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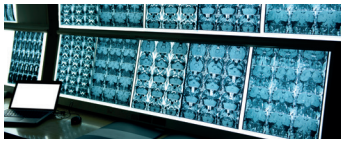

Optimizing Conditions for High Quality Data with ICP-MS

Ed McCurdy, Agilent Technologies Inc.

In this issue of the ICP-MS Journal, we look at some of the factors that can affect the quality of analytical results acquired using ICP-MS.

Researchers in Australia have shown that the higher sensitivity and better interference removal provided by ICP-QQQ enables laser imaging analysis to be performed with much higher resolutioin.

We also show how method setup tools help identify optimum MS/MS mode conditions for difficult applications using ICP-QQQ.

ICP-MS performance is also dependent on calibration standards, QC solutions, and the quality of sampling and skimmer cones, as shown in the article on page 7.

Figure 1. Agilent 8900 Triple Quadrupole ICP-MS.

High-Resolution Elemental Bio-Imaging of Gd in Skin Tissue using LA-ICP-QQQ

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Introduction

Gadolinium-based contrast agents (GBCAs) are drugs that are given intravenously to improve the contrast of Magnetic Resonance Imaging (MRI) scans. The retention of gadolinium (Gd) originating from GBCAs in biological tissues has caused major concerns in the past decade (*1, 2*). Patients with renal dysfunction have an increased risk of nephrogenic systemic fibrosis (NSF) after administration of GBCAs. The most obvious indication of NSF is fibrosis and necrosis of the skin; however, other organs, including the brain, may also be affected. It is currently thought that GBCAs undergo a transmetalation process in which Gd is released and precipitates together with calcium phosphate to form small insoluble plaques. It is suspected that these plaques trigger fibrosis (*2*).

Experimental

Sample preparation: NSF skin samples were obtained from a 25-year-old female patient in April 2013. The patient had undergone MRI examinations with Gd-DTPA and Gd-HP-DO3A in 2002 and 2005, respectively. The sample containing fibrotic skin areas was immediately frozen, then cut into 20 µm thick tissue sections, which were mounted on microscope slides for analysis.

Calibration: For quantification of Gd and other related elements in brain tissue, matrix-matched lamb brain tissue was spiked with a defined amount of elemental standard. A 20 µm section of each spiked brain tissue standard was cut and mounted on a microscope slide. For cross-quantification of the brain standard spikes, tissue sections were digested in 1 mL 30–32% H_2O_2 and 4 mL 70% HNO_3 and analyzed using conventional liquid sample introduction with an Agilent 7500cx ICP-MS (*3*). The elements of interest and their calibration standard levels are shown in Table 1.

Table 1. Calibrated elemental levels in matrix-matched tissue sections made of lamb brain. Units: µg/g

Level	P*	Ca	Fe	Zn	Gd
1	0	37.7	15.3	11.3	0.00
2	0.001	43.0	16.5	11.4	0.21
3	0.01	48.7	19.0	14.9	2.21
4	1	64.1	37.5	24.0	10.6
5	10	86.4	59.8	36.1	21.1

* High background levels of P in the matrix-matched tissue standards required the analysis of liquid standards to demonstrate the benefits of ICP-QQQ compared to ICP-QMS.

Instrumentation: A New Wave Research NWR193 laser ablation unit (Kennelec Scientific, Victoria, Australia) was coupled to an Agilent 8800 Triple Quadrupole ICP-MS (ICP-QQQ) and, for comparison, to an Agilent 7700 ICP-MS. For the ICP-QQQ method, oxygen cell gas was used and P and Gd were monitored as oxide ions with a +16 u mass shift. Ca, Fe and Zn were monitored on-mass. The 7700 ICP-MS tune was developed according to Lear *et al* (*4*). The lamb brain standards were analyzed by LA-ICP-MS and LA-ICP-QQQ. Because of the high endogenous P background in the lamb brain, P concentrations in the skin sections were quantified by comparison to the aqueous calibration standards instead. Element distribution images were processed using imaging software by Robin Schmid (University of Münster).

