Compact Mass Spectrometry: A Complete Reaction Monitoring Solution

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Background

Mass spectrometry is an ideal solution for reaction monitoring, however chemists are often required to send samples to a central lab and wait for results. A mass spectrometer at the bench is an ideal solution, and new developments in compact mass spectrometry allow for:

- A variety of novel sample techniques that are fit for an extensive variety of samples, including liquids, solids, volatiles, TLC plates, SPME fibers and more

- Minimal sample preparation for ease of use and results in less than 30 seconds

- Affordability, providing mass spectrometry to more labs than ever before

This white paper highlights the versatile features and multiple sample techniques of CMS, provides case studies, and looks into future potential as the MS market continues to grow.

INTRODUCTION

Real-time reaction monitoring, fast answers, ease of use, versatility – these are all essential components for a mass spectrometer in the modern chemistry lab. In an industry where waiting for a central lab to provide answers is often times not an option, the growth of benchtop Compact Mass Spectrometers (CMS) has grown to suit the needs of those across the globe. With a wide range of sample techniques to fit a variety of applications, CMS systems can offer results quickly, saving time and maximizing progress in the lab.

To speak to the acute need of an affordable, compact MS solution, chemists in the United Kingdom are now facing the loss of the EPSRC UK National Mass Spectrometry Facility at Swansea University. Their unfortunate announcement to close the center has left countless chemists in academia in search for alternative mass spectrometry solutions.

In addition to affordability, CMS systems can offer a variety of prep-free sampling techniques for solids, liquids, gases, and even air-sensitive compounds. The ability to quickly and easily switch ionization sources (ESI and APSI) as well as sample techniques make CMS systems an indispensable tool in a busy lab – all in a benchtop package.

This white paper highlights the versatile features and multiple sample techniques of CMS, provides case studies from current CMS users in a variety of applications, and looks into future potential as the MS market continues to grow. Learn from users using CMS systems in teaching environments, chemists in reaction monitoring applications, and even testing applications for cannabis-related compounds.

THE BACKGROUND OF MASS SPECTROMETRY AND THE PROGRESSION TOWARD COMPACT SYSTEMS

Mass spectrometry was developed in the early 20th century to measure the masses of atoms and was used to showcase the existence of isotopes. Fast forward 100 years, and mass spectrometry has advanced to become an essential tool in chemical analysis, ranging from application in drug discovery, clinical diagnostics, food and beverage analysis, natural products and more.

In recent years, and increasing ease of use has prompted a broader range of scientific professionals to explore how these instruments could benefit their work. In the pharmaceutical industry, for example, MS was used almost exclusively by researchers in drug metabolism and bioanalysis. Today, scientists in discovery chemistry, process chemistry, chemical engineering, manufacturing, and formulation sciences are also working with MS. New MS users are also appearing in academia and other industries. The medicinal and legal cannabis market, for example, has emerged as a growing segment.

A growing number of novel, prep-free sample techniques has also extended the utility of these compact systems, which are typically used for compound identification, reaction monitoring, mass-directed purification, and purity determination.

For example, with the Advion expression CMS system, multiple inlet techniques including the atmospheric solids analysis probe (ASAP), inert atmospheric solids analysis probe (iASAP), volatile atmospheric pressure chemical ionization (vAPCI) source, Plate Express thin-layer chromatography (TLC) plate reader, and direct syringe injection provide flexibility for sample analysis without the need for complex sample preparation. “The iASAP mode is ideal for our typically very air-sensitive compounds,” Krossing explains. “We are able to get MS spectra of very sensitive compounds like the Ni(I)-salt [Ni(cod)2]+[Al(ORF)4] –,” he says. (Note: cod stands for cyclooctadiene.)

TECHNIQUES USING ADVION CMS

Advion's versatility enables researchers to use a variety of techniques:

- Thin-layer chromatography (TLC)/compact mass spectrometry (CMS) using Advion's Plate Express allows automated analysis of TLC plates in less than 30 seconds.
- An atmospheric solids analysis probe (ASAP) provides direct mass analysis of liquid and solid samples, and an inert ASAP option can analyze air-sensitive compounds.
- A volatile atmospheric pressure chemical ionization source enables easy headspace analysis of volatile compounds.
- High-performance liquid chromatography and ultra-high-performance liquid chromatography (UHPLC) systems can be configured to suit the needs of any lab, from simple manual injection to a fully streamlined UHPLC system, are seamlessly integrated with the CMS.
- Flow injection/direct syringe injection.
- Flow chemistry reaction monitoring.
- Flash chromatography.
- Preparative liquid chromatography.

