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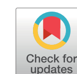
High ohmic resistor hyphenated gel loading tip nano-electrospray ionization source for mini mass spectrometer



Md. Matiur Rahman[a,*], Debo Wu[a], Konstantin Chingin[a], Wei Xu[b,c,**], Huanwen Chen[a]

[a] Jiangxi Key Laboratory for Mass Spectrometry and Instrumentation, East China University of Technology, Nanchang, 330013, China
[b] College of Information of Science, Shenzhen University, Shenzhen, 518060, China
[c] School of Life Science, Beijing Institute of Technology, Beijing, 100081, China

ABSTRACT

The deployment of mini mass spectrometers on the field strongly demands efficient ionization sources that are easy-to-operate. Nano-electrospray (nESI) ion source has been widely used in the field of chemistry, biology, medicine, pharmaceutical industry, clinical assessment and forensic science. In this study, a high ohmic resistor hyphenated gel loading tip nESI source was coupled with our home developed mini mass spectrometer. This ionization source has the advantages of simple-in-design, disposable and low-in-cost, therefore it could be frequently used for analysis of aqueous samples without leading to cross contamination. Performances of the gel loading tip nESI emitter were similar to pulled glass capillary, and highly compatible for the analysis of biomolecule in aqueous solution. Different peptide and small molecules have been confirmed with a continuous atmospheric pressure-interfaced (CAPI) mini mass spectrometer. The corona discharge, which was usually observed at nESI emitter tip under high aqueous solvent conditions, resulting in low ion intensity, has been successfully quenched using a 10 GΩ resistor in both a pulled glass capillary and a gel loading tip as nESI emitter in this study. Compared with conventional ESI, the metal wire assisted gel loading tip facilitated loading and direct analysis of biological samples without sample pretreatment.

1. Introduction

nESI is one of the most attractive methods in the field of mass spectrometry due to the high sensitivity and small amount of sample consumption. It is advantageous to conventional ESI on signal sensitivity, [1,2]removal of matrix suppression [3–5]. The main shortcomings for conventional nESI emitter are cleanliness and clogging. As is well known, pulled glass capillary is not easy to operate without a well experienced person [6] and its performance or sensitivity strongly depends on the emitter's geometry which could be easily changed within two minutes after application of high voltages during an experiment [7]. So, the reproducibility, sensitivity and the flow rate of nESI cannot be kept constant due to the arcing or breaking of the capillary tip during operation [8–11]'

To circumvent the problems, a wide variety of alternative ESI emitters have been developed in the field of electrospray ionization mass spectrometry [12–24]. Each of them has its own advantages and disadvantages. The performance of those emitters, however, are not as satisfactory as a pulled glass capillary for the analysis of samples in aqueous solution. A high spray potential is normally required to initiate the electrospray for analysis of aqueous samples. High voltage induced discharge would greatly reduce system stability and reproducibility. The corona discharge could be quenched in various ways, such as by placing emitters at higher pressure environments, [25–34]adding trace amount of trifluoroethanol [35], using pneumatic-assisted ESI like ion spray [36], using electrosonic spray [37] and using high dielectric nebulizing gasses [38–40]. Previously, pipette tips were placed in super atmospheric pressure regions to realize electrospray ionization [30]. High voltage combined with a resistor is another simple way to avoid the corona discharge between two electrodes [8,41,42].

On the other hand, miniature mass spectrometers equipped with simplified and easy-to-operate ionization sources would boost their applications on the field. In this study, a 10 GΩ resistor is hyphenated with gel loading tip emitter (with inner diameter of 120 μm) and coupled to our home developed miniature mass spectrometer [43] for the analysis of aqueous samples. Without generating a super atmospheric pressure chamber or adding extra gases, this high ohmic resister hyphenated gel loading tip nESI source is a preferable match with mini mass spectrometers. Performances of gel loading tip and pulled glass capillary nESI emitters were also compared in this study. The nESI flow rate of gel loading tip was measured. However, the accurate flow rate was affected by inner diameter of a gel loading tip. The results showed that the electrospray of gel loading tip was similar to established pulled glass capillary (~1–3 μm inner diameter) with respect to sensitivity, rapidness and signal stability due to the consumption of small amount of sample. In gel loading tip nESI method, only a small volume of

* Corresponding author.
** Corresponding author. School of Life Science, Beijing Institute of Technology, Beijing, 100081, China.
E-mail addresses: matiurrahmanbot@yahoo.com, matiurrahman@ecit.cn (Md. M. Rahman), weixu@bit.edu.cn (W. Xu).

