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Enhancing Low-Mass Ion Transmission in a Vortex Collision Cell via RF Voltage Optimization

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Introduction

Mass spectrometry (MS) is an invaluable tool for the identification and quantification of analytes within complex mixtures, owing to its high sensitivity and selectivity. The unique properties of MS instrumentation allow researchers to cover a large range of analytes, from large proteins to single ion fragments. As of recent, MS has become an especially important tool for small molecule analysis. Small molecules often include chemicals that are detrimental to human and environmental health. These hazardous compounds typically appear in many complex matrices, such as nitrosamine contamination in pharmaceuticals, accumulation of harmful short-chain PFAS within the environment, or formation of acrylamides in cooked foods. Therefore, instrumentation capable of identifying and characterizing these compounds is essential.

Here, through software tuning of ion guide RF voltages, we can achieve optimized sub *m/z* 50 ion transmission without physical changes to MS hardware. Instrument performance was optimized through software implementation enabling enhanced identification of ions down to *m/z* 27.

Experimental

Vortex Collision Cell

The vortex collision cell within an Ultivo LC/TQ is comprised of a high-pressure hexapole ion guide, with six resistive rods that converge and twist towards the rear—compressing and refining the ion beam for transfer into MS2. At normal operating parameters, ion abundance sharply decreases when approaching *m/z* 50. However, by decreasing RF voltages within the cell, we are able to recover sensitivity and enable enhanced detection <*m/z* 50.

(a) Vortex Entrance

(b) Vortex Exit

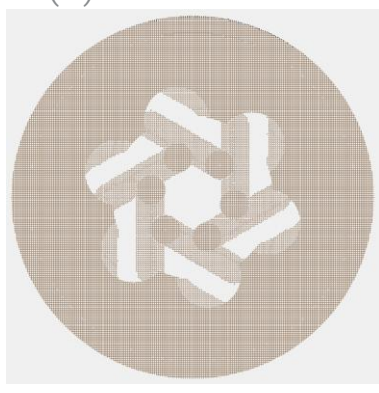

Figure 1. Vortex collision cell showcasing hexapole assembly from vortex (a) entrance and (b) exit.

Experimental

Materials

All solvents and standards used in this analysis were LC/MS grade. Ultrapure water was generated from a Milli-Q Advantage A10 with LC-Pak Polisher and 0.22 µm filter. InfinityLab Methanol for LC/MS was purchased from Agilent (PN 5191-5111). Acrylamide was purchased from Sigma-Aldrich (St. Louis, MO)

Standards containing a mixture of eight nitrosamines were purchased from Agilent (PN US-113N-1).

Instrumentation

Data was collected with an Agilent 1290 Infinity LC system coupled to a Ultivo triple quadrupole LC/MS with MassHunter 13 acquisition software. LC conditions listed in Table 1 and MS parameters in Table 2 and are based on previous application notes.[1,2]

Table 1. LC Conditions

Parameter	Value	
Analyte	Nitrosamines	Acrylamide
Column	Eclipse Plus C18, 3x50 mm 1.8 µm at 40 °C	
Mobile Phase	A: H_2O+0.1% FA; B: MeOH+0.1% FA	
Flow Rate	0.5 mL/min	0.5 mL/min
Gradient	1.5 min 5%B 3.0 min 90%B 3.5 min 90%B 3.51 min 50%B 4.0 min 5%B 5.0 min 5%B	1 min 5%B 2 min 90%B 2.5 min 50%B 3 min 5%B

Table 2. Source Parameters

Parameter	Value	
Analyte	Nitrosamines	Acrylamide
Ion Source	APCI	ESI
Polarity	Positive	
Drying Gas Temp. & Flow	290 °C 11 L/min	325 °C 12 L/min
Vaporizer Temp.	260 °C	---
Nebulizer Pressure	25 psi	60 psi
Capillary Voltage	1000 V	2500 V
Corona Current	4 µA	---

Decreasing RF voltages to achieve higher low-mass transmission.

Previous investigations have shown that a singular set of RF operating parameters can efficiently transmit ions above a *m/z* of 100 through the Vortex collision cell, but small molecules that cannot overcome the non-adiabatic pseudo-potential are lost. Simulation of the Vortex cell shows that by decreasing RF amplitude, we can attain higher transmission of low-mass ions in exchange for a decrease in transmission of higher masses (Figure 2), greatly enhancing detection of low-mass ions. In this study, small molecule mode was implemented into MassHunter 13 and evaluated using low-mass product ion fragments.

