

RESEARCH ARTICLE

# Plasma-Spray Ionization (PLASI): A Multimodal Atmospheric Pressure Ion Source for Liquid Stream Analysis

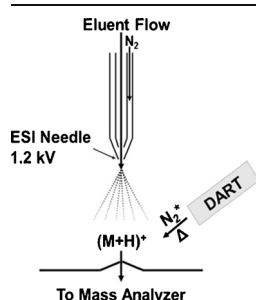
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**Abstract.** A new ion generation method, named plasma-spray ionization (PLASI) for direct analysis of liquid streams, such as in continuous infusion experiments or liquid chromatography (LC), is reported. PLASI addresses many of the analytical limitations of electrospray ionization (ESI) and has potential for real time process stream analysis and reaction monitoring under atmospheric conditions in non-ESI friendly scenarios. In PLASI-mass spectrometry (MS), the liquid stream is pneumatically nebulized and partially charged at low voltages; the resultant aerosol is thus entrained with a gaseous plasma plume from a distal glow discharge prior to MS detection. PLASI-MS not only overcomes ESI-MS limitations but also generates simpler mass spectra with minimal adduct and cluster formation. PLASI utilizes the

atomization capabilities of an ESI sprayer operated below the ESI threshold to generate gas-phase aerosols that are then ionized by the plasma stream. When operated at or above the ESI threshold, ionization by traditional ESI mechanisms is achieved. The multimodal nature of the technique enables readily switching between plasma and ESI operation. It is expected that PLASI will enable analyzing a wide range of analytes in complex matrices and less-restricted solvent systems, providing more flexibility than that achievable by ESI alone.

**Keywords:** DART, Mass spectrometry, Plasma ionization, Process and reaction monitoring, Liquid-phase separations

Received: 9 April 2014/Revised: 6 June 2014/Accepted: 6 June 2014/Published Online: 8 July 2014

## Introduction

Direct plasma ionization via direct analysis in real time (DART) has become a popular approach since first introduced by Cody in 2005 [1]. Several review articles describe the variety of ambient ionization techniques available and their applications, including DART [2–4]. Driving the growth of plasma ionization is the ability to allow high throughput and direct analyses of solid, liquid, and/or gaseous samples in both negative and positive ionization modes. DART utilizes a point-to-plane glow discharge that generates a plasma plume consisting of metastable species of the working gas such as helium, nitrogen, or argon. These metastables react with atmospheric water molecules to produce reactant ions, which in turn

undergo proton and/or charge transfer reactions with the analyte. The ionization process depends on the properties of the plasma itself as well as on the physicochemical properties of the analyte (i.e., ionization energy, proton affinity, vapor pressure) [1, 5, 6]. High throughput direct surface analysis is where DART has excelled, including applications to explosives, currency, pharmaceuticals, biological samples, and plant material, to name a few [2]. Typically, a solid or liquid sample deposited on a glass capillary is investigated by simply placing it, with minimal or no preparation, within the plasma plume exiting the ion source [2].

Analysis of highly complex samples by mass spectrometry (MS) usually requires some type of liquid-phase separation step prior to analysis, such as liquid chromatography (LC) or capillary electrophoresis (CE). In many cases, these separations would require buffer solutions or additives in the mobile phase to achieve optimum resolution and peak capacity, but salt deposition at the ESI-needle tip and/or MS inlet prevent the use of many mobile phases typically used in LC or CE with

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UV-visible or fluorescence detection. Incomplete ionization and limited dynamic range due to ion suppression are some of the other limitations stemming from the controlled current nature of the ESI process [7]. Using alternative ionization approaches such as atmospheric pressure chemical ionization (APCI) [8] or atmospheric pressure photoionization (APPI) [9] may alleviate some of these issues, but these techniques have their own drawbacks, such as increased fragmentation of thermally labile compounds because of the complete evaporation of the solvent and, in the case of APCI, a limited population of reactant ions because of the use of a low-current corona discharge for ionization.