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sample (2–3 μL) was consumed, generating long-duration electrospray ion signal for MS/MS [30]. Noteworthy, minimization of desired sample amount is important in any field of application, including medical [44], forensic [45] and biological studies [46]. The main advantages of gel loading tip method include the avoidance of cross contamination, low cost, easy to use and sample introduction speed. Reutilization of the used gel loading tips is also possible, thus allowing design of automatic sampling device. To the best of our knowledge, among the ambient electrospray ionization mass spectrometry methods, it might be the simplest ionization method for direct analysis of any biological sample in aqueous solution without sample pretreatment and without clogging problem.

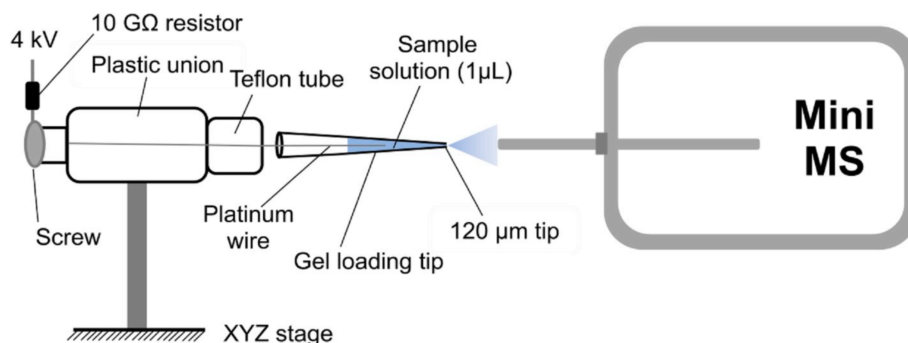

Fig. 1. High voltage gel loading tip nESI ion source with mini mass spectrometer.

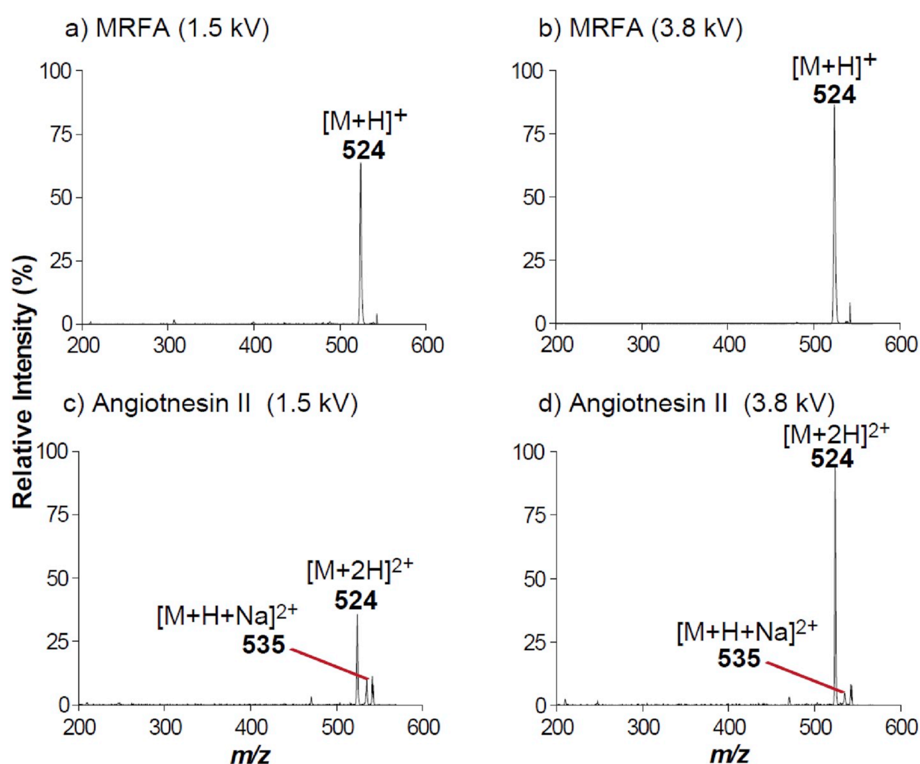

Fig. 2. Comparison of low and high voltage nanoESI ion source to obtain mass spectra of peptide MRFA; a) MRFA (1.5 kV), b) MRFA (3.8 kV), c) angiotensin II (1.5 kV) and d) angiotensin II (3.8 kV).

