

# Method for Improving Spatial Resolution of Liquid-assisted Surface Desorption Atmospheric Pressure Chemical Ionization Mass Spectrometry



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**Abstract:** Liquid-assisted surface desorption atmospheric pressure chemical ionization source (LA-DAPCI) technique shows good potential in complex matrix mass spectrometry imaging. Due to primary ions and high density charged droplets of solvent generated by corona discharge, analytes on sample surface are extracted and ionized efficiently. However, direct application of the DAPCI ionization for mass spectrometry imaging of complex matrix analytes usually tends to be challenging because of low spatial resolution. To resolve this problem, several ion source parameters and experiment conditions were optimized in the present work, including ion source configuration, chemical composition of the extraction solvent, geometry parameters, solvent flow rate and pressure of nebulizing gas. The results presented here confirmed that the spatial resolution of LA-DAPCI was improved (from  $(441 \pm 14) \mu\text{m}$  to  $(58 \pm 7) \mu\text{m}$ ). The proposed LA-DAPCI-MS/MS method was successfully used to profile the distribution of Rhodamine 6G with a limit of detection of  $0.01 \text{ ng cm}^{-2}$ .

**Key Words:** Liquid-assisted surface desorption atmospheric pressure chemical ionization; Spatial resolution; Detection limit; Mass spectrometry imaging

## 1 Introduction

Surface desorption atmospheric pressure chemical ionization (DAPCI) is a kind of direct ionization technique. Primary ions are produced by corona discharge, then the primary ions impact on the sample surface under the strong electric field. Charge and energy are transferred through ion/molecule reaction to ionize the analytes on sample surface<sup>[1–3]</sup>. The characteristics combination of low-temperature plasma (LTP) probe<sup>[4,5]</sup> and air flow assisted ionization(AFAI)<sup>[6]</sup> makes DAPCI more suitable for mass spectrometry imaging (MSI). The spatial resolutions of DAPCI mass spectrometry imaging (DAPCI-MSI) reported by previous researches were  $250 \mu\text{m} \times 250 \mu\text{m}$ <sup>[7]</sup>,  $450 \mu\text{m} \times 450 \mu\text{m}$ <sup>[8]</sup>,  $140 \mu\text{m} \times 140 \mu\text{m}$ <sup>[9]</sup> and  $500 \mu\text{m} \times 500 \mu\text{m}$ <sup>[10]</sup>,

respectively. Liquid-assisted surface desorption atmospheric pressure chemical ionization (LA-DAPCI) is an improved ionization source based on DAPCI. Comparing with the traditional DAPCI, the proposed LA-DAPCI ionization offers competitive advantages in desorption capability and high ionization efficiency<sup>[11]</sup>. In LA-DAPCI source, analytes on the sample surface are ionized by high-density reagent ions which produced by corona discharge. Moreover, desorption capability of LA-DAPCI is improved by high efficiency collision and extraction between spray drop and sample surface. Thus, LA-DAPCI has a strong ability to desorb macromolecules and substrate-adsorbed analytes, particularly suitable for mass spectrometry imaging of tissue sections and complex matrices analytes. In MSI experiments, the quality of imaging is directly affected by the spatial resolution.

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Therefore, an acceptable spatial resolution of LA-DAPCI source is required for MSI application.

In this study, the desorption ionization region on the sample surface was observed and measured directly. Several ion source parameters and experiment conditions were optimized, such as the ion source configuration, the chemical composition of the extraction solvent, geometry parameters, solvent flow rate and the pressure of nebulizing gas. Thus, the spatial resolution of LA-DAPCI was improved to meet the requirement of MSI research.

## 2 Experimental

### 2.1 Instrument and apparatus

Experiments were carried out using a commercial linear ion trap (LTQ) mass spectrometer (Finnigan, USA) coupled with a homemade LA-DAPCI source<sup>[16]</sup>. The samples were put on a moveable stage equipped with insulation sample holder controlled by SC series stepper motor controller (Beijing Optical Century Instrument Co., Ltd).