INCORPORATING CMS INTO UNDERGRADUATE CHEMISTRY EDUCATION

"Our undergraduate program in chemistry is fortunate to have a nice inventory of analytical instrumentation for use in various lab courses and student-faculty research," Flowers says. However, this hasn't always been the case. Until recently, its MS instrumentation comprised just two gas chromatography/MS systems and an ambient pressure gas analyzer, limiting his team to electron ionization of gaseous and volatile liquid samples.

The group chose to acquire an Advion CMS because of its low cost, portability, and flexibility. In particular, having the ASAP available for APCI mode was an attractive feature. Since it gives results in seconds, more students are able to directly participate in experiments within the time constraints of class sessions. "It supported our development of lab projects with forensic and pharmaceutical emphasis," Flowers says.

Since then, Pembroke students in an upper-level forensic chemistry course have used the ASAP to test for trace evidence of the presence of drugs and explosive compounds. In one experiment, mock evidence was prepared by the lab instructor by solution-depositing chosen analytes onto small fragments of glass and plastic. Students then subjected the samples to microscale solvent extraction followed by mass spectral analysis of the sample extracts. The analysis involved briefly immersing the ASAP tip into the extracts and then inserting it into the CMS APCI ion source port.

INCORPORATING CMS INTO UNDERGRADUATE CHEMISTRY EDUCATION, CONTINUED

Students in an upper-level analytical chemistry course used the ASAP to develop rapid quantitative methods for analyzing nonprescription pharmaceuticals containing acetaminophen, aspirin, and/or caffeine. Various approaches have been explored, including the use of an internal standard to improve precision for prepared sample (solutions) analysis. The students also investigated the direct analysis of intact preparations, including tablets and capsules.

Flowers and his colleagues are also developing various projects for introductory chemistry courses. These will serve relatively larger lab sections (approximately 24 students). Pairs of students will perform analyses using the ASAP during brief, reserved time slots (approximately 10–15 minutes long) within the lab section's normal two- to three-hour meeting time. "The work associated with these projects will involve analysis of standard samples to demonstrate basic measurement concepts and, perhaps, simplified adaptations of the upper-level lab projects already completed," Flowers says.

CMS IN A SELF-OPTIMIZING CHEMICAL SYNTHESIS WORKFLOW

"Standard detectors we use in our work can be problematic when trying to discern what is in a product mixture leaving a flow reactor," says Daniel E. Fitzpatrick, Ph.D. candidate and researcher in University of Cambridge's Steven Ley group and founder of ChemInventory. For example, ultraviolet detectors are useful only in very restricted flow-based situations and don't give compositional information. Infrared spectroscopy is a step up from this but suffers from issues when peaks in starting materials, products, and by-products overlap. Some transformations may also lead to undetectable changes in an IR spectrum. Flow-based nuclear magnetic resonance, meanwhile, is expensive and lacks resolution at a benchtop level.

Fitzpatrick says CMS struck the perfect balance between cost, ease of use, and detection capabilities his group needed. "We're able to get large amounts of relevant information about reaction mixtures in real time without worrying in most cases about overlapping peaks or detection signals." This information is analyzed by their control systems to make decisions about product stream composition and has allowed them to automate procedures such as reaction telescoping, process start-up, and self-optimization.

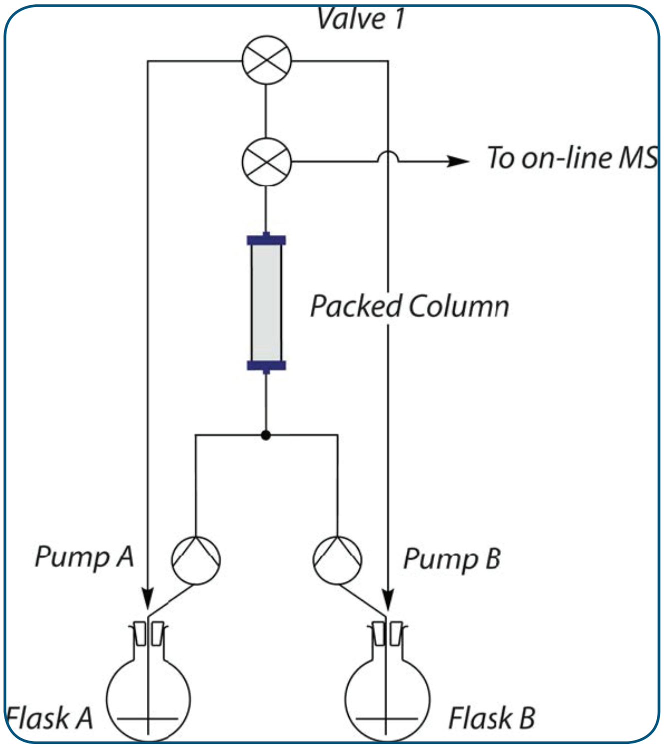

FIGURE 1:

