

Delivering the Power of Ion Mobility Spectrometry - Mass Spectrometry to the Point of Analysis

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Abstract

With ion mobility (IM) built into many of the newer mass spectrometry (MS) systems, ion mobility spectrometry – mass spectrometry (IMS-MS) instrumentation has become the frontier of mass spectrometry development. The advantages of adding IM to MS include added isomer separation, structure based separation capability, and pre-separation of complex mixtures. Field portable MS is a fast growing area, offering high performance analysis of chemicals and biologics in-situ. Bringing the IMS-MS instrumentation to the point of analysis will provide rapid chemical detection in two dimensions (mobility and mass), delivering speed, performance, and robustness like that of an in-field IMS system. Key applications have been demonstrated in illicit drug detection, clinical diagnostics, and other specific on-site analysis needs.

Introduction

An ion mobility spectrometer can measure ion mobility of a gas phase molecule which is related to the molecular size and shape, indicating structure characteristics, while a mass spectrometer measures the mass (mass to charge ratio) of the molecule. Integrated ion mobility spectrometry - mass spectrometry offers more than one way to understand a gas phase molecule: now we not only know how heavy (mass) the molecule is, we also know how big (collision cross section) the molecule is. In the 1990s, further understanding of large biomolecules was one of the major motivations for the development of modern ion mobility mass spectrometry (IMMS) [1]. Historically, combining IMS with MS was demonstrated in the 70s, mainly for the purposes of understanding the ions formed in the IMS device, and further improving the performance of the IMS [2,3]. IMS and MS provide complementary information on the structure and composition of analytes. Increasingly, each technique is being taken into the field to quickly identify chemicals of interest such as explosives or narcotics. However, users have paid a price for the portability of previous fieldable instruments: poor performance and/or a single dimension of separation. In this work, a field portable IMS-MS system (MC3100, Excellims Corporation, Acton, Massachusetts, USA)

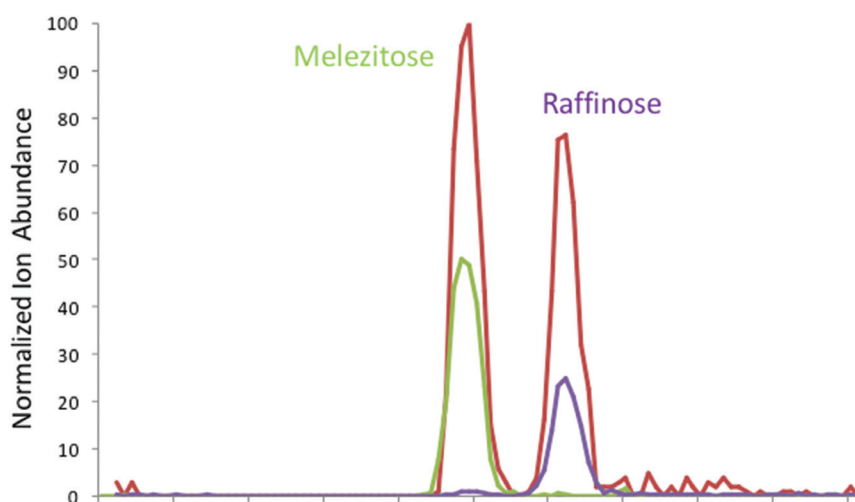


Figure 1. HPIMS ion mobility spectra of trisaccharide isomers, melezitose and raffinose; Red: melezitose and raffinose mixture, purple: raffinose only, and green: melezitose only.

with uncompromised IMS and MS system performance is presented. The desktop system integrates a high performance atmospheric pressure IMS with a linear ion trap MS, enabling chemical separation and identification based on both ion mobility and m/z . The IMS-MS system can detect chemicals based on their ion mobility and then introduce the same sample into the MS for m/z identification. Until now, ion mobility-mass two-dimensional (2D) chemical analysis could only be realised on laboratory scale models; now it has become a field portable compact instrument.