1
Major ion in parenthesis, AC frequency that gave the strongest ion signal and LOD for gel loading tip-ESI ion source.

Sample name	Molecular weight	Major ion	AC (kHz)	LOD
MRFA	523.65	$[M+H]^+$ (524)	379	1 μg/mL
Rhodamine B	442.55	$[M+H]^+$ (443)	379	1 μg/mL
GPRP	425.48	$[M+H]^+$ (426)	379	1 μg/mL
Vitamine B	265.35	$[M+H]^+$ (265)	379	1 μg/mL
Angiotensin I	1296.49	$[M+3H]^{3+}$(432), $[M + H + Na]^{3+}$(445)	224	10 μg/mL
Angiotensin II	1046.19	$[M+2H]^{2+}$(524) $[M + H + Na]^{2+}$(535)	379	10 μg/mL
Methyl α-D-mannopyranoside/Mannopyranoside	194.18	$[M+Na]^+$(217), $[2 M + Na]^+$ (411)	379	25 μg/mL
Methyl D-glucopyranoside/Methylglucoside	194.18	$[M+Na]^+$(217), $[2 M + Na]^+$ (411)	379	25 μg/mL
Maltopyranoside	510.62	$[M+Na]^+$ (533) $[M + NH_4]^+$ (528)	379	50 μg/mL

2. Experimental

2.1. Mass spectrometer

Continuous atmospheric pressure interfaced miniature mass spectrometer [43,47] and LTQ-XL linear ion trap mass spectrometer were used for all experiments. The experimental parameters for continuous atmospheric pressure miniature mass spectrometer has been explained in our recent report [43]. The inner diameter of the ion transport tube was 0.25 mm. The experimental parameters for LTQ-XL linear ion trap mass spectrometer were as follows: capillary temperature, 180 °C; multipole RF amplitude ($V_{p\text{-}p}$), 400 V. The normal scan mode was used. The ion trap mass range was set from 50 to 2000 Th. The maximum ion injection time was used and set to 0.7–0.001 ms according to our previous report [48,49].

2.2. Gel loading tip based nESI ion source

The photograph of HV-nESI ion source with gel loading tip is shown in Fig. S1. Fig. 1 shows the schematic diagram of HV-nESI ion source with gel loading tip. It was constructed with a gel loading tip holder device from a plastic union, a length of silver coated platinum wire, and a length of teflon tubing. The plastic union and teflon tube were used to support the wire electrode and provide a point of attachment to a clamp mounted on the x-y-z stage. The wire and teflon tube supported the gel loading tip. The other end of the wire was connected with a screw. A 10 GΩ resistor was placed between the screw and high voltage power supply. The gel loading tip was positioned ~2 mm away from the source of inlet capillary. Generation of ions were initiated by applying a potential difference of 1.4 kV–4.5 kV between the silver coated platinum wire and the inlet capillary.

2.3. Sample preparation

Analytical grade of MRFA (Met-Arg-Phe-Ala), rhodamine B, GPRP (Gly-Pro-Arg-Pro), vitamine B, angiotensin (I&II), methyl α-D-mannopyranoside, methylD-glucopyranoside and maltopyranoside were prepared in pure water then diluted with 5% methanol. All chemicals were used without further purification. The deionized water was purchased from Hangzhou Wahaha Group Co.,Ltd. China. All samples and methanol were purchased from Sigma Aldrich (St. Louis, MO, USA). All biological samples such as orange and small orange were purchased from local market of Beijing, China and analyzed without any sample preparation. The silver-coated platinum wire was inserted ~1 mm deep to collect a small amount of sample, which was then inserted into a gel loading tip pre-filled with 2–3 µL water/methanol (v/v 95:5) solution. After sampling, the high spray potential was applied to the silver-coated platinum wire for MS analysis. This silver-coated platinum wire with an outer diameter of ~50 µm was purchased from Ida Tianjin Co. (Tianjin, China). Commercial gel loading tip (*epT.I.P.S*, Eppendorf, Germany) with an inner diameter of 120 µm was used in this study. Importantly, when a solution was loaded into a gel loading tip with a pipette, the loaded tip should be disconnected from the pipette while its tip was still immersed into the solution. Otherwise, the filled solution would be pushed back, and air cushion was formed at the end of the tip during tip detachment. The air cushion at the end of the tip can greatly affect the accuracy of sample loading as well as the stability of electrospray. Note that during the sample loading the gel loading tip should not be immersed deeper than 1 mm into the sample solution. Otherwise, the sampling efficiency by the gel loading tip is very poor. To load juicy sample for analysis, the Pt wire was stabbed ~1 mm deep to the sample and then inserted into a pipette tip pre-filled with 1 µL water/methanol mixture (v/v 95:5). MS analysis started by applying a high voltage to the Pt platinum wire. Based on the sample consumption measurements, the flow rate of nESI using gel loading tip was estimated as ~50 nL/min using LTQ-XL linear ion trap mass spectrometer (Fig. S2).

