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Design and performance of air flow-assisted ionization imaging mass spectrometry system

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ABSTRACT

The imaging mass spectrometry (IMS) technology has experienced a rapid development in recent years. A new IMS technology which is based on air flow assisted ionization (AFAI) was reported. It allows for the convenient pretreatment of the samples and can image a large area of sample in a single measurement with high sensitivity. The AFAI in DESI mode was used as the ion source in this paper. The new IMS method is named AFADESI-IMS. The adoption of assisted air flow makes the sample pretreatment easy and convenient. An optimization of the distance between the ion transport tube and MS orifice increases the sensitivity of the system. For data processing, a program based on MATLAB with the function of numerical analysis was developed. A theoretical imaging resolution of a few hundred microns can be achieved. The composite AFAI-IMS images of different target analytes were imaged with high sensitivity. A typical AFAI-IMS image of the whole-body section of a rat was obtained in a single analytical measurement. The ability to image a large area for relevant samples in a single measurement with high sensitivity and repeatability is a significant advantage. The method has enormous potentials in the MS imaging of large and complicated samples.

1. Introduction

The imaging mass spectrometry (IMS) technology is a molecular imaging technique which features high chemical specificity, parallel detection, and microscopic imaging capabilities. The IMS image contains information of hundreds, or even thousands, of different molecules in the samples, and both molecular and spatial information can be obtained by analyzing a single sample [1–4].

IMS generally includes four steps: preparation of samples, mass spectrometry scanning, quality analysis, and data processing [5]. The important factors affecting the quality of imaging are the sensitivity of ionization, preparation of samples, spatial resolution, reliability of the system and speed of sampling. Significant progress has been made in the past 20 years in IMS techniques based on a variety of ionization sources, including secondary ion mass spectrometry (SIMS), matrix-assisted laser desorption ionization (MALDI), and desorption electrospray ionization (DESI), as examples [6–12].

In particular, the DESI-IMS technique has enabled imaging to be carried out in the ambient conditions and has greatly increased the application scope and applicability of IMS [13]. Thus, it is one of the most important and popular IMS technology. But in comparison with other techniques, such as MALDI-IMS, the sensitivity and the resolution of DESI-IMS still needs to be further improved.

MALDI-IMS, where a laser is used to complete sample desorption and ionization, features very high spatial resolution [14]. Since its introduction in the late 1990s, MALDI-IMS has witnessed a phenomenal expansion [15]. However, since ionization occurs in the vacuum environment, the imaging area of a sample is limited due to geometric constraints of the MS instrument [16–18].

The AFAI-IMS method uses air flow assisted ionization (AFAI) as the ion source [19]. AFAI is an ambient ionization method. In this paper, all IMS experiments were performed with the AFAI ion source in DESI mode, therefore the method is also called AFADESI-IMS. An ion transport tube is used to transport the sample ions which may be far away from the orifice. Even the entire large

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sample can be placed horizontally at a distance from the MS orifice, so that the sample pre-treatment is simple and convenient. The adoption of assisted air flow and an optimization of distance and alignment between the ion transport tube and MS orifice greatly improve the sensitivity of the AFAI-IMS. In this paper, the design of the AFAI-IMS method is described and the performance is further verified. It is used for the imaging of one sample with a large area (150 mm × 100 mm) in a single analytical measurement.

2. Experimental

The design of the AFAI-IMS (AFADESI-IMS) system is shown in Fig. 1. It includes the AFAI (ESI) source, high-precision imaging platform, synchronization circuit between the platform and mass spectrometer, and data processing program.

2.1. AFAI source

Air flow assisted ionization (AFAI) is an ambient ion source. As shown in Fig. 1, it includes a stainless steel ion transport tube (internal diameter: 3 mm, external diameter: 4 mm), a laboratory fabricated PMMA refluence tube (internal diameter: 16 mm, length: 60 mm, connected to the mass spectrometer), and a vacuum pump.

The AFAI source in DESI mode has an ESI nozzle through which a charged solvent is sprayed at high pressure and velocity onto the surface of the sample to complete the process of desorption and ionization. After the ionization, the ions are sucked into the ion transport tube by the air flow. Following the airflow, the ions and other constituents move toward the mass spectrometer orifice. When the samples reach the orifice, the solvent and uncharged molecules are driven by the airflow and move further toward the air outlet under reduced pressure, while the ions of the sample move through the orifice into the mass spectrometer under the influence of an electric field [19].

The ESI sprayer generate the initial charged droplets for desorption. In this paper, the spray gas was N_2, with a flow rate of 1.5 L/min, and a spray voltage of 4500 V. The spray solution was prepared by mixing methanol and water (4:1, v/v) with 0.1% formic acid, and was delivered to the sprayer by an Agilent LC pump at a flow rate of 10 μL/min.