Results and discussion

The comparison of the data obtained using LA-ICP-QQQ and LA-ICP-MS showed improved limits of detection for all elements with LA-ICP-QQQ, as shown in Figure 1. For P, there was a 16-fold improvement of the LOD using ICP-QQQ. Background signals for Gd dropped to zero using ICP-QQQ, allowing the measurement of individual Gd ion counting events. Compared to LA-ICP-MS, the Gd LODs with LA-ICP-QQQ were improved 6-fold.

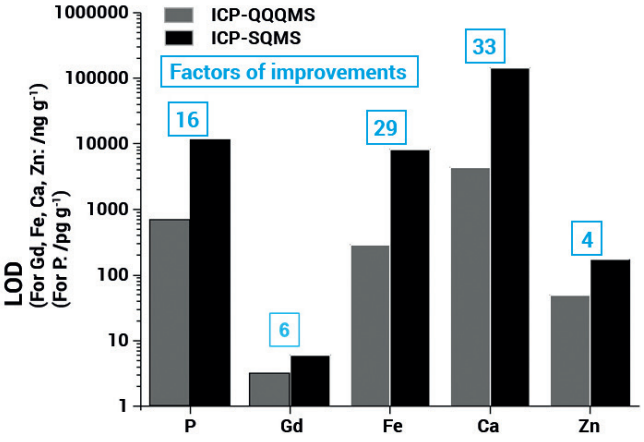

Figure 1. Comparison of LOD obtained by ICP-QQQ and ICP-MS.

Areas of interest of Gd in NSF skin tissue: Gd and associated elements were analyzed in NSF skin tissue. A skin biopsy section was first analyzed with a laser scan speed of 200 µm/s and a laser beam spot size of 50 µm. This overview acquisition showed high levels of Gd in the sub-cutis. A parallel tissue section was then analyzed at higher resolution.

High-resolution imaging: Laser spot size (and therefore spatial resolution) is inversely proportional to LOD. The improvement of the LOD for Gd using LA-ICP-QQQ enabled a high-resolution image to be acquired, as described in reference 5. This elemental distribution data was obtained using a laser scan speed of 20 µm/s and a laser beam spot size of 5 µm.

The higher resolution image revealed correlated hotspots of Gd, Ca, P, and Zn with diameters of approximately 50 µm. Fe distribution was not found to be correlated. Most Gd throughout the area of interest was located within the small deposits, where Gd levels exceeded 100 µg/g in the center. The correlations in shape and location indicated that Gd co-precipitated with calcium and zinc phosphate. Highest Gd levels were found within the center of the deposits, while the shell appeared to contain increasing fractions of P and Ca. This may indicate that Gd/Ca phosphate deposits function as nucleation centers, favoring subsequent crystal growth.

Conclusion

The improved detection limits of LA-ICP-QQQ allowed improved spatial resolution for interrogation of small deposits of Gd, P, Ca, and Zn with diameters of approximately 50 µm. Calibration of Gd using matrix-matched tissue standards revealed that Gd exceeded 100 µg/g within these deposits. The data supports the hypothesis that Gd co-precipitates with calcium and zinc phosphate, forming plaques that may trigger fibrosis.

References

1. FDA Drug Safety Communication, FDA warns that gadolinium-based contrast agents (GBCAs) are retained in the body; requires new class warnings, 2018, https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-gadolinium-based-contrast-agents-gbcas-are-retained-body
2. D. Clases, M. Sperling and U. Karst, *TrAC - Trends Anal. Chem.,* **2018**, 104, 135–147.
3. D. J. Hare, J. Lear, D. Bishop, A. Beavis and P. A. Doble, *Anal. Methods,* **2013**, 5, 1915–1921.
4. J. Lear, D. J. Hare, F. Fryer, P. A. Adlard, D. I. Finkelstein and P. A. Doble, *Anal. Chem.,* **2012**, 84, 6707–6714.
5. D. Clases *et al., J. Trace Elem. Med. Biol.* **2019**, 51, 212-218

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Tools and Techniques for Simple and Consistent Method Setup with ICP-MS/MS

Ed McCurdy, Naoki Sugiyama, and Glenn Woods, Agilent Technologies Inc.