3. Result and discussion

3.1. Comparison with low voltage and high voltage nESI

The effect of high voltage on the pulled glass capillary was investigated using two peptides such as MRFA and angiotensin II. As shown in Fig. 2, high voltage nESI mass spectra were sensitive than

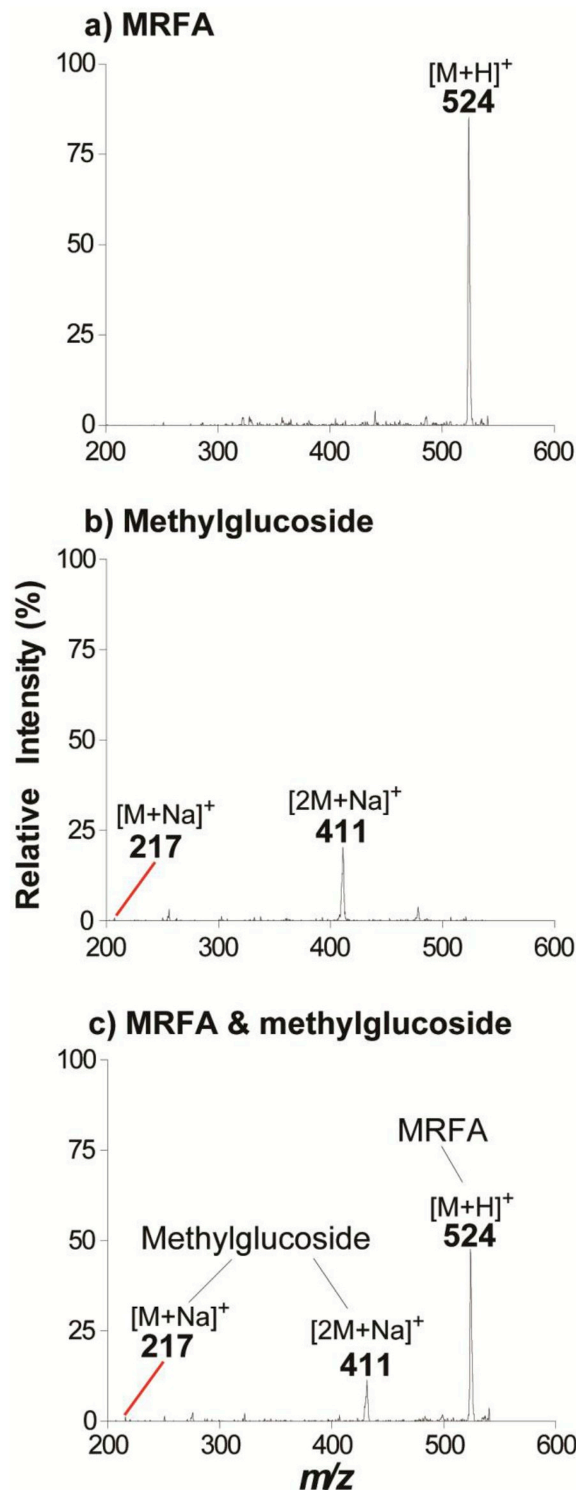

Fig. 3. The mass spectra for a) MRFA (50 µg/mL) in 5% methanol, b) methylglucoside (50 µg/mL) in 1 mM NaCl, **c)** the mixture of an equimolar concentration of MRFA (50 µg/mL) and methylglucoside (50 µg/mL).

those of low voltage nESI for aqueous solutions. A high voltage strategy combined with a 10 GΩ resistor has been shown able to produce highly charged fine droplet in nESI ion source. The fission step of highly charged droplet is reduced and high desolvation took place at the inlet of continuous atmospheric pressure mini-mass spectrometer. Thus, the adduct of Na^+ ion was almost removed by high voltage strategy, while Na + ion was not suppressed by low voltage nESI in angiotensin II. Therefore, this HV-nESI ion source could be useful to desalt the adduct of Na^+ from peptides and protein and increased ion intensities, which however, cannot be confirmed by low voltage nESI.

3.2. The detection limit of CAPI-mini mass spectrometer

The quantitation using high voltage nESI ion source was conducted with 95% aqueous solution of MRFA, rhodamine B, GPRP, vitamine B, angiotensin I and angiotensin II, respectively. Table 1 and Fig. S3 show the detection limits and calibration curves obtained for MRFA, GPRP, rhodamine B, vitamine B using high voltage nESI ion source. The detection limits were determined for MRFA, GPRP rhodamine B and vitamine B as 1 μg/mL in 95% aqueous solution. The detection limit was 10 times lower than those samples (MRFA, GPRP, rhodamine B and