High performance ion mobility spectrometry

Recent advances in IMS have not only improved the resolving power of ion mobility separation, but also increased its compatibility with various mass analysers. Unfortunately, most of the systems are developed as integrated IMMS systems. To benefit from the ion mobility separation, researchers are required to obtain a complete bulky lab based IMMS system. Conventional IMS devices have been extensively developed to fit security and

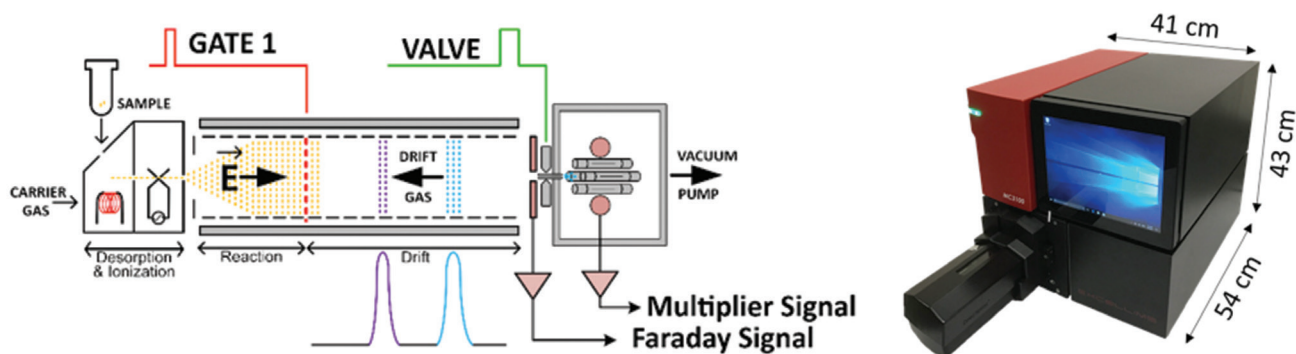


Figure 2. Novel small footprint high performance high mobility spectrometer - mass spectrometer Excelsims MC3100.

chemical detection needs; the performance of the ambient pressure IMS systems are rarely improved upon. The recent development of a high performance IMS (HPIMS) system (Excelsims Corporation, Acton, Massachusetts, USA) was an advance in small ambient pressure IMS systems, providing high resolving power, the capability for the rapid analysis of large organic molecules and biologics from a liquid sample (vs. volatile/semi-volatile small molecules only for conventional IMS), as well as a broader linear response range. In principle, IMS can deliver chromatography-like separation in the gas phase. One can consider it as gas phase electrophoresis. When an ionised sample mixture travels in the drift gas, in contrast to condensed phase media, a typical ion mobility separation can be achieved within 50 milliseconds with an average peak width (FWHM) of 180 microseconds.

Recent HPIMS developments have demonstrated ion mobility-based separation can deliver resolving power that is comparable to HPLC [4]. With added electrospray ionisation (ESI) capability, ESI-HPIMS is poised to be an alternative separation method to HPLC, especially in those applications where fast analysis is required at the point of origin. HPIMS inherited many unique features from the conventional IMS system, including its independence of operating environments; its high temperature operation conditions, which reduce carry over and contamination; and the little or no consumption of organic solvents which makes it much cheaper to operate.

Many examples of HPIMS applications can be found in the pharmaceutical process analytical technology (PAT) area where HPLC has been the most reliable workhorse for decades. However, typically the HPLC is set up in a lab environment and takes minutes to tens of minutes per sample. With a

rapid measurement-to-result time, HPIMS analysis only takes a few seconds and can be performed at-line, in-line or on-line in the manufacturing process. PAT applications may include reaction monitoring [5], dissolution studies, and cleaning validation in chemical and pharmaceutical manufacturing processes. IMS for cleaning validation has been well developed and adopted [6]. With HPIMS, superior analytical performance and the capability of analysing non-volatile Active Pharmaceutical Ingredients (API)s, excipients, and detergents become a reality. It can be set up in a lab with automation, or at line for a quick screening for contamination. For example, a typical cleaning validation procedure involves 50+ samples; if a typical HPLC analysis for this procedure takes 12 minutes, it will take 10 hours to complete the validation. With a typical <1 minute per sample analysis time, the HPIMS may complete the analysis within one hour. Another attractive feature of the HPIMS is that it eliminates the usage of large amounts

of solvents. Compared to HPLC, it is a green analytical technology with savings in running and waste disposal costs.

With the abundance of isomeric structures and lack of chromophores, sugar analysis has posed significant challenges to current HPLC methods. Refractive index detection for HPLC has poor sensitivity compared to UV and requires longer run times. Figure 1 shows the ESI-HPIMS ion mobility spectra of the isomers melezitose and raffinose. The x-axis is measured drift time and y-axis is the intensity. Typical resolving power ($R = t_d/t_{1/2}$, where t_d is the drift time and $t_{1/2}$ is the full width at half maximum for the peak) of the HPIMS is at 70 to 100. In this example, isomers melezitose and raffinose are baseline separated based on their ion mobility, while the measured resolving power is about 80, approximately 35,456 theoretical plates. HPIMS could be an ideal sugar analyser offering superior resolving power and analysis speed in seconds [7].