Coupling liquid streams to MS via higher current plasma-based ion generation techniques such as DART is an attractive alternative to ESI, APCI, and APPI. Klampfl [10, 11] has recently reported an ion source where the mobile phase streaming from an LC column was transported through a capillary to a DART plasma plume for ionization in the form of a drop hanging from the transport capillary, or as a continuous liquid jet, depending on the liquid flow rate and capillary diameter. Liu et al. [12], on the other hand, used a pneumatic sprayer to form aerosols from a CE effluent prior to DART ionization. Mixing of the CE effluent with organic solvent(s) as the sheath liquid was found to favor signal stability and ion intensity. In both of these examples, a DART ion source was positioned on-axis with respect to the mass spectrometer inlet, and helium was used as the plasma working gas. In addition, the original ESI source components of the instrument were removed to allow analyte stream introduction and DART source mounting. Here, we present a new method for coupling plasma ion sources, such as DART, to existing ESI-MS instruments by using the ESI sprayer at voltages below the ESI threshold. This approach, named plasma-spray ionization (PLASI) to reflect its multimodal nature, enables generating finer aerosols and coupling to plasma ion sources with minimal modifications to the ESI unit. The instrument can thus be readily toggled between ESI and plasma modes, and each mode can be optimized independently. Moreover, we demonstrate that the PLASI ion source can be operated, without loss of performance, with  $N_2$  instead of the more costly He used in previous approaches.

## Experimental

### Instrumentation

The ionization region of an ESI Agilent-6430 triple quadrupole (QqQ) mass spectrometer (Agilent Technologies, Santa Clara, CA, USA) was modified to implement the PLASI ion source while preserving ESI-MS capabilities. Ultrahigh purity nitrogen (>99.999%) was used as the collision gas and the boil-off of industrial grade liquid nitrogen as the nebulizing and desolvation gas. The nebulizing gas pressure was 25 psi, and the desolvation gas temperature and flow rate were 350°C and 10 L min<sup>-1</sup>, respectively. Liquid samples were introduced into the nebulizer via a syringe pump (WRL, Palo Alto, CA, USA) at flow rates ranging from 5 to 50  $\mu$ L min<sup>-1</sup>. Optimal potential differences between the nebulizer tip and spectrometer inlet

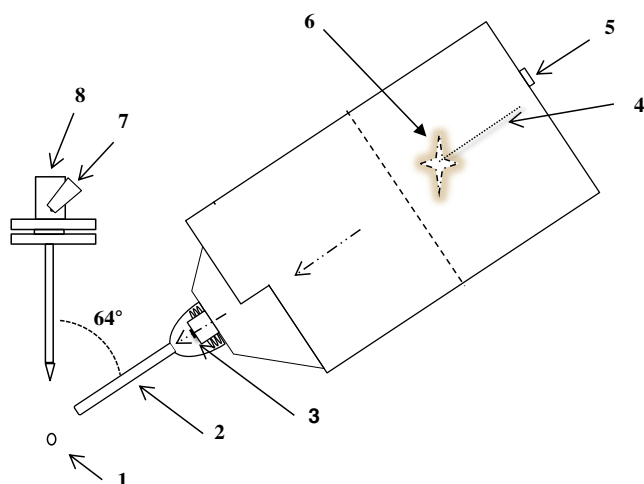
were determined to be 3.5 and 1.2 kV for ESI and PLASI modes, respectively. Note that the Agilent system uses a reversed potential bias where the ESI potential is applied to the inlet capillary with a sign opposite to that of the ionization mode with the sprayer at ground. The heated plasma plume was generated with a DART OS (IonSense, Saugus, MA, USA) ion source using industrial grade liquid  $N_2$  with flow rates monitored by a digital flow meter (Alicat Scientific, Tucson, AZ, USA) at 2 L min<sup>-1</sup>, a gas set temperature of 250°C, and a grid voltage optimized to 500 V in positive mode. The data presented here were collected in positive ion mode, monitoring the M + H peak. The PLASI system was evaluated in negative mode as well with comparable results obtained monitoring the M – H peak for methyl paraben utilizing a 350 V grid voltage. Data acquisition and processing were performed using Mass Hunter B.04.01 software (Agilent Technologies, Santa Clara, CA, USA) and analyzed using OriginPro 8.0 (OriginLab Corporation, Northampton, MA, USA). A DART Vapor interface was not required to maintain adequate operating pressure within the mass analyzer for either  $N_2$  or He DART operation.