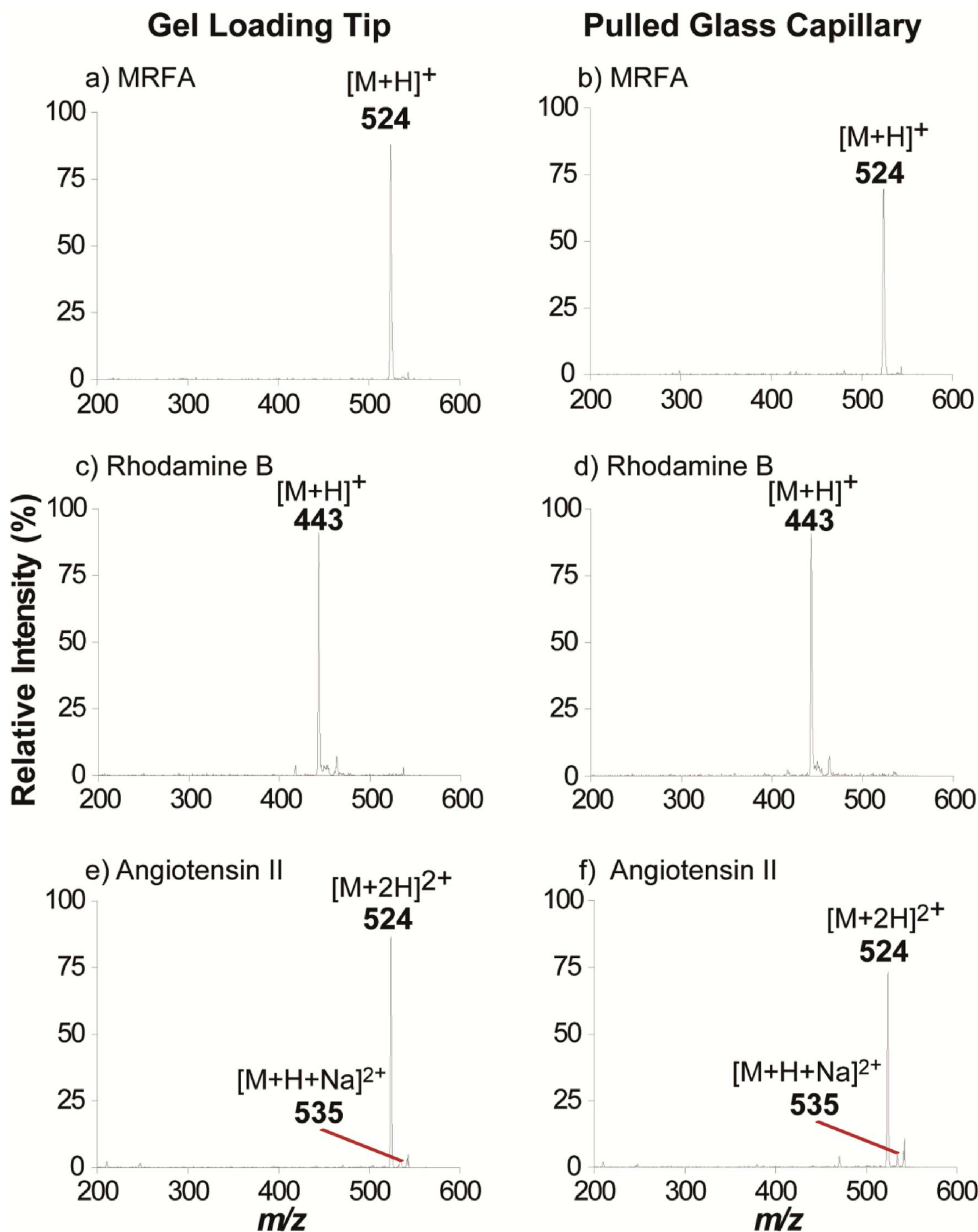

Fig. 4. Comparison of gel loading tip and pulled glass capillary mass spectra for 50 μg/mL MRFA, rhodamine B and angiotensin II prepared in aqueous solution. The high spray potentials applied to the nano capillary and gel loading tip were 2.1–3.5 and 3.5–4.5 kV, respectively.

vitamine B) prepared in organic solvent [47]. The detection limit of angiotensin I and angiotensin II was 10 μg/mL. According to Table 1, the detection limit of methyl α-D-mannopyranoside (25 μg/mL), methyl D-glucopyranoside/methylglucoside (25 μg/mL) and maltopyranoside (50 μg/mL) showed a poor sensitivity, which was probably attributed to its poorer ionization efficiency compared with other peptides or rhodamine B. In our hands, the LOD for glass capillaries and gel loading tips was roughly similar. However, the accurate construction of a calibration curve and evaluation of LOD for the glass capillaries were greatly complicated due to the poor tip-to-tip reproducibility and frequent tip clogging.