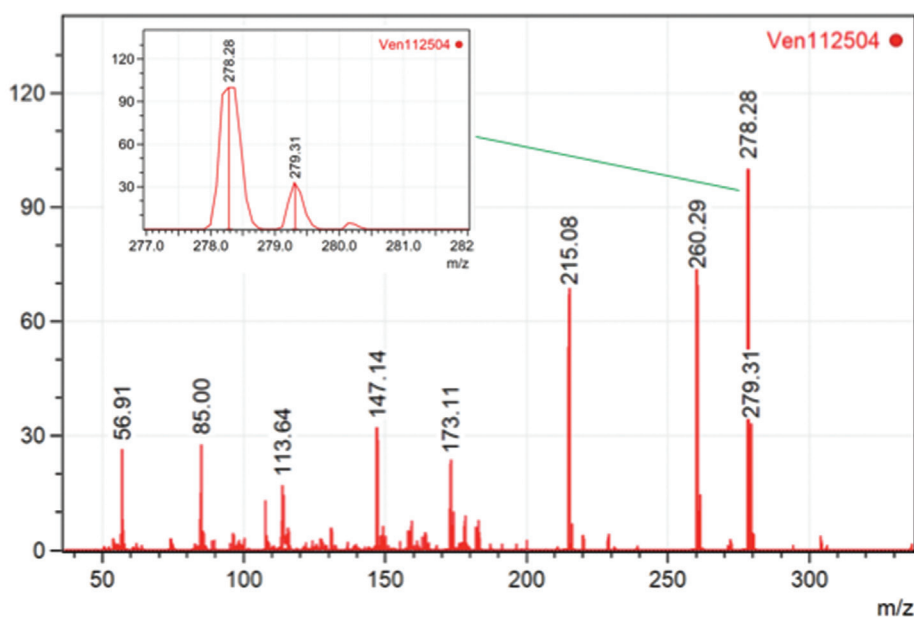


Figure 3. Mass spectrum of Venlafaxine obtained on HPIMS-MS.

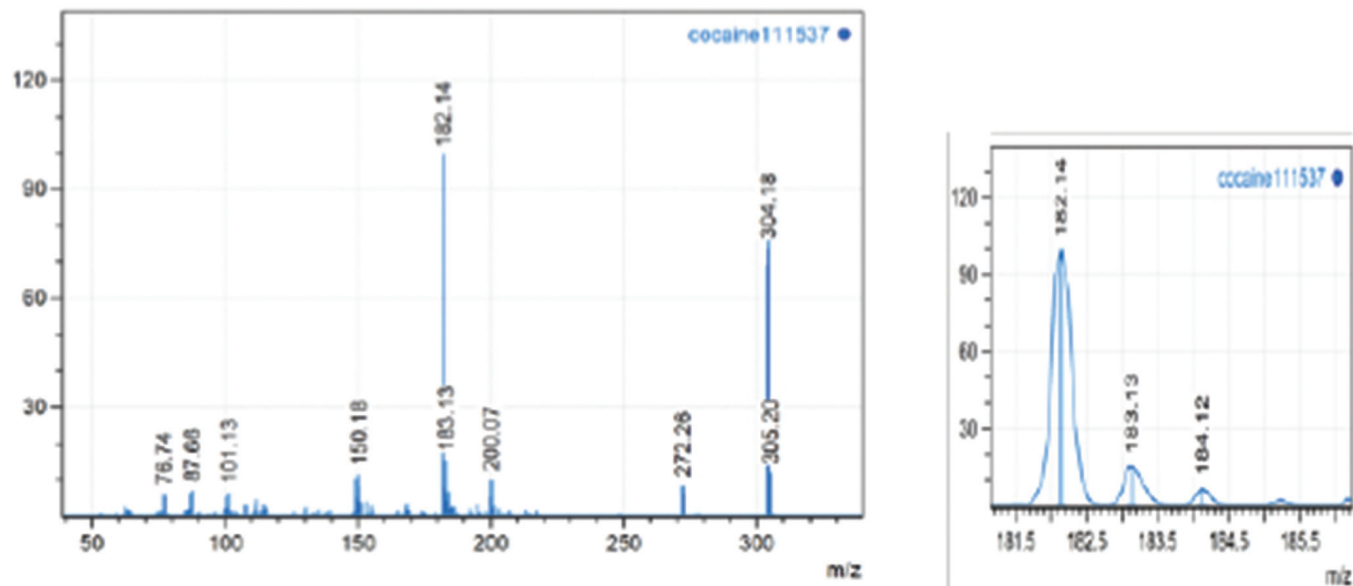


Figure 4. Mass spectrum of cocaine in MS-only mode of operation (left) and mobility-selected mass spectrum of cocaine. The IMS reactant ion peak is excluded from the trap, greatly reducing chemical noise from the ion trap MS.

