



ICP - Mass Spectrometry

Introduction

Ultrapure water is a critical utility in the pharmaceutical industry and is used at virtually every stage of drug development and manufacturing, including formulation, dilution, cleaning, rinsing, and as a component of Water for Injection (WFI) and Purified Water (PW) systems. Because this water comes into direct contact with active pharmaceutical ingredients, excipients, production equipment, and primary packaging components, its elemental purity is strictly controlled. Even extremely low concentrations of metallic and metalloid contaminants may affect product stability, catalytic processes, manufacturing equipment, and ultimately patient safety. As a result, reliable determination of elemental impurities at very low concentration levels is an essential requirement for pharmaceutical quality control and process monitoring.

The analysis of ultrapure water presents unique analytical challenges. Although the matrix itself is simple, the target analytes are often present at ultra-low concentrations, approaching instrumental detection limits. Under these conditions, background contributions, contamination from laboratory environments and sample handling, and spectral interferences originating from argon-, oxygen-, nitrogen-, and carbon-based species can significantly affect data quality. In addition, elements such as As, Se and Cd are particularly susceptible to polyatomic interferences, making robust interference removal a critical aspect of low-level elemental analysis. Therefore, highly sensitive instrumentation combined with effective interference control strategies is required to achieve reliable detection limits and stable long-term performance.

This work explores and compares the capabilities of helium KED mode and CH₄ DRC mode on the NexION® 2200 ICP-MS for low-level elemental analysis in ultrapure water intended for pharmaceutical applications. A multi-element panel including Zn, Pb, Mn, As, Cd, Ni, Se, and Sb was investigated, with selected isotopes measured using both interference removal strategies and monitored using multiple internal standards (Sc, Ge, Rh, In, and Tb). The primary objective of this study was to assess achievable limits of detection and overall analytical performance, providing insight into the suitability of both modes for routine monitoring of elemental impurities in pharmaceutical-grade ultrapure water.

Experimental

Samples and Standard Preparation

Ultrapure water produced in a laboratory purification system was used as the representative matrix for pharmaceutical water applications and served as the test sample throughout this study. No digestion or chemical treatment of the samples was required prior to analysis.

Calibration standards were prepared from a matrix-free aqueous multi-element certified reference material by serial gravimetric dilution in ultrapure water. All standards were prepared in high-purity containers using trace-metal-grade reagents in order to minimize background contamination.

A certified reference material for drinking water (LGC 6027) was used as a quality control (QC) sample to verify method accuracy and stability. To evaluate method performance at very low concentration levels, the CRM was additionally diluted 100-fold in ultrapure water. The dilution factors were taken into account during data evaluation.

Internal standards (Sc, Ge, Rh, In, and Tb) were added online to all standards and samples (after 20-fold dilution) to compensate for potential signal drift and to ensure reliable quantification across the full mass range. The calibration ranges applied for individual elements are summarized in Table X.

To further evaluate the practical performance of the method, five additional water samples originating from different laboratories were analyzed under the same conditions.

Instrumentation and Operating Conditions

All analyses were performed using a NexION® 2200 ICP-MS (PerkinElmer, Shelton, Connecticut, USA). The NexION platform is equipped with Universal Cell Technology (UCT), enabling three operational modes: Kinetic Energy Discrimination (KED), Dynamic Reaction Cell (DRC) with dynamic bandpass tuning, and Standard mode without cell gas. This flexibility allows effective and adaptable interference removal strategies depending on the analytical requirements.

In KED mode, helium collisions discriminate against polyatomic species based on differences in kinetic energy, providing a universal and robust approach for multi-element analysis with minimal method complexity. In DRC mode, a precisely controlled bandpass mass filter within the UCT selectively excludes undesired reaction by-products from the cell, preventing the formation of new interferences and enabling highly selective interference removal for challenging analytes. Standard mode can be applied when no collision or reaction gas is required. The NexION 2200 ICP-MS combines several hardware features which contribute to high stability and reduced maintenance requirements during routine operation. The

orthogonal ion path incorporating the Quadrupole Ion Deflector (QID) together with OmniRing™ interface technology minimizes matrix deposition and improves long-term instrument robustness. The LumiCoil™ RF coil and GreenCT™ cooling system reduce thermal load and contribute to stable plasma conditions, particularly important during extended multi-element analyses.

These design features, together with intuitive control through Syngistix™ for ICP-MS software, support efficient method development and reliable operation for low-level elemental analysis in high-purity aqueous matrices. Detailed instrumental parameters applied in this work are summarized in Table 1.