3.3. Suppression effect of high voltage nESI

The ion suppression effect was also tested using high voltage nESI ion source coupled with CAPI-miniature mass spectrometer. Equimolar concentrations of peptide (MRFA, m/z 524) and glucose (methylglucoside, m/z 194.18) were selected and prepared in 5% methanol and 1 mM NaCl aqueous solution respectively. The result showed that MRFA and glucose were detected at the same time by high voltage nESI ion source with CAPI-mini mass spectrometer. However, the ion intensity of glucose was much lower than that of MRFA (Fig. 3). The ion suppression for glucose is probably due to the gas-phase ion reactions in the ionization area. The ion suppression effect had also been observed with microESI [50], step voltage nESI [50], and high-pressure nESI [30] using conventional mass spectrometer.

3.4. Comparative study of a gel loading tip and a pulled glass capillary as a nESI emitter

In this study, comparison of a gel loading tip and a pulled glass capillary was also performed using continuous atmospheric pressure mini-mass spectrometer with the same experimental parameters and sample concentrations. Our results showed that peak intensity of the MRFA, rhodamine B and angiotensin II in aqueous solution acquired with a gel loading tip was equally well with a pulled glass capillary, as shown in Fig. 4. The nESI signal was strong in both gel loading tip and pulled glass capillary. The comparative study was repeated using three different capillaries and gel loading tips. At high voltages (2.1–3.5 kV), there was almost no occurrence of corona discharge by using a 10 GΩ resistor in nESI emitter. We did not observe any corona discharge for pulled glass capillary under the used voltage either. Therefore, similar mass spectra with similar signal intensities were also obtained following a gel loading tip and a glass capillary nESI-MS of MRFA and rhodamine B prepared in 5% methanol shown in Fig. 5. Note, however, that the sample consumption in gel loading tip nESI (ca. 50 nL/min) is higher than in pulled glass capillary nESI (ca. 10–20 nL/min), which is due to the larger tip i. d.: 120 μm in gel loading tips vs. ca. 1 μm in