HPIMS-MS Instrumentation

Arguably, a hyphenated HPLC-MS system is the most powerful analytical tool currently employed in most analytical laboratories. However, when an analytical tool is needed at the point of analysis, e.g. in a clinical setting or a biomanufacturing plant, HPLC-MS is not always practical. The instrumentation is big and bulky and not designed to be used outside a laboratory environment; it has a slow analysis time (minutes to hours); is complex to operate and requires a highly skilled user; and in addition, it is normally associated with higher instrument and operational costs.

HPIMS achieves, for example, isomer separation based on ion mobility. In layman's terms, ion mobility based separation is commonly considered to be based on molecular size. While there is a general relationship between molecular size and molecular weight, as a larger molecule is normally heavier, structural differences produce deviations from that overall trend. Efforts have been made to build libraries of molecular collision cross section [8] for large biomolecules.

Figure 2 shows a block diagram of a HPIMS-MS system, comprised of an atmospheric pressure drift tube ion mobility analyser coupled to a linear ion trap mass spectrometer with traditional hyperbolic geometry. After ion mobility separation, one or more ion packets may be selectively passed to the mass analyser. Similar to the HPLC-MS, a two-dimensional separation based on ion mobility and mass (m/z) can be achieved. For in-field applications, the

device is commonly used for targeted analysis, i.e. a targeted chemical can first be detected by IMS based on its mobility and then further confirmed by MS based on its mass; all of this occurs in one instrument, using a single sample.

1. Enabling MS to Perform at the Laboratory Level in the Field

The HPIMS-MS system provides lab-quality performance in an AC powered, compact, field portable unit with a small footprint. Outer dimensions are 17"H x 16"W x 26"L for the complete system, including all vacuum pumps, HPIMS analyser and linear ion trap mass analyser, instrument control and data processing hardware and software. During analysis of the HPIMS-MS system, a sample can be introduced via thermal desorption and a corona discharge ionisation source, or an ESI source. Ionised samples are first separated by the HPIMS, detected by the detector of the HPIMS, and then introduced into the MS.

Figure 3 shows the mass spectrum of Venlafaxine, a pharmaceutical drug sample, which was introduced to the HPIMS-MS via an ESI source. Unit mass resolution was achieved with scan rates slower than 12 kDa/s. The HPIMS-MS system is sensitive enough to detect less than ppb level of sample, and the mass accuracy is ± 0.15 Da. The instrument also performs well at high mass, with a confirmed mass range above m/z 2800. The resolving power does not appear to deteriorate across the working range.

2. HPIMS-MS Operation

The HPIMS can be used in IMS-only, MS-only, or IMS-MS modes of operation. For the IMS-only mode of operation, ion mobility is measured outside the vacuum chamber, completely independently from the MS. For the MS-only mode, the ion gate is open; all sample ions are transported through the IMS and enter the MS. The most powerful operating mode of the IMS-MS is when performing a linked scan, i.e. tandem IMS-MS measurement. In this mode of operation, the sample is first measured by the IMS; once a targeted chemical is detected, the chemical with a certain mobility (drift time) is introduced into the MS, and the mass analyser performs mass analysis of the mobility selected ions. This mode, also called 'detection and confirmation' mode, and offers chemical identification based on two orthogonal principles.

HPIMS-MS Applications

With the clear advantages of in-field operation, HPIMS-MS is one of the most powerful instruments available, providing high specificity, sensitivity and speed. With a small footprint and self-contained packaging, HPIMS-MS can be placed anywhere electrical power is available, for example, in field applications including security check points for explosive and drug detection, inspection laboratories for food quality and in hospital testing laboratories for biomarker analysis. The system can also potentially be used in a mobile laboratory