Table 1. NexION 2200 ICP-MS Instrument Components and Operating Conditions

| Instrument Component | Type/Value |
|-------------------------|---|
| Nebulizer | Meinhard Concentric |
| Spray chamber | Cyclonic quartz |
| Torch | Quartz with 2.0 i.d. fixed injector |
| Cones | Nickel |
| Peristaltic Pump Tubing | Int Std: Orange/Red (0.19 mm i.d.) Sample: Orange/Green (0.38 mm i.d.) Waste: Gray/Gray Santoprene (1.30 mm i.d.) |
| Sample Uptake Rate | 0.25 mL/min |
| Operating Conditions | Type/Value |
| RF Power | 1600 W |
| Plasma Gas Flow | 15 L/min |
| Auxiliary Gas Flow | 1,2 L/min |
| NEB Gas Flow | 1.02 – 1.06 L/min |
| Cell Gas | Helium, methane |

Results and Discussion

Low-Level Performance and Quality Control Evaluation in Aqueous Matrix

Before final measurement conditions were selected for each element, the analytical performance of both helium KED and CH₄ DRC modes was evaluated in terms of achievable limits of detection (LOD) and limits of quantification (LOQ). This comparison allowed selection of the most suitable interference removal strategy for

each analyte based on low-level analytical capability.

As a result of this evaluation, Zn, As, and Sb were measured in helium KED mode, while the remaining elements were determined in CH₄ DRC mode. A detailed comparison of LOD and LOQ values obtained for both modes is presented in Table 2.

Table 2. Comparison of LOD and LOQ for KED and DRC Modes

| Element | Isotope | KED (He) | | DRC (CH ₄) | |
|---------|---------|----------|------|------------------------|------|
| | | LOD | LOQ | LOD | LOQ |
| | | ng/L | ng/L | ng/L | ng/L |
| Zn | 64 | 92.8 | 155 | 178 | 297 |
| Pb | Sum | 20.0 | 32.9 | 4.8 | 8.0 |
| Mn | 55 | 11.0 | 17.9 | 2.6 | 4.4 |
| As | 75 | 3.43 | 5.73 | N/A | |
| Cd | 111 | 6.4 | 10.7 | 5.2 | 8.7 |
| Ni | 60 | N/A | | 14.6 | 24.4 |
| Se | 80 | N/A | | 5.3 | 9.0 |
| Sb | 121 | 2.0 | 3.3 | 4.9 | 8.1 |

Excellent calibration performance was obtained for all investigated elements. Over the applied working ranges (summarized in Table 3), correlation coefficients exceeded 0.999 for all analytes, confirming the suitability of the method for low-level elemental quantification.

The analytical performance of the method was evaluated using an aqueous matrix

representative of pharmaceutical water applications. Zn, Pb, Mn, As, Cd, Ni, Se, and Sb were determined at low concentration levels, and method behavior was assessed using a certified drinking water reference material (LGC 6027). In order to verify suitability for measurements at very low concentrations, the CRM was analyzed in duplicate after 100-fold dilution.

Table 3. Summary of Measurement Conditions for each elements

| Analyte | Zn | Pb | Mn | As | Cd | Ni | Se | Sb |
|-------------------|---------|---------|---------|---------|---------|---------|---------|---------|
| Isotope | 64 | Sum* | 55 | 75 | 111 | 60 | 80 | 121 |
| Mode | KED | DRC | DRC | KED | DRC | DRC | DRC | KED |
| Int STD | In | Rh | Ge | Tb | Tb | Ge | Sc | Tb |
| Calibration range | 0.2-10 | 0.01-5 | 0.01-5 | 0.01-5 | 0.01-5 | 0.05-5 | 0.01-5 | 0.01-5 |
| Unit | µg/L | µg/L | µg/L | µg/L | µg/L | µg/L | µg/L | µg/L |
| r | 0.99982 | 0.99995 | 0.99988 | 0.99997 | 0.99992 | 0.99995 | 0.99995 | 0.99989 |

* Pb measured as the sum of isotopes 206, 207, and 208

The certified drinking water CRM showed very good agreement with reference values for all analytes (Table 4). Recoveries remained within the expanded uncertainty of the certified material, confirming the accuracy of the method. Importantly, consistent results were also obtained after 100-fold dilution of the CRM, demonstrating that the method maintains robustness and

quantitative performance even at significantly reduced concentration levels. Precision was evaluated based on replicate measurements diluted solutions of the CRM. Relative standard deviations were generally low for all analytes (Table 4), indicating excellent instrumental stability and low background contribution under the applied conditions.

Table 4. Results for CRM

| Analyte | Zn | Pb | Mn | As | Cd | Ni | Se | Sb |
|-------------------|------|--------|-------|--------|--------|--------|--------|--------|
| Isotope | 64 | Sum* | 55 | 75 | 111 | 58 | 80 | 121 |
| Mode | KED | DRC | DRC | KED | DRC | DRC | DRC | KED |
| Int. STD | In | Rh | Ge | Tb | Tb | Ge | Sc | Tb |
| Unit | µg/L | µg/L | µg/L | µg/L | µg/L | µg/L | µg/L | µg/L |
| CRM 1 | 6.21 | 0.101 | 0.497 | 0.099 | 0.048 | 0.199 | 0.105 | 0.055 |
| RSD (%) | 1.2 | 0.5 | 0.5 | 7.0 | 0.6 | 1.1 | 0.6 | 0.5 |
| CRM 2 | 6.03 | 0.103 | 0.496 | 0.104 | 0.054 | 0.196 | 0.099 | 0.052 |
| RSD (%) | 8.4 | 3.9 | 3.5 | 1.9 | 3.6 | 1.9 | 5.9 | 3.8 |
| Reference value** | 6.13 | 0.101 | 0.499 | 0.100 | 0.051 | 0.200 | 0.102 | 0.052 |
| U (CRM)*** | 0.19 | 0.0020 | 0.011 | 0.0035 | 0.0024 | 0.0051 | 0.0039 | 0.0024 |

* Pb measured as a sum of isotopes 206 + 207 + 208

** Value obtained after the CRM dilution

*** Expanded uncertainty of the CRM (k = 2), calculated by taking into account the certified uncertainty of the CRM and the uncertainties of the automatic pipettes used to prepare the dilutions.