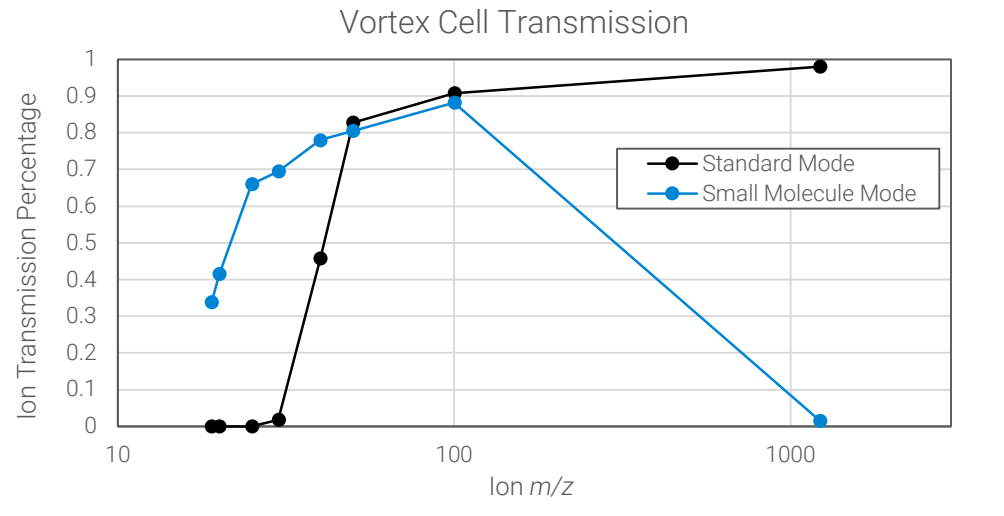

Figure 2. Simulation of Vortex collision cell ion transmission from *m/z* 20 to *m/z* 1000 in standard and small molecule modes.

Application of small molecule mode to nitrosamine fragments

Nitrosamines are commonly found as impurities in pharmaceutical substances and products produced during manufacturing. These byproducts have carcinogenic properties; therefore, detection is crucial. Nitrosamines can be classified as “small molecules”, which under CID, form fragments below a *m/z* of 50, making them ideal candidates for this new instrument mode. Eight nitrosamines were identified and peaks compared in standard and small molecule operating modes.

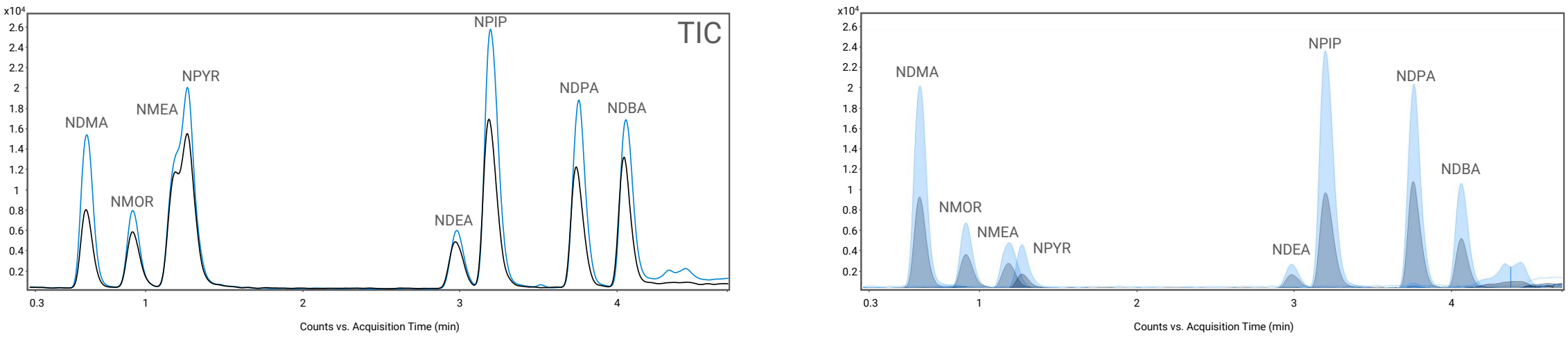

Figure 3. Chromatograms of nitrosamine standards in standard mode (black) and small molecule mode (blue). TIC (left) and extracted MRM chromatogram (right).

The resulting chromatograms are shown in Figure 3, with the TIC to the left, and MRM chromatograms on the right. Small molecule mode performance was evaluated by comparing peak areas of nitrosamines using transitions featuring product ions below a *m/z* of 50. From the TIC, it is clear that overall peak area was increased with the implementation of the small molecule mode. This enhancement of peak area was further emphasized when comparing the areas of sub-*m/z* 50 product ions. On average, in small molecule mode, analytes experienced an average of a 2.61-fold increase in peak area.

