



WHITE PAPER

An introduction to ion chromatography mass spectrometry (IC-MS)

Ion chromatography mass spectrometry (IC-MS) is a powerful tool that can handle many challenging analytical tasks which cannot be performed adequately by IC alone. IC-MS is a robust, sensitive, and selective technique used for the determination of polar contaminants like inorganic anions, organic acids, haloacetic acids, oxyhalides, or alkali and alkaline earth metals. The ion chromatograph separates different ions and even the different ionic forms of the same element (speciation), and reduces matrix interferences from the sample. An integrated suppressor prevents salt contamination in the MS, and hence elongates the MS signal stability. After separation of the sample components via IC, mass selective detection guarantees peak identity with

low detection limits. The inclusion of automated Metrohm Inline Sample Preparation (MISP) allows not only water samples, but also chemicals, organic solvents, or post-explosion residues to be readily analyzed without need for extensive manual laboratory work. Automation of sample preparation steps besides the analysis results in more reliable and reproducible data with the elimination of human error.

This White Paper explains the benefits of IC-MS over IC in certain cases, the hyphenation of IC and different MS systems, as well as related norms and standards.

INTRODUCTION

Ion chromatography tackles difficult separation problems using the interactions between ionic species in liquid samples and a stationary separation column, typically utilizing conductivity detection. Mass detection as a secondary independent detector for IC records the mass-to-charge ratios of selected analytes of interest. As such, MS detection confirms the identity of compounds present in challenging matrices to ensure that the correct results are obtained without question. Co-eluting components can be quantified and detection limits are considerably improved.

Liquid chromatography mass spectrometry (LC-MS) is a well-established analysis technique. One drawback is that highly ionic compounds are difficult to separate on a typical high pressure liquid chromatography (HPLC) column [1]. For these analytes, IC-MS is able to succeed with specific columns tailored for ion separation. An inline suppressor reduces the ion load from the mobile phase to a minimum in order to optimize signal-to-noise ratios for both the conductivity and the MS detectors.

IC-MS is a robust and easy-to-use technique for the determination of analytes such as inorganic anions, organic acids, haloacetic acids, oxyhalides, or alkali and alkaline earth metals. Adding Metrohm Inline Sample Preparation (MISP) to the analysis allows not only water samples, but also chemicals, organic solvents, or post-explosion residues to be readily analyzed [2].

BENEFITS OF ION CHROMATOGRAPHY

All kinds of ionic species can be separated with ion chromatography, including different ionic forms of the same element. For instance, sulfur species (e.g., sulfate, sulfite, thiosulfate, and thiocyanate) are separated on ion exchange columns and not only are these individual components measured, but the total dissolved sulfur content can also be determined. Other typical speciations which can be measured by IC include chlorine (e.g., chloride, chlorite, chlorate, perchlorate), bromine (e.g., bromide, bromate), or nitrogen (e.g., nitrite, nitrate, azide). Additionally, ion chromatographs utilize a metal-free flow path (PEEK capillaries) that enables the trace detection of metal ions in liquid samples.

– INTERFERENCES

Matrix components that are uncharged, or that have the opposite charge of the analyte, usually elute with the solvent peak at the beginning of the chromatogram. Otherwise, matrix-rich fractions can be diverted to the waste by a time controlled switch valve. Only the eluted fractions with the analytes of interest are directed to the MS detector. Hence an initial chromatographic separation step significantly reduces matrix interferences for analyte detection when compared to direct injection to a mass spectrometric detector.

– SOLVENT COMPATIBILITY

Suppression of the aqueous mobile phase buffer (eluent) converts it into water, reducing background conductivity and also preventing contamination or precipitation in the MS detector. Any eluent can be used because the IC suppressor is resistant to organic solvents (up to 100%) and is pressure stable. Organic modifiers (up to 100%) can be added directly to the eluent to improve sample evaporation and MS signals. Since the Metrohm suppressor module (MSM) is solvent compatible, solvent addition after suppression is not necessary (this would further dilute the sample and reduce the sensitivity and robustness of the setup).



– SAMPLE PREPARATION

Adequate sample preparation should remove interferences prior to injection and improve detection limits of the analytes. Completely automating this step saves a significant amount of labor and time. Manual preparation steps are reduced to a minimum which guarantees more reproducible and reliable results.

These benefits and more can be achieved with Metrohm Inline Sample Preparation (MISP). Inline Ultrafiltration or Inline Dialysis can remove particles, oils, or proteins from samples before they reach the IC. Inline Dilution or Inline Neutralization can be used to automatically inject a sample with the optimal concentration and pH value for analysis. Injection of precise sample volumes (from the μL range up to the preconcentration of much larger volumes) can also be automated. A matrix elimination step removes any nonionic solvent from the sample matrix, if required.