Introduction

As ICP-MS has become more widely used in routine applications, the technique has been steadily getting easier to use. Some functions – such as autotuning and preset methods – are aimed at improving ease-of-use. Other developments – for example improved matrix tolerance and increased dynamic range – contribute to simpler overall analytical workflow.

Helium (He) cell gas mode simplifies routine single quadrupole ICP-MS applications by attenuating most of the common (polyatomic) spectral interferences using a single set of conditions. However, no equivalent universal approach applies to reactive cell gas methods.

ICP-QQQ uses double mass selection – MS/MS – to provide much more effective control of reaction chemistry than single quadrupole or bandpass ICP-MS configurations. MS/MS ensures that only the target analyte mass and any on-mass interferences enter the reaction cell, so variability in sample composition does not affect the reaction processes or measured ions. Reaction gas modes are, however, more analyte-specific than helium collision mode, so method setup tools are beneficial to simplify routine operation.

Predefined and Published Methods

Preset methods for ICP-QQQ define standard settings (including cell gas mode and flow rate, preferred analyte isotope and product ion mass) for many common analytes. For other analytes and methods, published application notes and peer-reviewed journal articles provide a useful resource for users setting up new ICP-MS/MS reaction mode methods.

ICP-MS/MS methods can often be applied to a range of sample types. But the optimum cell gas mode is usually specific to the analyte/interference(s) being separated.

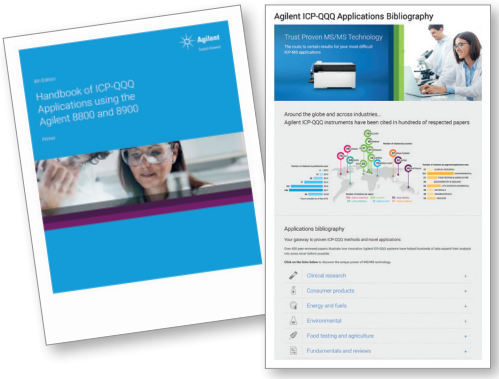

Figure 1. Proven Agilent ICP-MS/MS methods can be obtained from published application notes and journal articles.

Published tables of ion/molecule reaction rates can help identify the best reaction gas for a given application (*1, 2*). Reaction rates for all elements have been assessed for common reaction gases H_2, O_2, and NH_3 (Figure 2). The classification of elements according to the type and rate of reactions can assist with developing a new method.

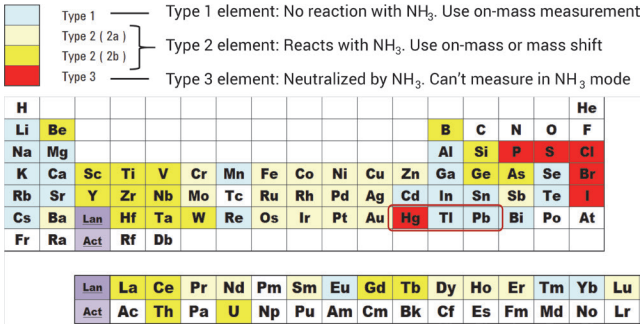

Figure 2. Reactions of elements with NH_3 cell gas.

For example, Hg is a Type 3 element, whose ions are neutralized by reaction with NH_3 cell gas, as shown in Figure 2. Pb (Type 1) does not react, so NH_3 cell gas can be used to resolve the ^{204}Hg isobaric overlap on ^{204}Pb.

In this article, we use ^{176}Hf as a case study to show how element reactivity classification can be used to guide

method setup. The usual preferred isotope for Hf analysis is ^{178}Hf, but ^{176}Hf is used for some applications, such as Hf isotope geochronology. The ^{176}Hf isotope can be difficult to measure in geological materials due to isobaric overlaps from the rare earth elements (REEs) ^{176}Lu and ^{176}Yb and oxide ions of ^{160}Gd and ^{160}Dy.