To further confirm the applicability of the method, five water samples originating from different laboratories were analyzed. The samples were not subjected to any preparation other than acidification to 1% HNO₃ prior to measurement.

The obtained results demonstrate that the NexION 2200 ICP-MS operated in

both helium KED and CH₄ DRC modes provides reliable multi-element performance in an aqueous matrix and supports accurate and precise elemental measurements at very low concentration levels.

Table 5. Results for measurements of real samples

| Analyte | Zn | Pb | Mn | As | Cd | Ni | Se | Sb |
|----------|------|-------|-------|-------|-------|-------|-------|-------|
| Isotope | 64 | Sum* | 55 | 75 | 111 | 58 | 80 | 121 |
| Mode | KED | DRC | DRC | KED | DRC | DRC | DRC | KED |
| Int. STD | In | Rh | Ge | Tb | Tb | Ge | Sc | Tb |
| Unit | µg/L | µg/L | µg/L | µg/L | µg/L | µg/L | µg/L | µg/L |
| Water 1 | 1.52 | 0.217 | 0.023 | 0.015 | 0.024 | 0.11 | 0.024 | 0.012 |
| Water 2 | 1.57 | 0.221 | 0.016 | 0.012 | 0.022 | 0.17 | 0.018 | 0.015 |
| Water 3 | 1.77 | 0.178 | 0.017 | 0.011 | 0.017 | 0.12 | 0.012 | 0.022 |
| Water 4 | 1.60 | 0.085 | 0.022 | 0.013 | 0.019 | 0.22 | 0.021 | 0.017 |
| Water 5 | 0.22 | <LOQ | <LOQ | <LOQ | <LOQ | 0.065 | <LOQ | <LOQ |

Conclusion

The results presented in this study demonstrate the capabilities NexION® 2200 ICP-MS for low-level elemental analysis in ultrapure water relevant to pharmaceutical applications. Excellent linearity, low detection limits, and stable analytical performance were achieved across a broad multi-element panel.

The ability to reliably quantify elements at very low concentration levels, combined with

robust interference removal and minimal method complexity, highlights the suitability of both, helium KED and DRC modes for routine monitoring of elemental impurities in pharmaceutical water systems. These results confirm that the NexION 2200 ICP-MS provides a powerful and versatile platform for low-level elemental analysis in high-purity aqueous matrices

Consumables Used

| Component | Description | Part Number |
|--|--|-------------|
| Nebulizer | Quartz Nebulizer, Type C Plus, 0.5 mL/min, low internal volume | N8152372 |
| Spray Chamber | Quartz Cyclonic High Sensitivity Spray Chamber with Matrix Gas Port | N8152383 |
| Torch | One Piece Quartz Torch with 2.0 mm injector | N8152472 |
| Sampler Cone | Nickel sampler cone for NexION 1000/2000/2200/5000 ICP-MS | W1033612 |
| Skimmer Cone | Nickel skimmer cone for NexION 2200 ICP-MS | N8171142 |
| Hyper-skimmer Cone/OmniRing | Nickel hyper-skimmer cone with OmniRing | N8160120 |
| Peripump Tubing | Int Std: Orange/Red (0.19 mm i.d.) | N8152401 |
| | Sample: Orange/Green (0.38 mm i.d.) | N8152403 |
| | Waste: Gray/Gray Santoprene (1.30 mm i.d.) | N8152415 |
| Internal Standard Mix | Standard includes: 50 mg/L Sc, Ge 10 mg/L Rh, In, Tb Matrix: 2% HNO ₃ | N9308591 |
| Multi-Element Standard (used for preparing calibration standard) | 100 µg/mL of Ag, Al, As, Ba, Be, Ca, Cd, Co, Cr, Cu, Fe, K, Mg, Mn, Mo, Na, Ni, Pb, Sb, Se, Sn, Sr, Ti, Tl, V, and Zn in 5% HNO ₃ /Trace Tartaric Acid/Trace HF | N9301721 |

References

1. NexION 2200 ICP-MS, PerkinElmer Interactive Brochure, 2023.
2. Badiei H. et al., Advantages of a Novel Interface Design for NexION 2200/5000 ICP-MS”, PerkinElmer Technical Note, 2023.
3. Badiei H. et.al., Novel Interface for NexION 2200/5000 ICP-MS Systems – Innovative Design, Uncompromised Performance, PerkinElmer Technical Note, 2023

Author

Magdalena Muszyńska