CHARACTERISTICS OF MASS DETECTION FOR SMALL IONIC COMPOUNDS

With IC, most analytes can be detected via conductivity. Identification is done by comparing the retention time of defined peaks in a chromatogram with those of prepared standards. This can be challenging for samples with multiple components or with extreme concentration differences between matrix and analyte. With a mass detector used in series, correct peak identification is assured by correlating the conductivity signal with the respective mass-to-charge signal. Hyphenation of IC with a mass detector results in substantial broadening of the application field [3].

When placed in series after a sensitive (but non-selective) conductivity detector, a mass detector used as a second independent detector delivers valuable information about the mass-to-charge (m/z) ratio of compounds, and it can further increase the analysis sensitivity. Molecular ions are typically analyzed using single quadrupole mass spectrometers (**Figure 1**). High-end mass spectrometers such as triple quadrupoles have even greater sensitivity and can elucidate structural details with fragmentation studies. In contrast to molecular ions, elements are detected with ICP-MS [4]. IC-ICP/MS is a suitable solution for such studies.

Information about retention time, molecular mass, isotope patterns, and fragmentation are useful data

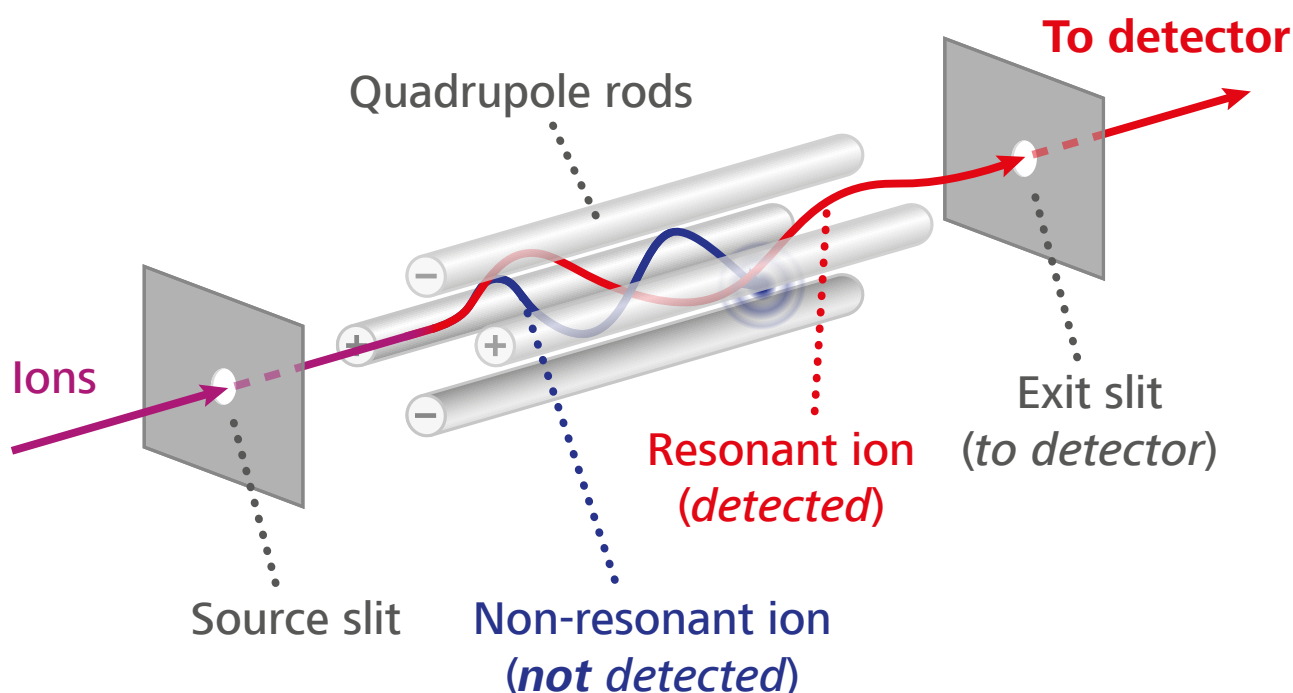


Figure 1. Illustrated schematic of the working principle of a single quadrupole mass spectrometer.

when screening samples for unknown ions. The two independent detection techniques (conductivity and mass detection) enable analysts to identify and confirm eluting substances with certainty.