The experiment was set up on a Vapourtec R2/R4 unit, which provided support for pump A, pump B, and valve 1, along with temperature control.

CMS IN A SELF-OPTIMIZING CHEMICAL SYNTHESIS WORKFLOW, CONTINUED

The group published a paper on a novel platform they devised for reaction monitoring, control, and autonomous self-optimization for chemical synthesis. They developed a modular software system that lets researchers monitor and control chemical reactions via the internet.

They then used this system (dubbed LeyLab) to demonstrate reaction automation to maximize the output from a fixed volume of catalyst. The process involved passing a fixed volume of reaction solution through a small volume of catalyst in a packed column multiple times. A commercial flow reaction system connected to an Advion CMS provided the required pump, temperature, and switching valve support.

READ THE PAPER

A Novel Internet-Based Reaction Monitoring, Control and Autonomous Self-Optimization Platform for Chemical Synthesis to use a variety of techniques:

http://pubs.acs.org/doi/abs/10.1021/acs.oprd.5b00313

USING CMS AS A STANDARD REACTION MONITORING TOOL

“We investigate ionic systems to the fullest extent, both experimentally and theoretically. In doing so, we want to understand and exploit the fundamental principles that determine the behavior of such systems,” University of Freiburg’s Krossing says.

As a result of bringing an expression CMS into his lab, “We can now use mass spectrometry as a standard analysis tool for reaction monitoring,” he says. Ph.D. students can measure their own samples directly after synthesis. They can even change the ion source on their own according to the nature of their samples. Samples with large memory effect are no longer problematic because the inlet capillary can easily be cleaned. In addition to allowing highly air-sensitive compounds to be analyzed without difficult outside a glove box, Krossing says the Advion CMS they use has a “simple but very effective inlet for air-sensitive compounds in the ASAP mode.”

This iASAP technique is adapted from the ASAP, which is used for fast analysis of liquids and solids. The ASAP allows chemists to simply swipe or dip the tip of the probe into the sample of interest, then insert it directly into the CMS to see results in less than 30 seconds. With the iASAP adaptation, the probe now serves as a seamless sample transport technique from a glove box or Schlenk line to the MS without decomposition.

CANNABIS ANALYSIS

Scientists at Advion have also used CMS to detect and quantitate cannabis-related compounds—an area of growing interest as the medical use and legalization of the drug has become more common.

Cannabis produces more than 400 compounds, approximately 80 of which are unique to the plant. Many strains of cannabis have been bred, but only some of them are used medicinally. A major challenge is that many strains have high levels of the psychotropic compound tetrahydrocannabinol (THC). Labs making products for medicinal uses are sometimes more interested in other cannabinoids, terpenes, and secondary plant metabolites, such as cannabidiol (CBD), which may be down regulated in plants with a high THC content.