### Materials and Reagents

The PLASI interface was tested using a 10  $\mu$ M solution of caffeine (Sigma-Aldrich, St. Louis, MO, USA). Solutions were prepared in 50% LC-MS grade methanol (Sigma-Aldrich) and 50% ultrapure water with 18.2 M $\Omega$  cm resistivity (Barnstead; Thermo Scientific, Marietta, OH, USA). For ion suppression experiments, a 10  $\mu$ M methyl paraben (Sigma-Aldrich) solution was prepared in 50:50 v/v water:methanol with 40 mM potassium dihydrogen phosphate (Sigma-Aldrich) at pH 6.9. Industrial grade liquid nitrogen was obtained from Airgas, Inc. (Atlanta, GA, USA).

### PLASI Ion Source Design

Though incorporation of a PLASI ion source into any specific MS system will depend on its particular design, the Agilent 6430 QqQ spectrometer required minimal source compartment changes and no ESI sprayer modification. Removal of the ESI source enclosure exterior cover and viewing windows allowed mounting of the plasma source and introduction of the plasma plume in the existing ESI needle/capillary interface region via an extension nozzle. The optimized configuration for the PLASI source with the Agilent 6430 QqQ is schematically illustrated in Figure 1. The nozzle of the plasma ion source was extended to enable proximity of the plasma plume with the nebulized aerosol produced at the needle tip for maximum plasma plume-aerosol interaction. A custom designed glass nozzle, made of 1/4" i.d. glass tubing was affixed with high temperature O-rings on to the DART cap, extending the plasma nozzle length to 57 mm. An x,y,z stand was built in-house to allow for PLASI optimization by fine-tuning the position of the plasma exit relative to the nebulizer tip and mass spectrometer inlet in the those coordinates. Continuous infusion of 10  $\mu$ M caffeine solution in 50:50 v/v water:methanol was used for

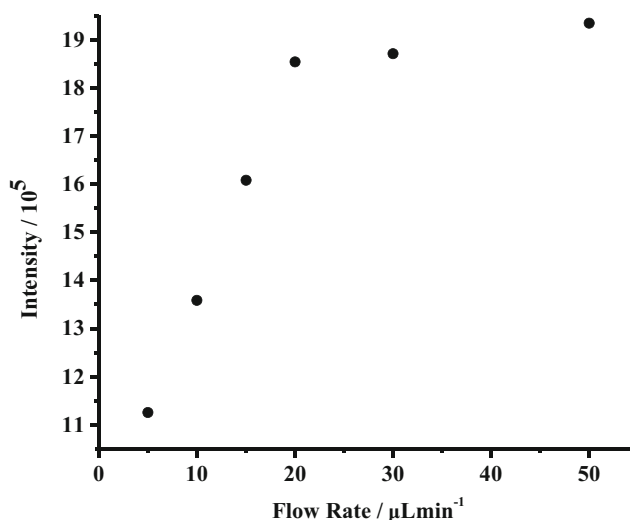


**Figure 1.** PLASI schematic as designed for the Agilent 6430 QqQ mass spectrometer (1) metal-coated glass capillary inlet (2) DART extension nozzle (3) DART grid electrode (4) DART needle (5) DART gas inlet (6) DART glow discharge (7) nebulizer gas inlet (8) analyte solution inlet to nebulizer

optimization experiments. Variation in the angle between the plasma extension capillary and the sprayer indicated an effect on overall signal intensity. Optimized ion intensity was achieved at an angle of  $64^\circ$  relative to the nebulizer. Optimization of the plasma extension capillary angle with respect to the spectrometer inlet was limited because of constraints imposed by the ion source enclosure design. No substantial change in signal was observed over a  $\pm 10^\circ$  range. Coupling the PLASI source with the Agilent QqQ required no software modification or safety interlock overrides for proper instrument functioning.