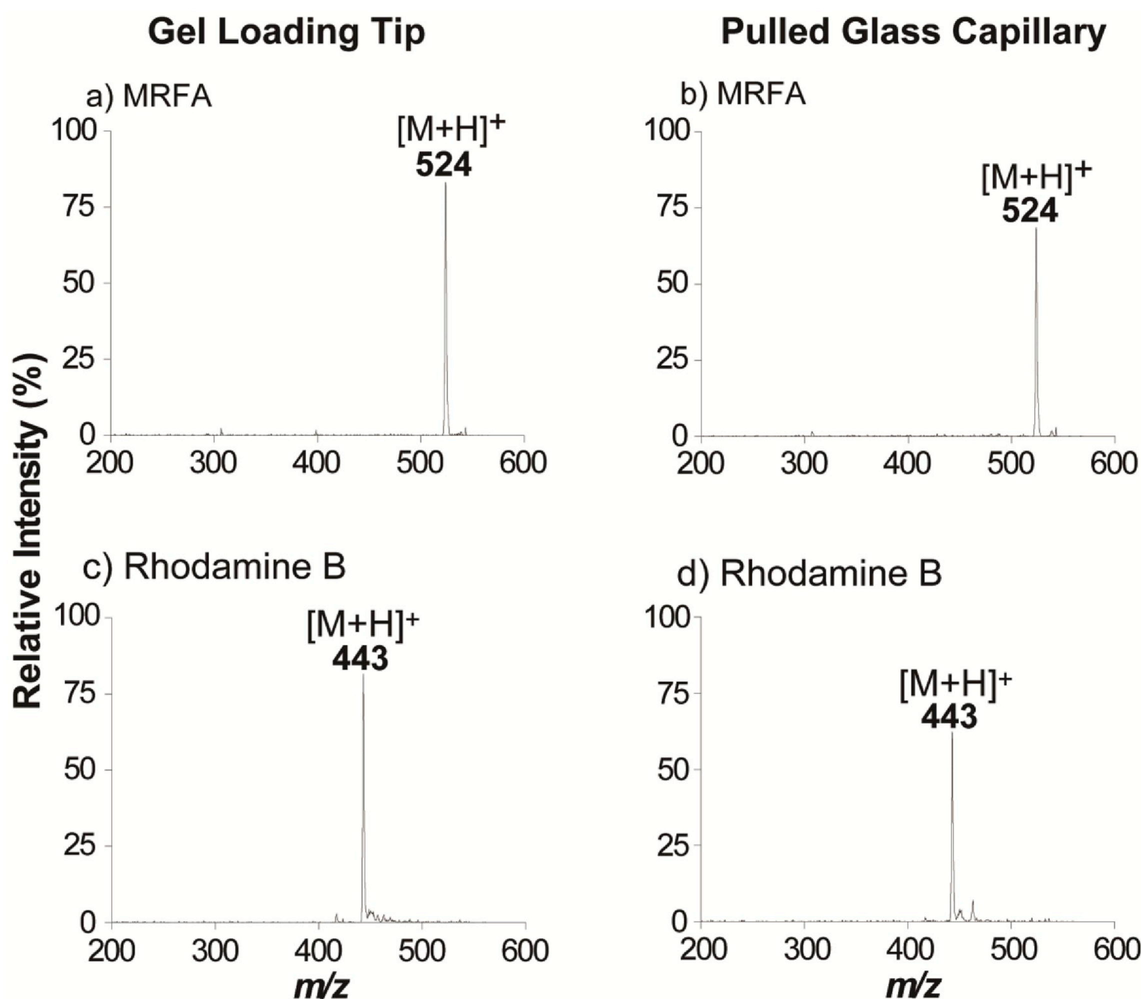

Fig. 5. The mass spectra obtained from the gel loading tip (a&c) are compared to those obtained from a pulled glass capillary (b&d) in a concentration of 50 μg/mL MRFA and rhodamine B prepared in 5% methanol.

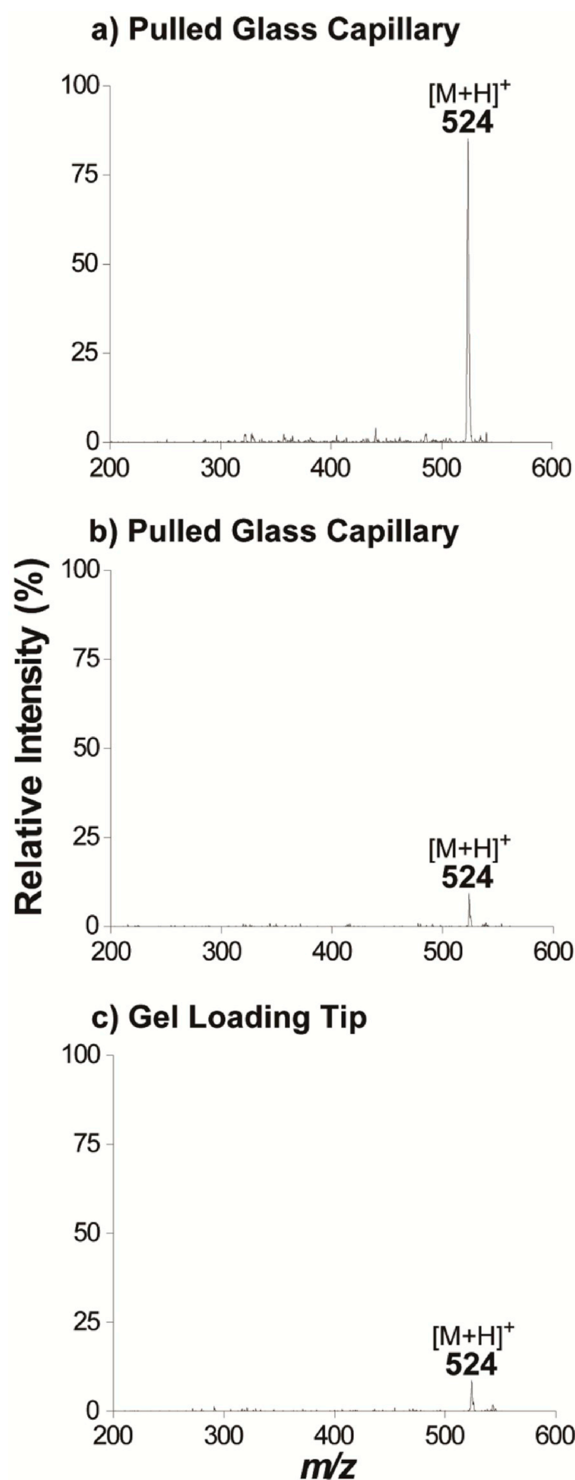

Fig. 6. Mass spectra of 50 μg/mL MRFA prepared in aqueous solution (a); The detection of 50 μg/mL MRFA prepared in 10 mM NaCl solution using pulled glass capillary (b) and gel loading tip (c).

pulled glass capillaries. The result indicated that HV-nESI with gel loading tip could be a useful ionization technique in the near future.