CANNABIS ANALYSIS, CONTINUED

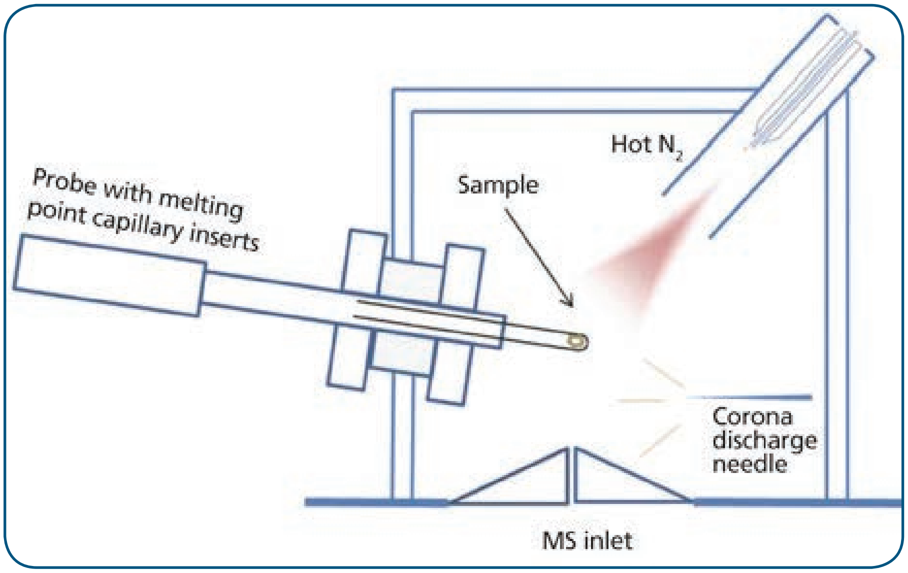

FIGURE 2:

Schematic of the ASAP ion source inlet as deployed in a single-quadrupole CMS.

Cannabis can also be contaminated with pesticides. Although it is currently illegal to use pesticides on this crop, analyses have shown significant levels of pesticides, particularly bifenthrin. Since most cannabis is smoked and pesticides can pass into the mainstream smoke at rates of over 50%, there is a major risk to consumer health.

Finally, cannabis is still illegal in many states, so it is important to be able to detect its presence in products that would be deemed contraband. With these issues in mind, the Advion team set out to create analytical chemistry workflows to explore three potential aims: (1) creation of a simple and legally defensible cannabis detection method to test suspected contraband material, (2) detection and quantification of pesticides, and (3) characterization of the major cannabis components to support labeling of products for consumer consumption. The team devised three CMS-based workflows with different sample inlet systems: the ASAP, the Plate TLC extraction device, and an HPLC inlet.

All three workflows provided excellent results. With the contraband-detectionfocused workflow, even a brief exposure of fingers and shirt sleeves to contraband material provided sufficient residue of cannabinoids for detection via swabs. The researchers also point out that a CMS system is easily transportable by applying a mobile attenuation module. This makes the CMS comply with MIL-STD-810 (rev G), a U.S. Military Standard that evaluates how equipment stands up to environmental stress, and makes it fit for field work in drug enforcement.

The pesticide detection workflow provided sufficient sensitivity for detecting and quantifying four common pesticides—carbaryl, carbofuran, captan, and malathion. However, the authors note that maximum tolerance levels of these have not yet been established.

Quantitation of compounds in cannabis is complicated by the fact that both THC and CBD are isobaric compounds that cannot be identified by mass alone. Nonetheless, using automated TLC plate sampling and CMS, the researchers were able to separate cannabinoids from their matrix components. The advantages of using TLC/CMS, the researchers note, “lie in its low cost and simple integration into standard laboratory workflows with quick and unequivocal compound identification.”

IN BRIEF

Compact mass spectrometry detectors have numerous advantages and can be applied to many types of analytical challenges. With the introduction of these instruments, diverse researchers are now exploring novel uses in a wide range of applications. We expect the technology to continue to advance, with an even wider range of prep-free sample techniques under development for fast reaction monitoring at the bench.

ELEVATED SOFTWARE FEATURES FOR ADVANCED DETECTION RESULTS

With compact mass spectrometry (CMS) systems, your ability to process samples quickly and efficiently also requires a robust integrated software platform for clear, easy-to-interpret results. The Advion CMS offers several integrated software modules that provide high-level quantitative and analytical results.

- Mass Express: The software has been developed to provide chemists with answers in the fewest steps and shortest period of time possible in an easy-to-use interface. The simple software incorporates a mass detection tool, Peak Express, and offers an optional quantitation module, Quant Express.
- Peak Express: This patented software provides a new type of mass spectrum, Delta Spectrum (ΔS). The ΔS can look beyond chemical noise and automatically detect even the smallest peaks without knowing the mass-to-charge ratio in advance.
- Quant Express: Optional with the Mass Express 4.0 software suite, Quant Express is a full feature quantitation application for liquid chromatography/mass spectrometry data. The quantitation method can be configured in Mass Express before the analysis or in Quant Express post-analysis, and it supports calibration curves, internal standards, quality controls, and unknowns using selective ion monitoring or scan mode data. An enhanced peak detection algorithm ensures highest accuracy and ease of use.
- CheMS: Perfect for teaching labs, the interface allows users to quickly select the workflow and type of compound they wish to analyze in just a few clicks of the mouse. The software automatically optimizes the ion source and data acquisition parameters to ensure they get the data they need for decision-making.

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