## Results and Discussion

For PLASI-MS experiments, the analyte or solvent solution was introduced into the ESI sprayer (Figure 1) held typically at a potential difference  $\sim 60\%$ – $75\%$  lower than that needed for traditional ESI to occur. With nitrogen as the nebulizing gas, a continuous aerosol/fine spray plume exited the ESI capillary. In the absence of the nebulizing gas, liquid drops or a liquid stream were observed depending on the infused solution flow rate. Initial parameter space exploration for PLASI operation demonstrated an increased range of acceptable solvent/sample flow rates compared with standard ESI in the instrument employed. Increasing sample introduction flow rates resulted in a corresponding linear increase in signal intensity up to  $20 \mu\text{L min}^{-1}$ , where a plateau was reached (Figure 2). This increase in signal with higher flow rates implies a behavior fundamentally different than ESI, where high flow rates result in a general decrease in ionization efficiency [7]. For the purpose of the experiments presented here, the PLASI source was operated in the plateau region to ensure that optimal ionization efficiency occurred. Once the aerosol was delivered into the ionization region (i.e., the region where the inlet and



**Figure 2.** Mass flow sensitivity range for PLASI operation mode, monitoring the  $[M + H]^+$  caffeine signal, with flow rates in the  $\mu\text{L min}^{-1}$  range, when infusing a  $10 \mu\text{M}$  solution in 50:50 v/v methanol:water

the plasma extension capillary exit are located), ion signals were observed only for ESI potential differences above 700 V. Direct entrainment of the aerosol plume with the plasma plume was necessary for observing any signal. In the absence of the plasma plume, no ions were detected by the mass spectrometer with ESI potential differences below 1500 V. Interestingly, no ion signals corresponding to sodiated adducts of any analyte introduced, one of the typical characteristics associated with ESI mechanisms, were detected below ESI capillary potential differences of 1.5 kV. With the plasma source on, and ESI potential differences between 700 and 1200 V, only the protonated analyte and solvent ions were detected. Furthermore, ion identity and/or intensity did not change with the type of plasma gas used, whether He or  $\text{N}_2$ .

Though not fully characterized but still widely accepted, the predominant positive ion mode DART ionization mechanism involves the generation of a pool of diverse reactant ions. These reactant ions are generated through Penning ionization where plasma metastables transfer their energy to sample solvent or atmospheric gas molecules, resulting in the formation of the corresponding molecular ions and, subsequently, producing protonated water-clustered species [3, 6]. Reactant ions interact with gas-phase analyte neutrals to generate analyte ions, usually through proton transfer. It is also possible for the metastables to interact directly with analyte neutrals of ionization energy (IE) lower than the internal energy of the plasma metastables, generating analyte molecular ions. However, the probability of this interaction occurring is substantially lower than the probability of a metastable interaction with solvent/background gas molecules, which is particularly the case in the presence of a continuously-introduced liquid analyte stream. Song et al. investigated the effects of a solvent “micro-environment” surrounding the analyte in the DART ionization region [5]. They concluded that large concentrations of solvent

present in the atmosphere provided a transient microenvironment (TME), effectively surrounding the analyte molecule and preventing any direct analyte ionization from metastables. It is postulated that the PLASI uses this metastable interaction with sprayed solvent molecules to generate protonated solvent clusters that undergo proton transfer with gas-phase analytes as schematically depicted in Figure 3. The required low potential differences ( $\sim 700$ – $1200$  V) on the sprayer for PLASI ion detection are speculated to provide a favorable potential gradient between the analyte ion generation region and the MS inlet for effective ion transfer into the mass spectrometer. Without the potential difference applied to the ESI sprayer, ions generated by the plasma stream, which is orthogonal to the inlet capillary and has a mean linear velocity of  $2.6 \text{ m s}^{-1}$ , could not be efficiently turned  $90^\circ$  solely by the drag created by the vacuum system of the mass spectrometer, as is usually the case in traditional DART-MS experiments. It is also possible that the moderate potential difference on the ESI capillary partially assists in decreasing the mean droplet size initially formed with assistance of the nebulizing gas. Facilitation of finer droplet formation may be a result of combined polarization of the liquid analyte due to applied potentials on the sprayer and nebulization [13, 14]. It is believed that the applied potential