3.5. Detection of peptides from high concentration of salt solution

Salts and buffers are regularly used for isolation and stabilization of protein and peptides. However, salt has a harmful effect on electrospray ionization mass spectrometry (ESI-MS), which causes a dramatic decrease in sensitivity and often create mass measuring accuracy due to the suppression of the ionization of desired analytes. To test this effect, gel loading tip and pulled glass capillary were used and compared as nESI emitter with 50 μg/mL MRFA prepared in 10 mM NaCl aqueous solution. The results showed that 50 μg/mL MRFA was still detected by a gel loading tip and a pulled glass capillary as a nESI emitter as shown in Fig. 6. The result suggested that the gel loading tip worked well as a nESI emitter although its inner diameter was 120 μm. It is worth noting that, the desalination effect had also been observed in some ionization techniques, probe electrospray ionization (PESI) [51], ultra-sonication assisted spray ionization (UASI) [52], desorption electrospray ionization (DESI) [53,54], fused droplet electrospray ionization (FD-ESI) [55], and so on mass spectrometry.

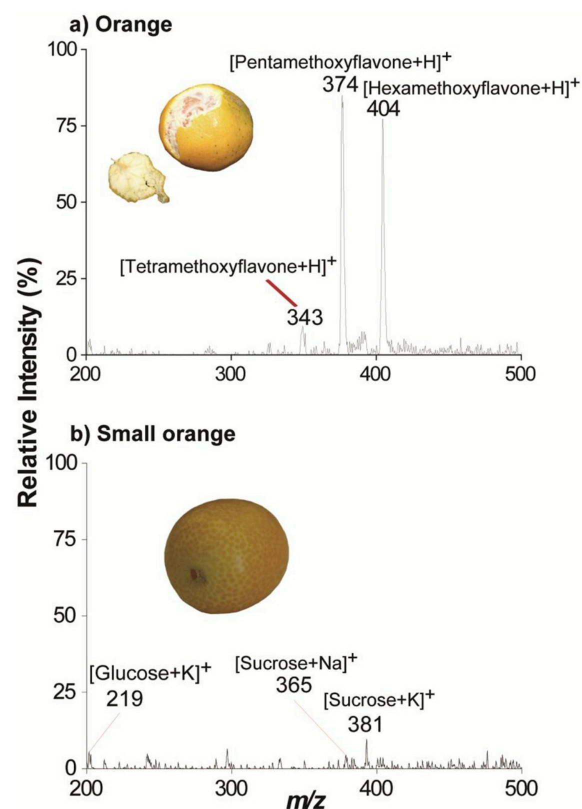

Fig. 7. The biological sample analysis by tip ESI-MS a) orange peel b) small orange. The sample was collected by solid probe then the probe was inserted into solvent (5% methanol) preloaded pipette tip for nESI. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.6. Biological sample analysis

Biological sample can be directly analyzed by nESI-MS with metal wire assisted gel loading tip as an emitter. A small amount of sample was simply collected by a silver coated platinum wire which was then inserted into the gel loading tip already preloaded with ~ 2–3 μL (95% aqueous solution) solvent. The gel loading tip was mounted onto the nESI holder and then placed in front of the inlet of mass spectrometer. A high voltage of 3.5–4 kV was applied via the resistor and metal wire to ionize the spray droplets for immediate MS analysis. Fig. 7 shows the direct detection of bioactive compounds of orange and small orange. Most of the bioactive compounds such as flavonoids, glucose and sucrose can be detected as protonated, sodiated and potassiated species. The gel loading tip technique could be used for highly sensitive point of care diagnosis before and after surgery. This technique could be cheap and promising as the separation of tissue or sample is not required for tissue imaging or diagnosis. Future

work could be extended and coupled with liquid extraction surface analysis (LESA) [56,57]or mass spec pen [58] for the analysis of biological sample by the robotic system with miniature mass spectrometer.

4. Conclusion

We have demonstrated that combined with a 10 GΩ resistor at ambient condition high voltage nESI with a gel loading tip can be successfully applied to the analysis of various samples in aqueous solution. The gel loading tip HV-nESI in series with a high-ohmic resistor exhibited a very similar overall performance to the conventional capillary nESI, but also added many new advantages, including high signal duration (20 min), tolerance to high salt concentration and high voltage, obviation of tip clogging and corona discharge, high cost-efficiency and operational simplicity. Furthermore, in advantage to conventional nESI approaches, pipette tip emitters open the opportunity for the direct nESI analysis of untreated biological sample. Due to the low sample consumption and high chemical sensitivity, gel loading tip HV-nESI is also potentially suitable for offline analysis of low-abundance metabolites in samples with limited volumes such as single cell level or even at the subcellular level. The work is ongoing to automate this method for high throughput operation and biomarker search. With regard to these goals, it is of particular interest for future research to further reduce the flow rate and rate of sample consumption in tip-ESI by developing pipette tips with smaller inner diameters (< 100 μm).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.talanta.2019.04.052.

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