### 2.2 Materials and reagents

Rhodamine 6G was purchased from SIGMA Co., Ltd (California, USA). Ultrapure water (specific conductivity, 18.2 MΩcm) was produced with a Milli-Q device (Thermo Scientific, USA). HPLC grade methanol was purchased from ROE Scientific Inc (Delaware, USA). pH strips (B-Universal indicator paper) were purchased from SSS Reagent Co., Ltd (Shang Hai, China). Qualitative filter paper was purchased from Fushun City Civil Affairs paper factory (Fushun, China).

### 2.3 LA-DAPCI source and mass spectrometry

N<sub>2</sub> pressure was 0.8–1.6 MPa. MeOH/H<sub>2</sub>O solvent was used as extractant with the flow rate of 1–5 μL min<sup>-1</sup>. The angle between discharge needle and horizontal plane was 30°–65°. The distance between discharge needle tip and MS inlet was 3–8 mm, and the distance between discharge needle tip and sample surface was 0.5–3.0 mm.

The LTQ mass spectrometer was operated in the positive mode, and the corona discharge voltage was set at 4.5 kV. Mass scan range was *m/z* 120–500. The temperature of the heating capillary of the LTQ-MS was maintained at 150 °C. The voltages for the heating capillary, tube lenses, conversion dynode, detectors, etc. used default values in the tune file. All collision induced dissociation (CID) experiments were performed at 20% collision energy and ions of interest were isolated using an *m/z* window width of 1 unit.

### 2.4 Methods

Filter paper strips were soaked in Rhodamine 6G solvent (1 μg mL<sup>-1</sup>) and dried in the air. The strips were stick on the glass slides using double-sided adhesive to keep flat. Glass slides were fixed on the three-dimensional moveable stage, sampling was achieved while moving the glass slides along x direction (orthogonal to LTQ inlet) at the speed of 1.492 mm min<sup>-1</sup>, and the characteristic fragment ion at *m/z* 415 was recorded simultaneously.

## 3 Results and discussion

### 3.1 Observation of desorption ionization region

Spray droplets produced by LA-DAPCI source could worked on the sample surface directly, and the desorption ionization region could be observed intuitively. In positive ion mode, the desorption ionization region experiment was completed by desorbed pH test strip using LA-DAPCI source for a period of time. Variation of pH test strip was studied and recorded, as shown in Fig.1.

Charged droplets of high density were produced by corona discharge; the droplets sprayed from the discharge needle tip to pH test strip in a conical spray plume and formed an approximate circular spots under the action of nebulizing gas. The process of desorption lasted for 1 min. Figure 1 shows that only the central area of the spot had color changed because colored substance on the pH test strip surface was extracted and desorbed by methanol/water. Ionized colored substance turned to gas phase ions and left the surface of pH test strip got fade. The area around the color changed region resulted from wetting or diffusion effect of spray solvent acted on pH test strip, while colored substance in these areas were not desorbed in fact. Therefore, no color changes had been observed. This phenomenon proved that only the central area of circular spray spots was the effective desorption ionization region.

After the charged droplets impacted sample surface, diffusion would occur on the surface and the colored substance surrounding would be extracted. So faded region inside the spot observed in pH test was larger than effective desorption ionization region on sample surface. Therefore, more accurate experiments were needed to carry out on diameter determination of desorption ionization region.

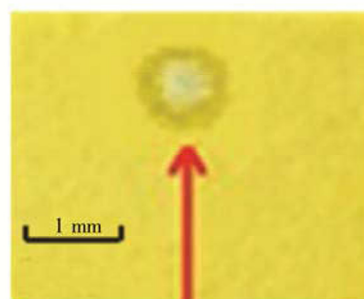


Fig.1 pH test strip desorbed by LA-DAPCI-MS

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