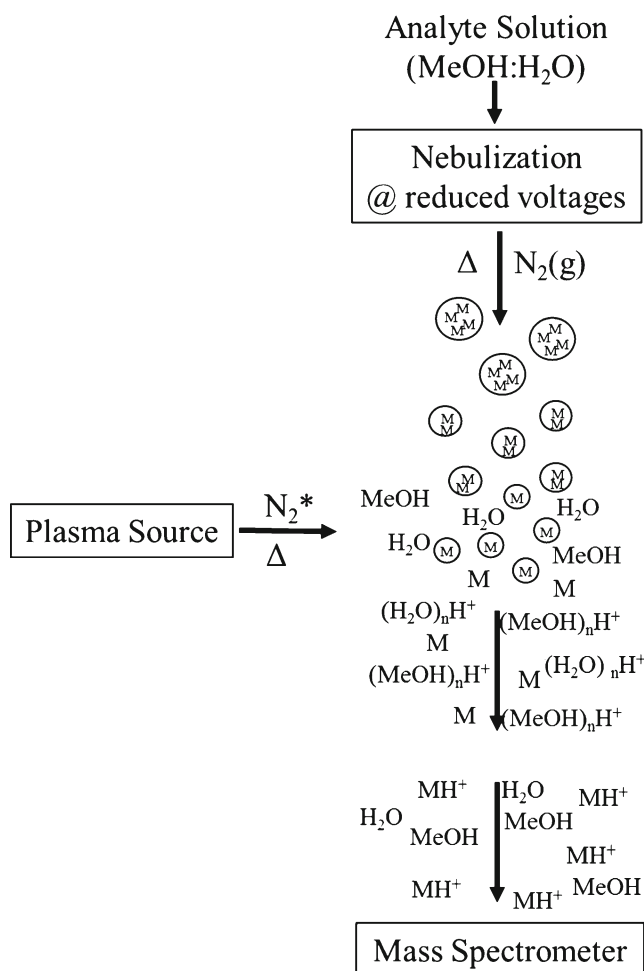


Figure 3. Proposed primary PLASI mechanism

difference, shear forces impinged by the nebulizer gas, and the thermal energy provided by the heated ( $350^\circ\text{C}$ ) desolvation and DART ( $250^\circ\text{C}$ ) gases are the major forces responsible for the progressive atomization and subsequent desolvation of analyte droplets to form analyte aerosols. Gas-phase analytes are believed to be formed by molecular thermal desorption from these aerosols. It is unclear if ion evaporation mechanisms [15] could be present under the conditions studied here, and experimental evidence (vide infra) does not support the existence of these processes to a major extent.

He gas is traditionally utilized in DART experiments because of the higher thermal conductivity of the gas and the higher energy He metastables generate compared with  $\text{N}_2$  [16]. For solid and liquid sample analysis, the use of He has been shown to improve analyte thermal desorption off surfaces and efficiently ionize desorbed neutrals. Since in the PLASI plasma mode the plasma gas is believed to aid in droplet desolvation and analyte thermal desorption, the plasma gas thermal conductivity was also evaluated. Hypothetically, a He plasma should provide higher signal intensity than a  $\text{N}_2$  plasma. Interestingly, no significant differences in signal intensity were observed between these two gases (Figure 4). It is possible that this effect is caused by the thermal energy contribution from the plasma gas being relatively minor compared with that of the desolvation gas.

Supporting our proposed mechanism is the finding that in the absence of a glow discharge, no ion signal was observed when the potential difference between the ESI sprayer and the inlet capillary was below  $1500$  V. When increasing the voltage above  $1500$  V, ion signals were observed with intensity increasing with the sprayer potential difference. Since ESI sources are usually operated at a  $2.5$ – $4.5$  kV potential difference, ESI ion generation processes are expected to increase in relative importance with higher potentials, even with the plasma gas flow on. Under full ESI conditions, liquid exiting the

