MS and tandem MS scans are normally required. When using ambient ionization techniques, especially for trace or on-line chemical analysis, scan speed or duty cycle of a mass spectrometer is critical to improve the analyte coverage ratio and/or the number of analyte that could be identified. The rapid sample analysis capability of the presented mass spectrometer was demonstrated by coupling with a paper spray ionization source. Due to the limited amount of sample and solvent that could be loaded on the triangular paper, the ion current from a paper spray ionization source would typically last for a few seconds.[69,70] As shown in Figure 6, a 5 Hz scan speed could be achieved for the continuous API miniature-MS, and four chemical components (GPRP 100 ug/mL, rhodamine B 100 ug/mL, MRFA 100 ug/mL, and reserpine 100 ug/mL) within a mixture could be identified through MS and tandem MS analyses within 1 second. In the full MS scan, the ion introduction, cooling and MS scan durations are 95, 5 and 100 ms, respectively. In each tandem MS scan, the ion introduction, cooling, isolation, dissociation, and MS scan durations are 45, 5, 25, 25 and 100 ms, respectively. In the tandem MS analyses, ions were first isolated by a SWIFT[71] signal and then subjected to collision induced dissociation with applied AC excitations. The *q* values for isolation and AC excitation were 0.43, 0.33, 0.25, and 0.21, respectively. The corresponding AC frequency for disassociation was 190 kHz, 150 kHz, 100 kHz, and 80 kHz, respectively for GPRP, rhodamine, MRFA,

and reserpine ions.

4. Conclusion

In this study, a miniature mass spectrometer with a continuous atmospheric pressure interface was developed and characterized. Coupling of the mass spectrometer with APCI, nanoESI and paper spray ion sources was demonstrated for the analysis of organic, peptide and protein samples. Elimination of the use of mechanical switches makes the mini-MS robust, stable with high repeatability (RSD < 7%), and fast in MS analysis (scan rate 5 Hz). Under optimized conditions, a LOD of 1 ug/mL and LOQ from 1 to 100 ug/mL were obtained for a peptide, GPRP. The mass range of the mass spectrometer could be extended up to 2500 Da by lowering the ejection AC frequency, and a mass resolution of 0.5 Da (FWHM) was achieved with a scan rate of 1590 Da/s.