To further compare the two operating modes, both small molecule and standard operating modes, nitrosamine standards maintained high calibration linearity as shown in Figure 4.

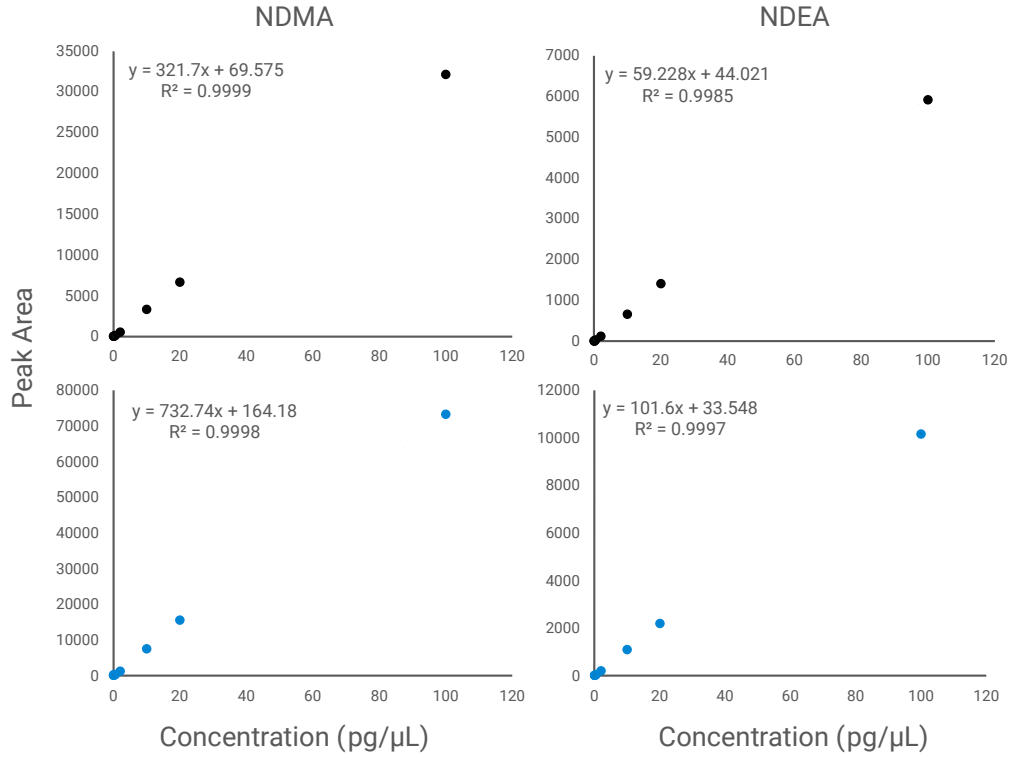

Figure 4. Calibration curves of two select nitrosamines (NDMA and NDEA) in standard mode (black) and small molecule mode (blue).

Results and Discussion

Analysis of acrylamide in small molecule mode

Acrylamide is a substance that forms during the cooking process of starch-based foods. This substance is classified as a potential carcinogen when present in high concentrations. Acrylamide is considered a small molecule with a precursor ion *m/z* of 72.04, with important product ion transitions at *m/z* 55, *m/z* 44, and *m/z* 27. On Ultivo, detection of product ion *m/z* 27 has remained difficult due to limited transmission of low-mass ions. Therefore, the acrylamide product ion *m/z* 27 was evaluated as part of the small ion mode analysis.