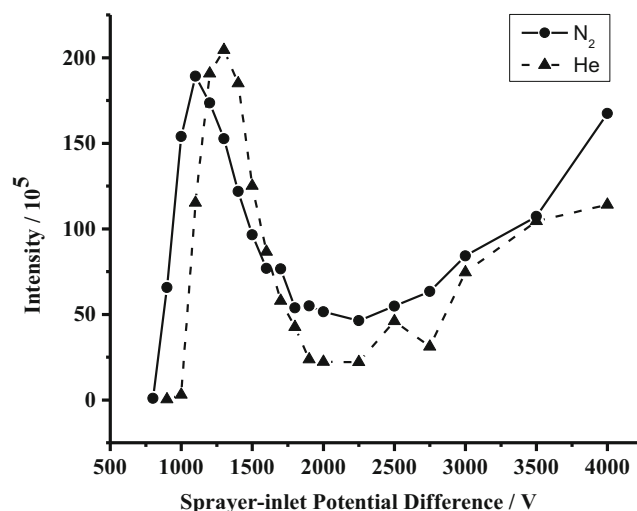
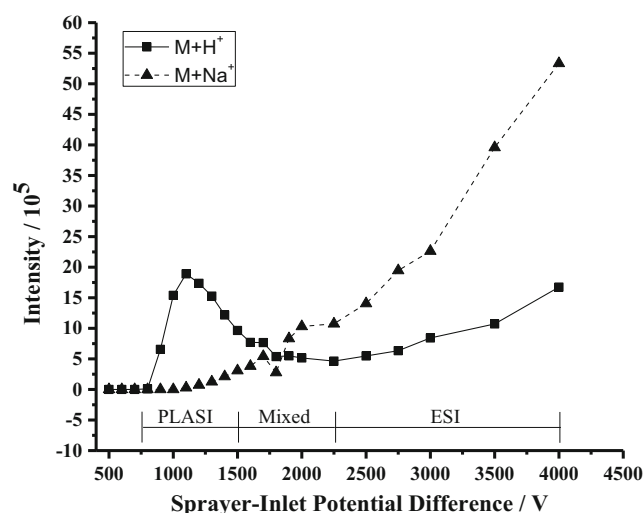


Figure 4. Ion intensity of the  $[\text{M} + \text{H}]^+$  caffeine signal as a function of the potential difference between the nebulizer and the inlet capillary, and type of PLASI discharge gas,  $\text{N}_2$  versus He

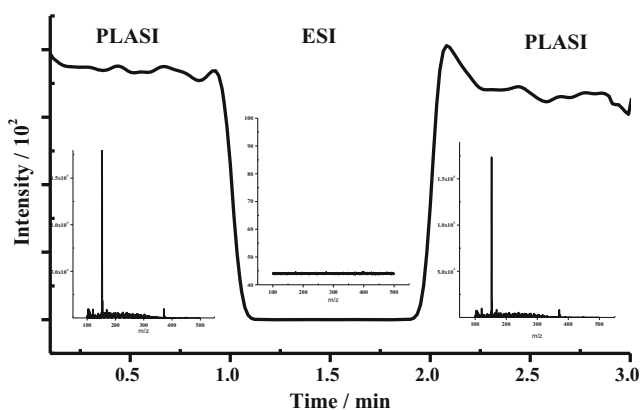
ESI capillary tip acquire enough charge to form multiply charged droplets that, upon progressive desolvation, reach their Rayleigh limit and undergo Coulombic fission [15, 17]. Subsequent fission and desolvation of droplets generates protonated ions, clusters, and alkali ion adducts.