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Figure 1

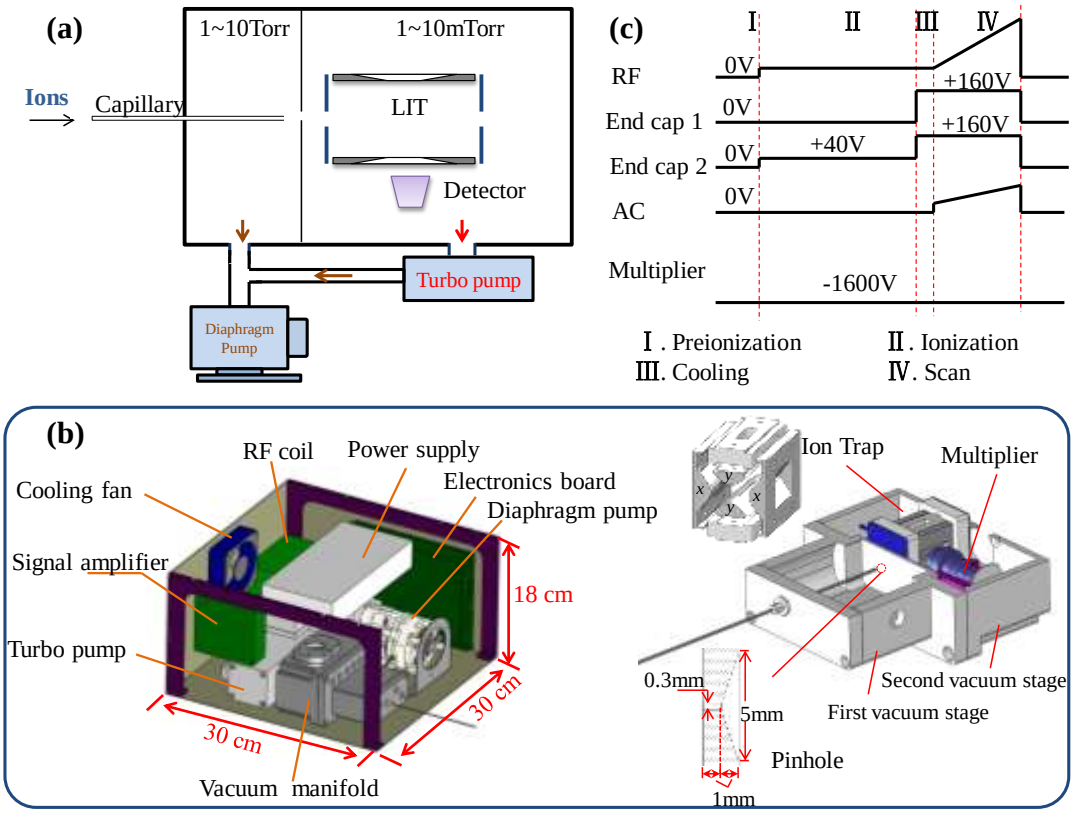

Figure1 (a) Schematic structure of the miniature mass spectrometer. (b) 3D assembly of the miniature mass spectrometer (left) and internal assembly of the vacuum chamber and the linear ion trap (right). (c) Typical MS scan function of the instrument.

Figure 2

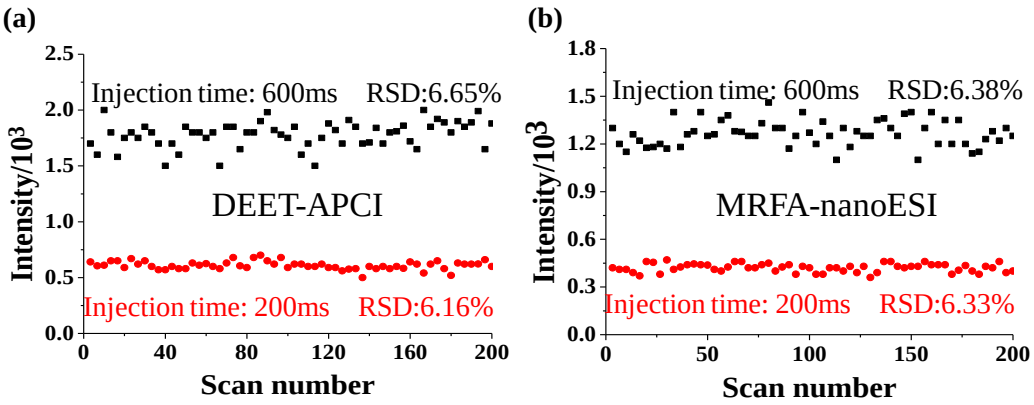

Figure 2 Stability of the miniature mass spectrometer. (a) Recorded ion intensity of DEET dimer ions using an APCI source. (b) Recorded ion intensity of MRFA ions using a nanoESI source.