The element classification in Figures 2 and 3 indicates that Hf (Type 2b) reacts with NH_3 and should be easily separated from Yb (Type 1), which doesn't react.

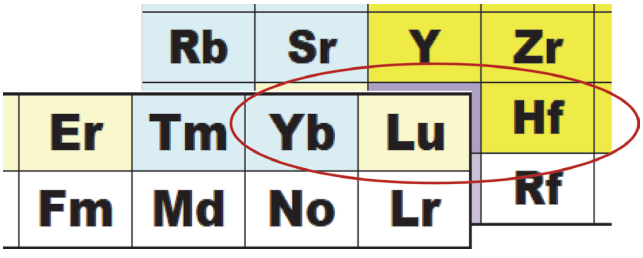

Figure 3. Element reactivity with NH_3 to guide method setup for Hf.

However, Lu (Type 2a) does react with NH_3, so resolving ^{176}Hf from ^{176}Lu relies on the two analytes reacting differently with NH_3 cell gas. This can be investigated and confirmed by Product Ion Scanning using ICP-MS/MS.

Product Ion Scanning

Product Ion Scanning uses Q1 to select the mass of the target analyte ion, *m/z* 176 in the case of ^{176}Hf. Q2 is then scanned across the mass range where useful product ions might appear (*m/z* 175 to 265). A scan is acquired for a single element Hf standard and for a representative sample or synthetic matrix. The two scans indicate product ions that are formed from:

a. The target analyte isotope (^{176}Hf) alone, and

b. Any other ions present at *m/z* 176, from sample matrix elements, interferences, or other analytes

Comparing the two scans shows which ^{176}Hf product ions are free from overlap by product ions from other components of the sample. This comparison is illustrated in the overlaid spectra in Figure 4, which shows NH_3 product ions from *m/z* 176 for a 10 ppb Hf standard (in grey) and a 1 ppm REE mix (in pink). The product ions that only appear in the grey (Hf) solution are clearly identifiable.

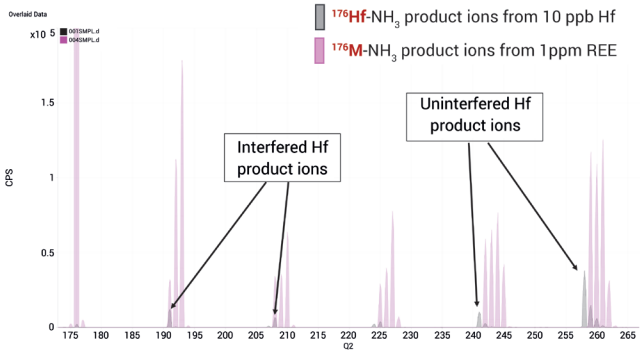

Figure 4. Product ion scans for *m/z* 176 in Hf standard and REE mix. Preferred, interference-free product ion is $HfN(NH_3)_4^+$ at *m/z* 258.

MS/MS is essential for product ion scanning, as it ensures that only ions from the target mass can enter the cell and react. Without MS/MS, other product ions can form, overlapping the target analyte product ions, as illustrated in Figure 5. The left spectrum shows a detail from Figure 4 (in MS/MS mode), and the right spectrum shows the same product ion scan with a Q1 resolution of 3 u (bandpass operation). The target product ion $^{176}HfN(NH_3)_4^+$ is overlapped by $^{175}LuNH(NH_3)_4^+$ in bandpass mode, as ^{175}Lu is not excluded from the cell.

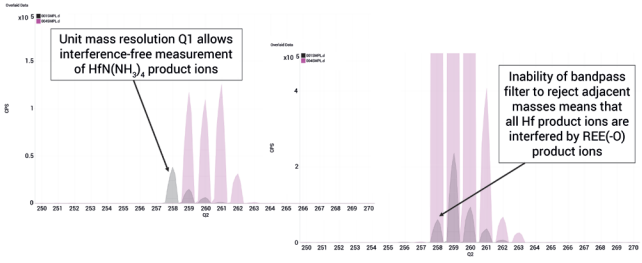

Figure 5. Product ion scans with MS/MS (left) and bandpass (right). $^{176}HfN(NH_3)_4^+$ is overlapped by $^{175}LuNH(NH_3)_4^+$ with bandpass.