– CONSIDERATIONS

Some technical details must be considered when coupling an IC instrument with a mass spectrometer. With IC-MS all relevant analytes are ions, i.e. they are already charged, which makes them easy to introduce into a mass detector.

Electrospray ionization is a soft ionization technique suitable for all IC-MS applications. In order to detect small ions such as chloride (m/z 35), the MS must be sensitive to low m/z values. This is achieved by optimizing the tune settings with suitable tuning solutions. A diverter valve placed between the IC and MS can be used to switch the sample flow from the IC to the MS when analytes of interest are expected. During instrument equilibration, automated sample preparation, or the elution of matrix components, the flow is diverted to the waste. This minimizes the chance of contaminating the MS, which also means less downtime and maintenance. Apart from ion detection, the conductivity signal is also a good tool to monitor the

status of the system (e.g., the background conductivity indicates the performance of the suppressor and the eluent stability).

Metrohm ion chromatographs can be coupled with different MS detectors (e.g., single quadrupoles, triple quadrupoles (MS/MS), ion traps, or Q-TOFs) from any manufacturer. Metrohm IC instruments can be fully operated by Waters Empower™ 3 software or Agilent OpenLab™ CDS software. The hyphenation of IC with single quadrupole detectors such as these examples is a user-friendly one software solution.

NORMS AND STANDARDS

Reliable determination and accurate quantification of contaminants has tremendous importance in many industry sectors. Norms assist laboratories from around the world to align their methods of analysis, determining the best course of action depending on the sample requirements. Expert panels in different workgroups debate and vote on the minutia of these standards, allowing industries to put great trust in them. Even though methods with IC-MS are not yet regulated in most cases, the technique is recommended in the following norms and standards (**Table 1**).



Table 1. Selection of norms that suggest IC-MS or IC-MS/MS as the analytical method. IC, being a special form of liquid chromatography, can also be used to fulfill norms that mention LC.

Norm	Title	Analytes	Technique
EPA Method 332.0	Determination of Perchlorate in Drinking Water by Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry	Perchlorate	IC-MS
EPA 6860 SW-846	Perchlorate in Water, Soils and Solid Wastes using Ion Chromatography/Electrospray Ionization/Mass Spectrometry (IC/ESI/MS or IC/ESI/MS/MS)	Perchlorate	IC-MS or IC-MS/MS
EPA Method 557	Determination of Haloacetic Acids, Bromate and Dalapon in Drinking water by Ion Chromatography Electrospray Ionization Tandem Mass Spectrometry (IC-ESI-MS/MS)	Haloacetic acids	IC-MS/MS
EPA Method 331.0	Determination of Perchlorate in Drinking Water by Liquid Chromatography Electrospray Ionization Mass Spectrometry (LC/ESI/MS)	Perchlorate	LC-MS or LC-MS/MS or IC-MS/MS
EPA 6850 SW-846	Perchlorate in Water, Soils and Solid Wastes using High Performance Liquid Chromatography/Electrospray Ionization /Mass Spectrometry (HPLC/ESI/MS or HPLC/ESI/MS/MS)	Perchlorate	HPLC-MS or HPLC-MS/MS
ASTM D 7599 - 16	Standard Test Method for Determination of Diethanolamine, Triethanolamine, N-Methyldiethanolamine and N-Ethyldiethanolamine in Water by Single Reaction Monitoring Liquid Chromatography/ Tandem Mass Spectrometry (LC/MS/MS)	Amines	LC-MS/MS

HYPHENATION OF IC AND MS DEVICES

An IC can be coupled to any MS type from any instrument supplier. Synchronization of both instruments typically utilizes a remote box (**Figure 2**) and a suitable cable connection to notify the MS detector to start recording once the sample is injected.

Regarding the hardware connection, a simple capillary connection between the conductivity detector and the MS detector is sufficient. The conductivity detector is a non-destructive detector with little dead volume (>1 µL) and its outlet capillary (a PEEK capillary with 0.25 mm inner diameter) is typically connected to either the injection valve of the MS, or directly to its source inlet.

Further additions may improve the application. A splitter can optimize the sample flow rate that reaches the MS for optimal signal-to-noise ratios. A switch valve can be used to channel the flow into the MS only when elution of analytes of interest is expected. The

flow is diverted to the waste when matrix peaks elute, during instrument equilibration, and automatic sample preparation, in order to keep contamination of the MS to a minimum. Some applications require reagent addition prior to the MS analysis, or even need an additional suppressor module to adjust the pH value.



Figure 2. Remote Box used to synchronize IC and MS instruments.