Figure 3

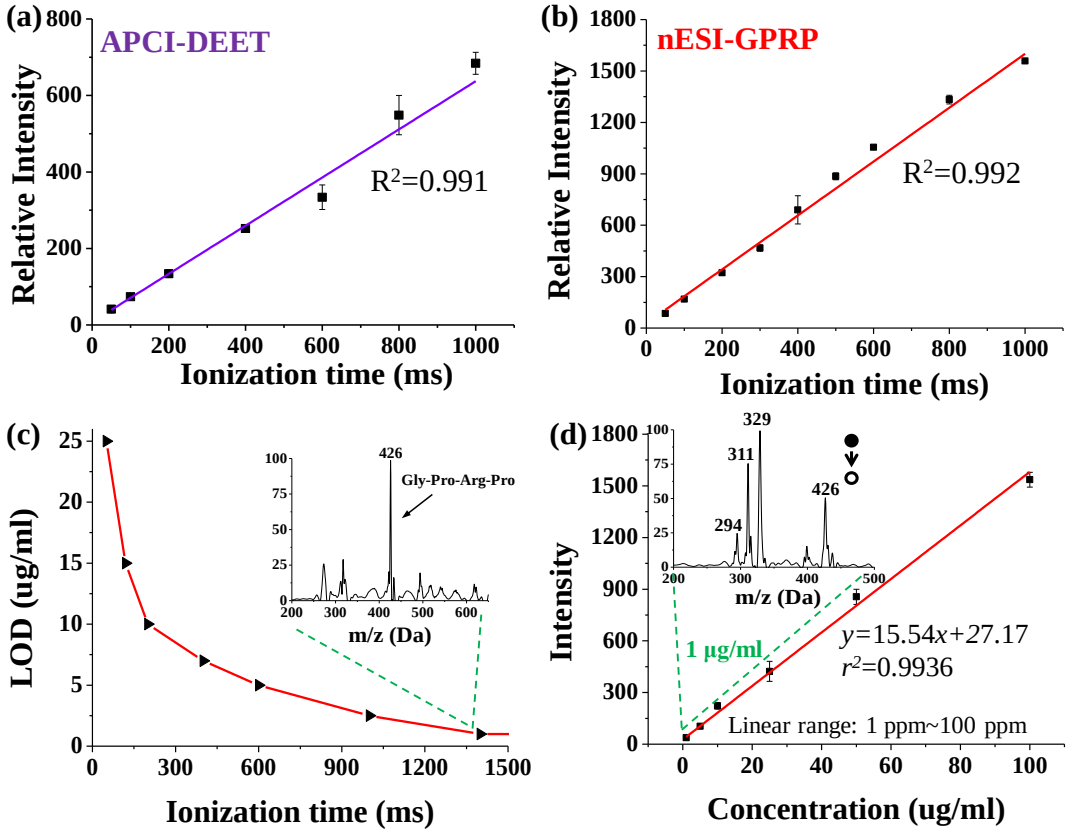

Figure 3 Effects of ion introduction duration. Ion intensity versus ion introduction duration for (a) DEET dimmer ions using an APCI source, (b) GPRP using a nanoESI source. (c) LOD of GPRP with increased ion introduction duration. (d) LOQ for GPRP with an ion introduction duration of 1400 ms.

Figure 4

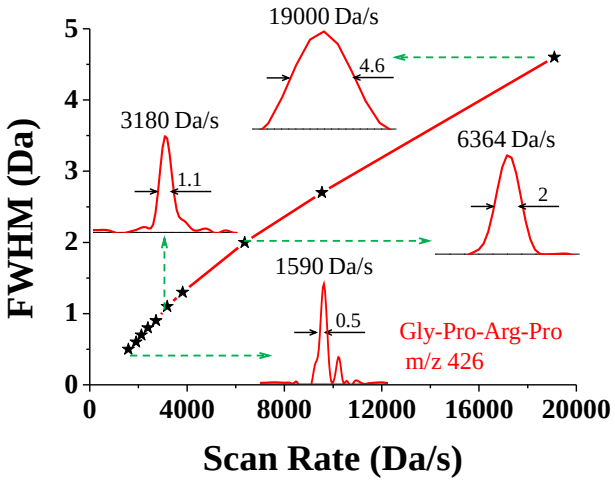

Figure 4 MS resolution of the miniature mass spectrometer with different scan rates. 50 ug/mL GPRP using nanoESI source.

Figure 5

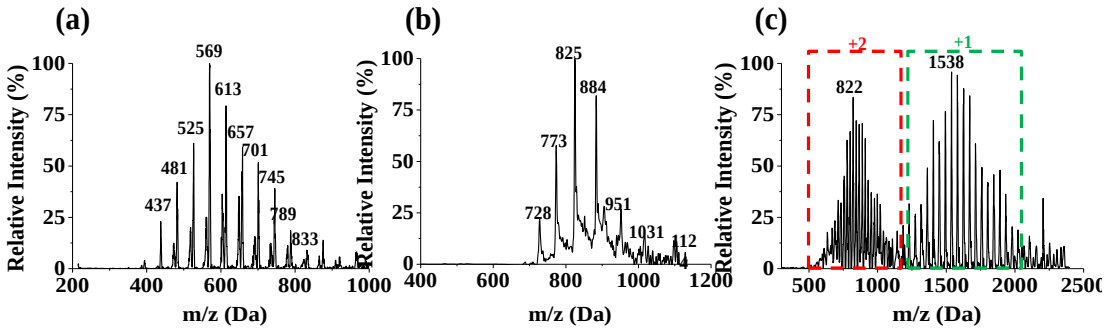

Figure 5 Mass range of the miniature mass spectrometer. (a) Mass spectrum of PEG 600 (100 ug/mL), AC ejection frequency 369 kHz. (b) Mass spectrum of cytochrome C (100 ug/mL), AC ejection frequency 345 kHz. (c) Mass spectrum of PEG 1500 (1000 ug/mL), AC ejection frequency 149 kHz.