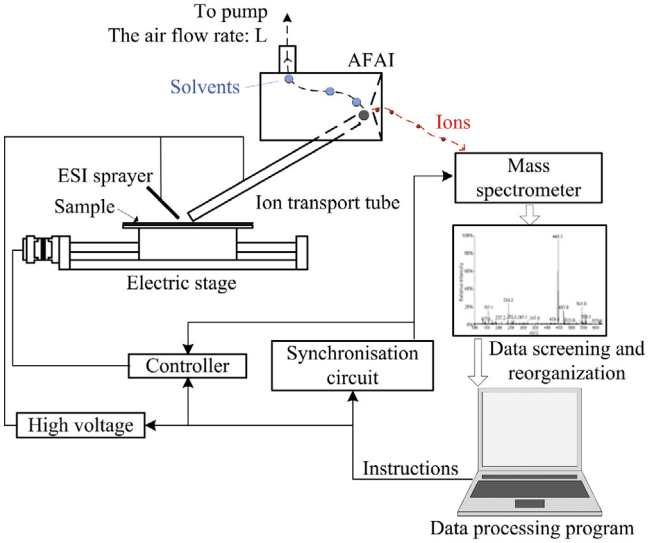

Fig. 1. A general view of the AFAI-IMS (AFADESI-IMS).

2.2. Mass spectrometer and synchronization circuit

The AFAI-IMS experiments were completed using a QTRAP 5500 and a QSTAR Elite QTOF mass spectrometer (AB SCIEX, Foster City, CA, USA). The mass spectrometry synchronization circuit ensures that the mass spectrometer runs simultaneously with the sample scanning, so that each pixel in the imaging map corresponds to the sample. It makes use of the communication port between the mass spectrometer and IMS stage controller.

The major portion of the synchronization circuit is a solid-state relay, whose output (2-pin) is connected to the communication port of the mass spectrometer. When the output of the solid-state relay is connected, the communications port of the mass spectrometer receives a short-circuit signal, and the mass spectrometer starts to run and acquire the raw mass spectra.

2.3. Sample preparation

The experiments use four samples. The first sample which is shown in Fig. 2A is three red stripes (each 3-mm wide). The stripes are printed on glossy photographic paper with an ink-jet printer. And the ink was Rhodamine B (*m*/*z* 443.2). This sample was designed for complete the optimization of AFAI-IMS.

The second sample was used to check the performance of the AFAI-IMS system as shown in Fig. 3A. Additionally, several letters and lines of three different colors (red, blue and black) were written on a glass slide, representing three target mass/charge values. The Rhodamine B (*m*/*z* 443.2) was the major constituent of the red pattern. The Basic Blue 7 (*m*/*z* 478.4) was the major constituent of the blue pattern. Molecular ions at *m*/*z* 322.2 ($[M+H]^+$) and *m*/*z* 344.2 ($[M+Na]^+$) were generated by the major constituent of the black pattern. The size of glass slide sections was 150 mm × 100 mm, and the imaging area of the pattern was 130 mm × 40 mm.

The third sample is shown in Fig. 4A. Whole-body section of a rat was used to complete the AFAI-IMS experiment for drugs and metabolites [20–22]. The target drug is the antitumor candidate drug, S-(+)-deoxytylophorinidine (CAT) [23]. CAT was prepared as a 4 mg/mL aqueous solution in 0.7% NaCl. The rat was administered 15 mg/kg CAT *via* the tail. After 30 min, the rat was euthanized by ether overdose and then frozen entirely in dry ice/

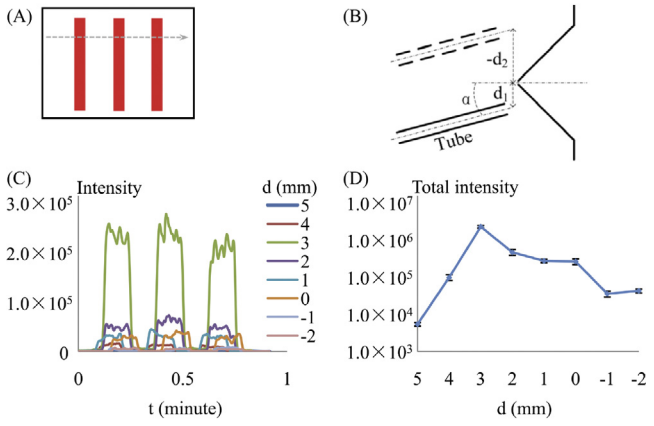

Fig. 2. Experiment designs and results of different distances between the ion transport tube and orifice. The sample is shown in (A) and the distance is shown in (B). (C) MS analysis under different distances (*m*/*z* 443.2); (D) Relationship between total intensity and distance after integrating each peak area.