To further clarify the differences between plasma and ESI modes of PLASI ion generation, identities of the MS signals detected were studied using a 10  $\mu$ M methylparaben solution in 50:50 v/v methanol:water. The only parameter experimentally varied was the applied potential difference between the sprayer and the capillary inlet. As shown in Figure 5, no ion signal was observed below 700 V. As the ESI sprayer potential difference was increased toward 1000 V,  $[M + H]^+$  methylparaben ions began to dominate the mass spectrum. Ions of  $[M + Na]^+$  type only started to appear intermittently when the ESI capillary voltage was above 1500 V. Sole formation of protonated methylparaben ions below the ESI threshold suggested that gas-phase proton transfer processes was predominant. As the ESI capillary voltage was systematically increased to 2000 V, a transitional region of very low ionization efficiency was clearly observed where both the protonated and the sodiated methylparaben ions were detected in the mass spectrum, but at much lower ion counts. The exact origin of this transitional region is still a matter of active research, but it is possible that the transit time of the smaller micro/nanodroplets generated under these conditions within the ionization region is further decreased so as to prevent full desolvation followed by thermal desorption/proton transfer. As the ESI capillary voltage was further increased ( $>2000$  V), ion populations of both  $[M + H]^+$  and  $[M + Na]^+$  ions also increased; however, the mass spectrum was dominated by  $[M + Na]^+$  species as in traditional continuous infusion ESI-MS experiments. Similar trends in ion signal intensity and ion types were also observed for caffeine.



**Figure 5.** PLASI ionization regime changes based on potential difference between the sprayer and the mass spectrometer inlet capillary as demonstrated by proton/sodium adduct formation for methylparaben when infusing a 10  $\mu$ M solution in 50:50 v/v methanol:water

These observations suggest that the presence of high concentrations of non-volatile salts in solution should not affect ionization efficiency when PLASI is operated in plasma mode. As ionization in plasma mode occurs in the gas phase, non-vaporized salts should not affect charge competition and ion suppression as usually observed in ESI. The effect of salt concentration on ionization efficiency was evaluated in PLASI when operated in both plasma and ESI modes utilizing a 10  $\mu$ M methylparaben solution in 50:50 v/v methanol:water with 40 mM phosphate buffer. Experiments were performed under identical instrumental and experimental conditions by simply toggling the voltage applied to the inlet capillary between 1.2 kV for plasma mode and 3.5 kV for ESI mode, with all elements of the DART plasma source kept on during the entire experiment. Figure 6 shows the acquired mass spectra and measured total ion current during the ESI and the plasma mode phases of the experiment. The capability of PLASI to ionize a solution of methylparaben in a phosphate buffer without significant loss in signal intensity due to ion suppression was clearly observed. When the voltage was increased to 3.5 kV, suitable for ESI to take place, complete loss of ion signal was observed. This suggested that the presence of phosphate buffer interfered with the ESI process of ion formation, probably because of ion suppression. Switching the ESI capillary voltage back to 1.2 kV resulted in full recovery of the analyte signal. The ability of the system to be toggled voltage-wise to operate in both regimes again highlights its multimodal capabilities and may be useful for ionizing molecules in a wider range of polarities. Tolerance to mobile phase modifiers indicates that the use of PLASI would enable a less-restrictive optimization of the liquid phase separation conditions without the typical constraints posed by ESI limitations.



## Conclusions

PLASI has the potential to provide high throughput multimodal analytical capabilities for liquid sample analysis. The PLASI ion source takes advantage of both chemical ionization and ESI ion generation mechanisms in a single instrumental design. Depending on the experimental needs, PLASI can be used in either plasma or ESI modes by simply toggling the sprayer-inlet capillary potential difference between low (1000–1200 V) and high (>3500 V) settings. Because PLASI efficiency was found to be unaffected by the type of plasma gas used, the use of N<sub>2</sub> instead of He will result in lower daily operating costs and avoid the need for costly auxiliary pumping interfaces (e.g., Vapur). In PLASI, the transition of analytes from liquid to gas phase is primarily mediated by the thermal energy imparted by the plasma plume and the desolvation gas. Protonated ions are predominantly generated in plasma mode and ionization efficiency is unaffected by high salt concentration in the solvents or sample matrix. It is envisioned that PLASI has the potential to be applied to the analysis of samples with complex matrices, and could specifically be useful when the optimization of the chromatographic method requires non-ESI friendly mobile phases. These advantages could greatly expand its usage in demanding LC-MS pharmaceutical and process analysis applications for which ESI-MS is not readily compatible. It is envisioned that PLASI can also be used as an ion source for other analytical instruments, such as ion mobility spectrometers, and implemented with a variety of ambient plasma ion sources.