Figure 6

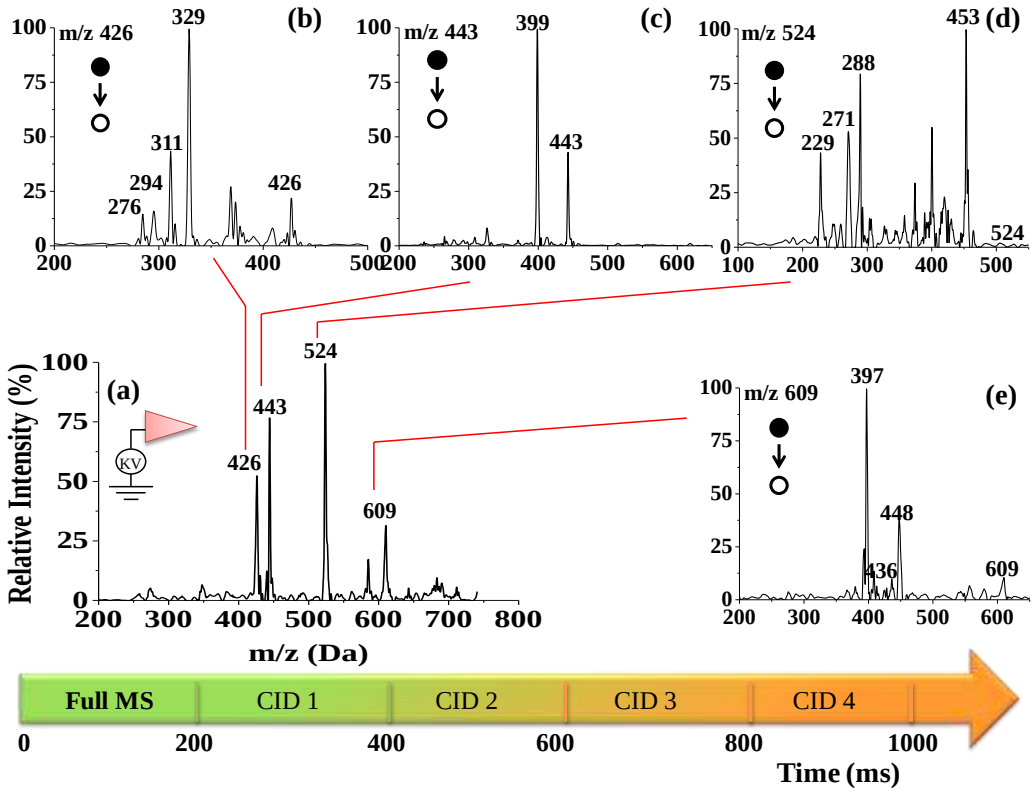

Figure 6 Rapid analysis of multiple components in a complex mixture by the miniature mass spectrometer coupled with paper spray. (a) Full scan mass spectrum. The CID mass spectrum of (b) GPRP (m/z 426), (c) rhodamine (m/z 443), (d) MRFA (m/z 524) and (e) reserpine (m/z 609).

Table 1

Table 1 Calculated pressures within the two vacuum stages in terms of capillaries and pinholes with different IDs. All capillaries are 20 cm long.

d_2 (mm)	d_1 (mm)	P_1 (Torr)	P_2 (mTorr)
0.2	0.12	2.1	0.25
	0.18	2.7	0.34
	0.25	3.5	0.51
0.3	0.12	2.1	0.98
	0.18	2.7	1.4
	0.25	3.5	2.2
0.4	0.12	2.1	2.6
	0.18	2.7	3.96
	0.25	3.5	6
0.5	0.12	2.1	6.1
	0.18	2.7	8.6
	0.25	3.5	25

Table 2

Table 2 Pressures measured within the two vacuum stages, and compared with those from theoretical calculations.

d_1 (mm)	P_1 theoretical (Torr)	P_1 real (Torr)	P_2 theoretical (mTorr)	P_2 real (mTorr)
0.12	2.1	1.7	0.98	1.3
0.18	2.7	3	1.4	2.2
0.25	3.5	6.6	2.2	6.6

TOC only