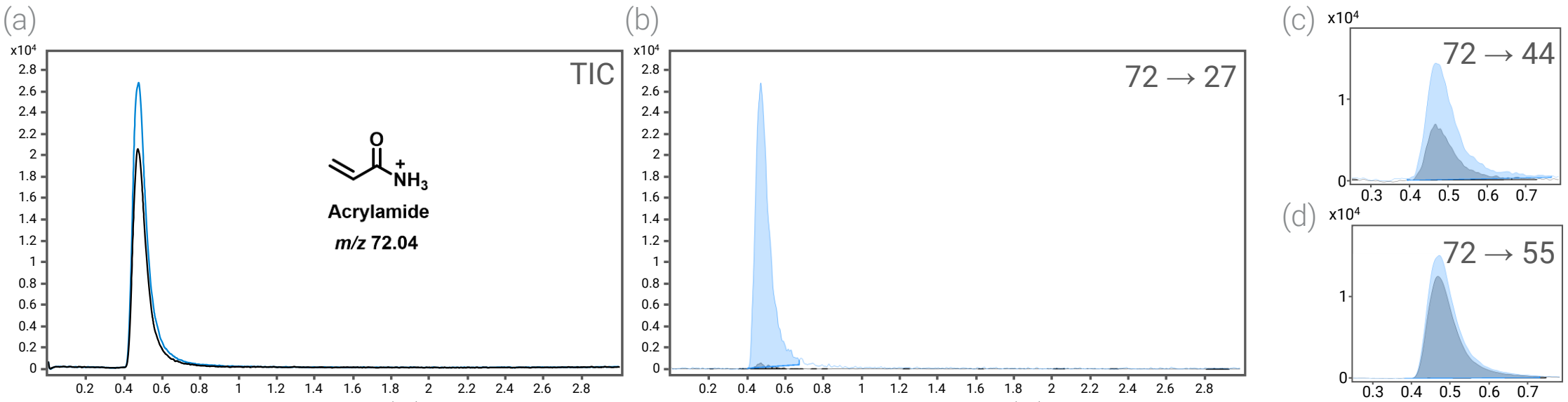

Figure 5. Overlaid chromatogram of acrylamide standard in standard mode (black) and small molecule mode (blue). TIC (a) and extracted MRM chromatogram at *m/z* 27 (b). Additional extracted MRMs at *m/z* 44 (c) and *m/z* 55 (d).

LC-MS analysis of acrylamide was completed and the TIC and extracted MRM chromatograms are shown in Figure 5. Similar to the analysis of nitrosamines, small molecule mode performance was evaluated by product ion transitions with a *m/z* of <50, notably product ion *m/z* 27. At every product ion transition, small molecule mode offered superior performance, with this enhancement being particularly evident for *m/z* 27, where it offered a 62-fold peak area increase at a concentration of 1 µM.

In standard mode, when using *m/z* 27 as the quantifier ion, <20% relative standard deviation (RSD) could not be maintained below a concentration of 100 nM. However, small molecule mode improves this limit (Figure 6, left), maintaining an %RSD of <20% down to 5 nM; offering a 20-fold increase in sensitivity with high calibration linearity (Figure 6, right)

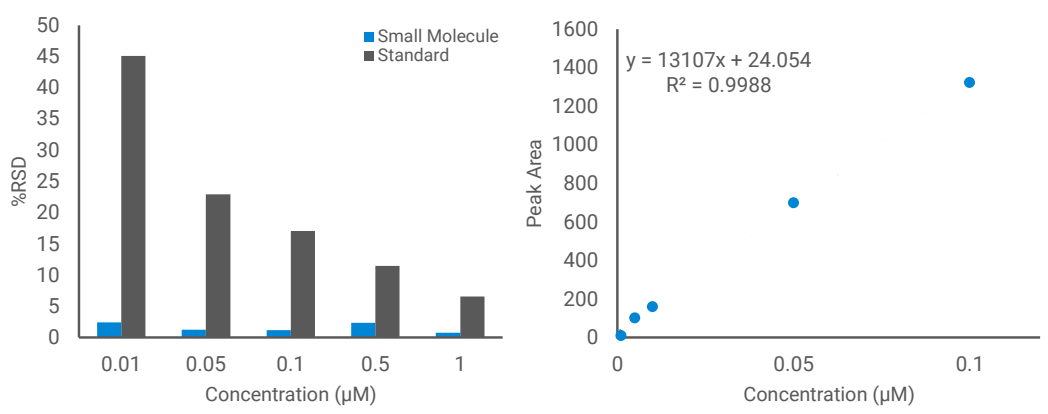

Figure 6. Comparison of %RSD of standard and small molecule modes within detection range of standard mode (left). Calibration curve of acrylamide using *m/z* 27 (right).

Conclusions

Low-mass ion transmission was enhanced by reducing the RF voltage amplitude applied to the vortex collision cell ion guide. This approach was first identified through ion-transmission simulations, leading to the implementation of a new operating mode, small molecule mode, which reflects the reduced RF voltage conditions.

The performance of small molecule mode was evaluated using low-mass product ion fragments below *m/z* 50. For nitrosamines with fragment ions near *m/z* 50, small molecule mode produced a 2.61-fold increase in peak area. In acrylamide, which generates a much lower-mass fragment at *m/z* 27, small molecule mode demonstrated substantially improved transmission, yielding a 61-fold increase in peak area at high concentrations and a 20-fold improvement in sensitivity. Overall, data suggests that low-mass ion transmission can be greatly enhanced by RF voltage tuning.

References

[1]Agilent Application Note 5994-6834

[2]Agilent Application Note 5994-0820

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