– GENERAL APPROACH FOR ALL MS TYPES

If there is no common software, both instruments are operated via their own software. The sample tables therefore must be copied to both softwares, and data evaluation is typically done in the software of the respective instrument (e.g., processing of the conductivity signal in the IC software and of the MS signals in the MS software). This approach is often used for high-end MS analysis with dedicated MS software.

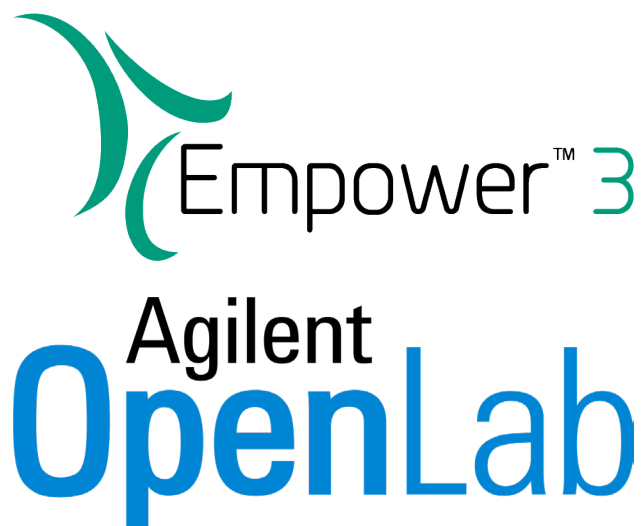
For example, the IC is operated with MagIC Net from Metrohm, and the MS is controlled by the Agilent MassHunter™ software, or the Waters MassLynx™ MS software. The operation of such instrumentation requires trained personnel and full compliance since the complete combination is not simple. These flexible and high performance setups unleash their full potential in development laboratories and research institutes.

– IC DRIVERS FOR ONE COMMON SOFTWARE

Native IC drivers allow the control and operation of the IC equipment in the same software as the MS (including autosamplers and Dosinos). One software for both IC and MS enables user-friendly handling and ensures robust operation. Software trainings take less time since only one software is involved. **Data integrity and full compliance are guaranteed.**

Currently, only single quadrupoles are integrated in chromatography data system (CDS) software platforms. These IC-MS setups are not only found in universities, but they are also suitable for use in high throughput laboratories (e.g., for process monitoring or in quality control).

Metrohm offers solutions for Waters Empower™ 3 and Agilent OpenLab CDS (Metrohm IC Driver for Empower™ 3, Metrohm IC Driver for OpenLab CDS).



SUMMARY

IC-MS is a powerful analytical tool in the laboratory, especially for challenging samples which contain multiple analytes in highly varied concentrations. LC-MS is already a well-established measurement technique, and the unique combination of IC with MS is becoming more and more popular for applications involving ionic and polar molecules.

Ion chromatography utilizes a suppression module to minimize the background ions and to increase the signal-to-noise ratio in both conductivity and MS detectors. The conductivity detector is highly sensitive to small inorganic ions and has a wide linear range of detection. A mass detector is specific for m/z and is very sensitive for a wide range of molecules. That is why the combination of IC and MS is ideal to solve analytical challenges in many application fields.

References

[1] Metrohm AG. *When HPLC fails: IC in food, water, and pharmaceutical analysis*, Metrohm AG: Herisau, Switzerland, 2019. **WP-045**.

[2] Metrohm AG. *Analysis of Anions and Oxoanions using Ion Chromatography Mass Spectrometry (IC-MS)*, Metrohm AG: Herisau, Switzerland. **8.000.6101**.

[3] *Application of IC-MS and IC-ICP-MS in Environmental Research*; Michalski, R., Ed.; John Wiley & Sons, Inc: online, 2016. **DOI:10.1002/9781119085362**

[4] Metrohm AG. *Coupling of ion chromatography and plasma mass spectrometry*, Metrohm AG: Herisau, Switzerland, 2017. **WP-008**.

Further related Metrohm literature

A strong combination – Coupling of Metrohm ion chromatography and mass spectrometry **8.000.5250**

Metrohm meets Empower 3 – Ion chromatography with the Chromatography Data Software (CDS) from Waters **8.102.5004**

IC Driver for Agilent OpenLab CDS – A perfect combination: Metrohm Ion Chromatography and OpenLab CDS Software **8.102.5007**

IC-ICP/MS with Metrohm – Coupling of Metrohm ion chromatography and mass spectrometry with inductively coupled plasma **8.000.5241**

Metrohm Application Finder: Selection of IC-MS Applications

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