Conclusion

The Q1 mass filter of ICP-MS/MS ensures that reaction processes are controlled and consistent. This makes reaction mode method setup simpler with ICP-MS/MS than with single quadrupole or bandpass MS.

References

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2. Agilent technical note, 2014, 5991-4585EN

Agilent Expands Inorganic Chemical Standards Portfolio

Fred Chan and Mitesh Patel, Agilent Technologies Inc.

Expanded Range of ICP-MS Standards

Agilent recently acquired ULTRA Scientific Inc., a provider of chemical standards and certified reference materials (CRMs), expanding its range of ICP-MS chemical products to over 1,000 items.

The new ULTRA products extend Agilent's existing range of individual inorganic standards and ICP-MS tuning, calibration, and internal standard mixes. The expanded range includes workflow-specific reference materials, CRMs, quality control (QC) and calibration standards, together with spiking solutions, interference standards, mixes, and kits. We also offer a variety of standards and kits for many regulatory methods such as US EPA 200.8 or CLP, and USP<232>/ICH Q3D.

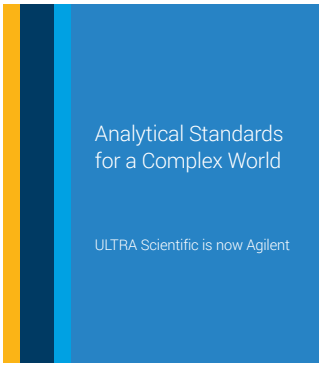
All Agilent CRMs are formulated to the highest standards using high-purity raw materials that are traceable to NIST SRMs, and concentrations are confirmed against independent, second-source standards. The final products are packaged in an ISO Class 7 clean room to guarantee the highest possible purity.

You can also order custom ICP-MS standards online. A dedicated custom ordering portal quickly generates a competitively priced quote, and fast delivery is assured. Custom products are manufactured to each customer's specific quality requirements. They are then certified by a team of expert chemists in Agilent's ISO 9001, 17025, and 17034 accredited facility in Rhode Island, USA. To request a quote, visit www.agilent.com/chem/standards.

Tips and Tricks for Agilent ICP-MS Standards

- Store CRMs at a controlled room-temperature per USP 35 (10.30.60). Do not freeze, heat, or expose solutions to direct sunlight. Minimize exposure to moisture or high humidity.
- Don't underestimate the importance of good mixing when preparing standards. A simple swirl is not enough. Make a habit of inverting and shaking the container several times.
- Avoid pipetting directly from the standard container. Decant a small volume into a clean, metal-free container and pipette from this container. Never return unused standard to the original container.
- Standards should be replaced well before the expiry date. This ensures accuracy by minimizing transpiration losses (water loss) and contamination risks. The chemical stability and transpiration losses determine the shelf life.

More Information and How to Order



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We Put our ICP-MS Interface Cones to the Test in a Cone Comparison Study

Gareth Pearson, ICP-MS Supplies Product Manager, Agilent Technologies Inc.

Introduction

Agilent ICP-MS interface cones are manufactured to strict specifications, confirmed by our 100% quality inspection, and protected by our custom packaging. As a result, you can be sure you'll get the sensitivity and stability that you expect from your single-quadrupole and triple-quadrupole ICP-MS systems. In our study, we compared Agilent interface cones with cones from third-party suppliers, focusing on properties critical to ICP-MS performance. Here's what we found.

Not All Cones Are Created Equal

We uncovered differences in weight between Agilent cones and third-party manufactured cones, as shown in Figure 1. This indicates that third-party cones deviate from Agilent's design, which might negatively impact performance.