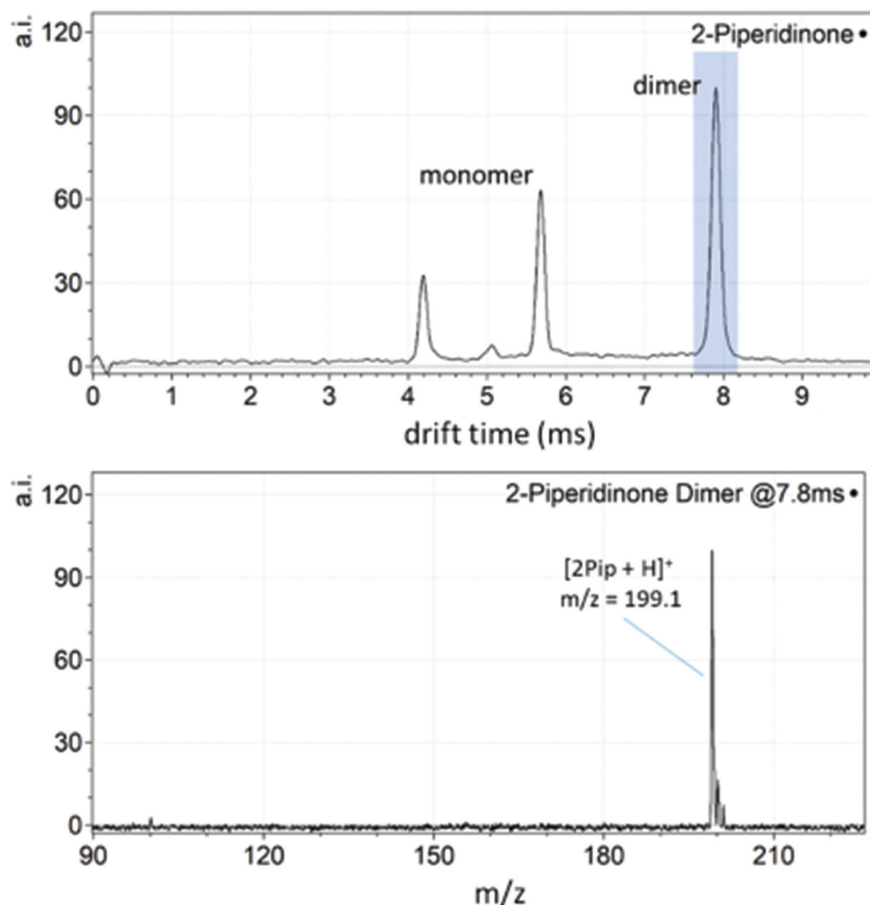


Figure 5. Ion mobility spectrum 2-piperidinone (top) and mass spectrum of mobility selected 2-piperidinone dimer at $m/z = 199$ Da.

setting with an AC power outlet.

Figure 4 shows an example of detecting illicit drug molecules. A cocaine sample was introduced to the HPIMS-MS from a sample swab by inserting the swab into the thermal desorber where the cocaine sample was evaporated and ionised via corona discharge ionisation. The full mass spectrum is shown on the left in Figure 4. To increase the ion trap sensitivity and overall system specificity toward the targeted molecule cocaine, only samples with a certain ion mobility were allowed to enter the MS. The greater than unit mass resolution mass spectrum of a cocaine fragment ion is shown in the right spectrum in Figure 4. In many forensic applications, mobility pre-separation, i.e. independent ion mobility identification of the target molecule, is critical. The data obtained based on both ion mobility and mass identification of targeted contrabands can be presented in court similar to conventional GC-MS or HPLC-MS. However, the HPIMS-MS analysis can be done in seconds. With high resolving power from both ion mobility and m/z , HPIMS-MS provides a powerful in-field analytical instrument for complex samples,

such as fentanyl and its analogues, which present constant challenges to current low resolution IMS and spectroscopy systems.

HPIMS-MS can be used for indoor VOC monitoring in an effort towards understanding the VOC compounds related to human health. Figure 5 shows the ion mobility and mass spectra of 2-piperidinone that was investigated related to multiple diseases. 2-piperidinone was introduced to the HPIMS-MS by directly pumping the air sample into the ionisation source where it was ionised by corona discharge ionisation. Multiple peaks were observed in the ion mobility spectrum (top). A pre-defined instrumental method may select, based on drift time, any subset of the mobility-separated ions to pass to the MS. This powerful tool can be used to probe the identity of any ion in the mixture, including detecting clustered analytes and/or neutral adducts. The bottom mass spectrum corresponds to the shaded section in the ion mobility spectrum. From the measured m/z , the mobility separated ions were identified as the dimer of 2-piperidinone with an m/z of 199 Da.

Summary

Benefiting from high resolution ion mobility separation and the unit mass resolution that is consistent with MS used in routine chemistry labs, HPIMS-MS brings the capability of 2D separation and identification outside the laboratory. The proven record of in-field robustness of IMS systems enables the HPIMS to shield the delicate MS device from harsh environments and improves the reliability of the in-field MS. The improved detection achieved by HPIMS, where the MS is used on-demand, greatly improves the lifetime and mean time between maintenance of the MS system. HPIMS-MS is in a rapidly-accelerating phase of application development; being fast, accurate, and a sensitive two-dimensional detection method of chemicals and biologics at the point of origin, it will become the new normal of routine analytical performance.

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