## Acknowledgments

The authors gratefully acknowledge financial support from Pfizer through a joint PTxPS Alliance Project, and additional support from the US Pharmacopeial Convention to AK in the form of a Global Fellowship.

## References

1. Cody, R.B., Laramee, J.A., Durst, H.D.: Versatile new ion source for the analysis of materials in open air under ambient conditions. *Anal. Chem.* **77**, 2297–2302 (2005)
2. Gross, J.H.: Direct analysis in real time—a critical review on DART-MS. *Anal. Bioanal. Chem.* **406**, 63–80 (2014)
3. Harris, G.A., Hostetler, D.M., Hampton, C.Y., Fernandez, F.M.: Comparison of the internal energy deposition of direct analysis in real time and electrospray ionization time-of-flight mass spectrometry. *J. Am. Soc. Mass Spectrom.* **21**, 855–863 (2010)
4. Monge, M.E., Harris, G.A., Dwivedi, P., Fernandez, F.M.: Mass spectrometry: recent advances in direct open air surface sampling/ionization. *Chem. Rev. (Washington, DC)* **113**, 2269–2308 (2013)
5. Song, L., Gibson, S.C., Bhandari, D., Cook, K.D., Bartmess, J.E.: Ionization mechanism of positive-ion direct analysis in real time: a transient microenvironment concept. *Anal. Chem.* **81**, 10080–10088 (2009)
6. Harris, G.A., Fernandez, F.M.: Simulations and experimental investigation of atmospheric transport in an ambient metastable-induced chemical ionization source. *Anal. Chem.* **81**, 322–329 (2009)
7. Tang, K., Page, J.S., Smith, R.D.: Charge competition and the linear dynamic range of detection in electrospray ionization mass spectrometry. *J. Am. Soc. Mass Spectrom.* **15**, 1416–1423 (2004)
8. Page, J.S., Kelly, R.T., Tang, K., Smith, R.D.: Ionization and transmission efficiency in an electrospray ionization–mass spectrometry interface. *J. Am. Soc. Mass Spectrom.* **18**, 1582–1590 (2007)
9. Hanold, K.A., Fischer, S.M., Cornia, P.H., Miller, C.E., Syage, J.A.: Atmospheric pressure photoionization. 1. General properties for LC/MS. *Anal. Chem.* **76**, 2842–2851 (2004)
10. Eberherr, W., Buchberger, W., Hertsens, R., Klampfl, C.W.: Investigations on the coupling of high-performance liquid chromatography to direct analysis in real time mass spectrometry. *Anal. Chem.* **82**, 5792–5796 (2010)
11. Beißmann, S., Buchberger, W., Hertsens, R., Klampfl, C.W.: High-performance liquid chromatography coupled to direct analysis in real time mass spectrometry: investigations on gradient elution and influence of complex matrices on signal intensities. *J. Chromatogr. A* **1218**, 5180–5186 (2011)
12. Chang, C.L., Xu, G.G., Bai, Y., Zhang, C.S., Li, X.J., Li, M., Liu, Y., Liu, H.W.: Online coupling of capillary electrophoresis with direct analysis in real time mass spectrometry. *Anal. Chem.* **85**, 170–176 (2013)
13. Hayati, I., Bailey, A.I., Tadros, T.F.: Investigations into the mechanisms of electrohydrodynamic spraying of liquids. 1. Effect of electric-field and the environment on pendant drops and factors affecting the formation of stable jets and atomization. *J. Colloid Interface Sci.* **117**, 205–221 (1987)
14. Zeleny, J.: Instability of electrified liquid surfaces. *Phys. Rev.* **10**, 1–6 (1917)
15. Kebarle, P., Peschke, M.: On the mechanisms by which the charged droplets produced by electrospray lead to gas phase ions. *Anal. Chim. Acta.* **406**, 11–35 (2000)
16. Monge, M.E., Harris, G.A., Dwivedi, P., Fernandez, F.M.: Mass spectrometry: recent advances in direct open air surface sampling/ionization. *Chem. Rev.* (2013)
17. Kebarle, P., Verkerk, U.H.: *Electrospray and MALDI Mass Spectrometry*. Wiley, Hoboken Second edn. 4–38 (2010)