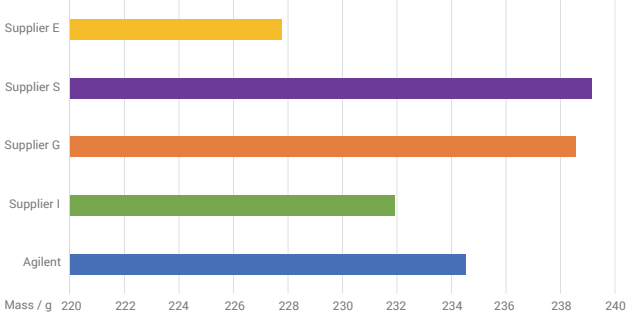

Figure 1. Average weight of sampling cones, as received.

Agilent Cones Deliver Superior Sensitivity

Genuine Agilent cones provided higher sensitivity as received, as shown in Figure 2, and after following our conditioning guidelines. Agilent cones also gave the lowest background and, as a result, the best detection limits and BECs.

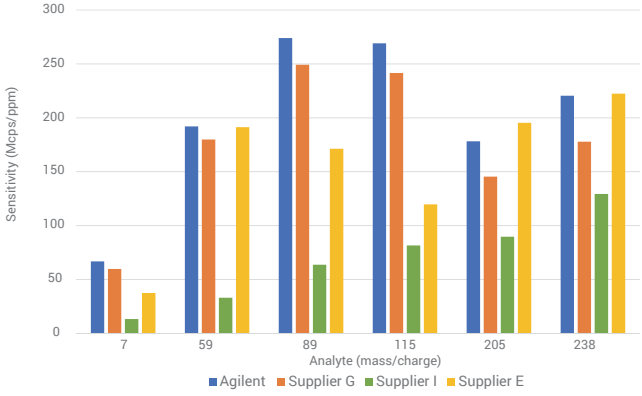

Figure 2. Sensitivity for new cone pairs straight out-of-the-box.

Agilent Cones Provide Excellent Stability

Agilent ICP-MS cones are designed for matrix tolerance, ensuring good signal stability and lower maintenance. Third-party cones can compromise short- and long-term stability, leading to sample reruns and lost productivity.

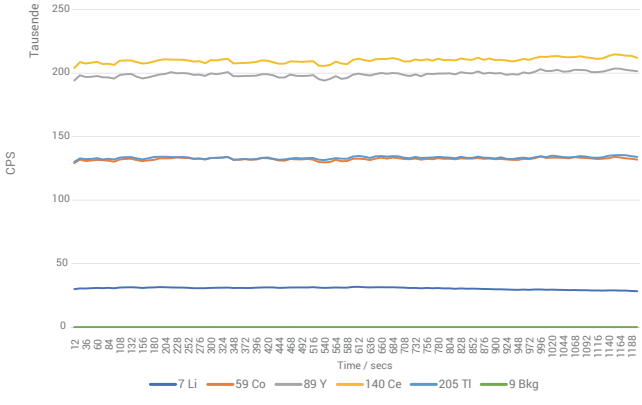

Figure 3. Long-term stability of genuine Agilent cones.

More Information

Download the full Technical Overview from www.agilent.com /en/promotions/cone-comparison, look for publication 5994-0798EN

Discover More About ICP-QQQ With This On-Demand Webinar

Title: How ICP-MS/MS Improves Data Quality in Everyday Analytical Challenges and for Emerging Contaminants
Abstract: Learn how ICP-MS/MS might be able to improve the accuracy and reliability of your current analyses.
Speaker: Ed McCurdy, ICP-MS Product Marketing, Agilent Technologies Inc.
Host: Spectroscopy

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Hear Analysts Describe How Agilent ICP-QQQ Opens Up New Applications

Watch highlights from the second ICP-QQQ user group meeting held in Germany in September 2018.

Video

Articles and Publications

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- **Application note:** Multiple Element Nanoparticle Analysis of Semiconductor Grade Chemical Reagents using spICP-MS with MS/MS, 5994-0987EN
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- **Application note:** High Throughput Analysis of Animal Feed using the Agilent 7800 ICP-MS with HMI and ISIS 3, 5994-0846EN
- **Application note:** Routine Elemental Analysis of Dietary Supplements using an Agilent 8900 ICP-QQQ: Effective removal of doubly charged and oxide ion interferences ensures accurate measurement of As and Cd, 5994-1156EN
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