# Alternative sample preparation and analysis approach for ICH/USP controlled metals by ICP-MS

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## Introduction

The presence of impurities in pharmaceutical ingredients is a concern, not only because some contaminants are inherently toxic, but also because they may adversely affect drug stability and shelf-life or may cause unwanted side-effects. As a result, both organic and inorganic (elemental) impurities must be monitored and controlled in raw materials, including water (used for drug manufacturing), intermediates, active pharmaceutical ingredients (APIs), excipients (stabilizers, fillers, binders, colors, flavors, coatings) and in the final dosage form. Impurities resulting from the production process, such as catalyst residues and contaminants from production process equipment, must also be monitored.

The United States Pharmacopeial Convention (USP), is extending the list of elements in line with the ICH (International Conference on Harmonization), for metal impurities in pharma products and ingredients. United States Pharmacopeia (USP) chapters <232> (Elemental Impurities-Limits) and <233> (Elemental Impurities-Procedures) specify limits and procedures for elemental impurities in drug products. Elemental impurity analysis plays an important role in any pharmaceutical development and manufacturing and it is now vital and mandatory for pharmaceutical organizations to demonstrate compliance to the specified levels of elemental impurities in chapter <232>.

For the analysis of elemental impurities in pharmaceutical ingredients, the USP chapters suggest four different sample preparation methods:
1. Use neat, undiluted sample, if in a suitable liquid form
2. Dilute in aqueous solution, if soluble in water
3. If not soluble in water, dilute in appropriate organic solvent
4. Use closed-vessel microwave acid digestion for insoluble samples

All the sample preparation methods have their unique applications and capabilities, but the use of organic solvents such as Dimethyl Sulfoxide (DMSO), is gaining more popularity due to ease of use, less sample ingredient requirement and high throughput in sample preparation when compared to closed vessel microwave acid digestion. Analysis using the Agilent 7800 ICP-MS with a developed and optimized method has shown an excellent capability to handle the organic solvent with accurate and precise results, demonstrating a robust solution option for the analysis of elemental impurities in pharmaceutical ingredients.

## Experimental

**Instrumentation:**

An Agilent 7800 ICP-MS was set up using the Micromist nebulizer, Peltier-cooled quartz spray chamber, torch (1.5mm injector), Platinum cones, 3-bridged, gray/gray tubing and Argon-Oxygen mix gas as an optional gas to remove the carbon deposition from the cones. Sampling was facilitated using the Agilent SPS 4 auto sampler and internal standards were added on-line via the sample delivery peristaltic pump.

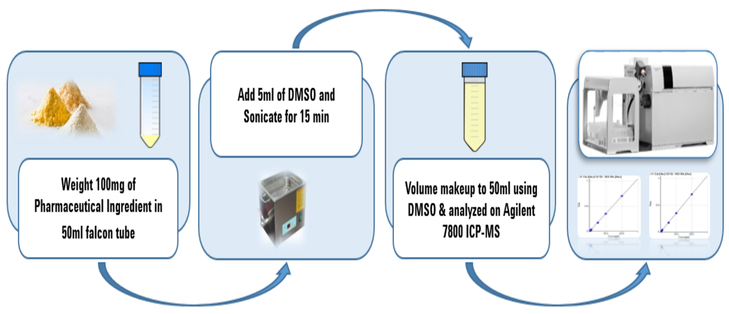
The sample introduction system of the 7800 includes a low pulsation, high precision, 10 rollers peristaltic pump, an efficient low flow Micromist nebulizer and a Peltier-cooled spray chamber, with a controllable temperature range of -5 °C to +20 °C. This Scott-type double pass spray chamber has the capability to run in both aqueous and organic solvents. The 4th generation cell, the ORS$^4$, provides fast cell gas switching and the most effective interference removal in all modes with proven high-performance hyperbolic quadrupole and latest generation simultaneous dual mode discrete dynode detector. The Agilent ICP-MS Mass Hunter 4.3 software is intuitive with ready preset methods for the USP chapters.

| Parameter | Setting Value |
|---|---|
| Plasma Mode | General Purpose |
| RF Power (W) | 1550 |
| Carrier gas (mL/min) | 0.99 |
| Sample Depth (mm) | 8.0 |
| S/C Temp (ºC) | 17 |
| Cell gas flow rate (mL/min) | 4 |
| Energy Discrimination (V) | 3 |
| Optional gas (%) | 10 |

## Experimental

**Sample and Standard Preparation:**

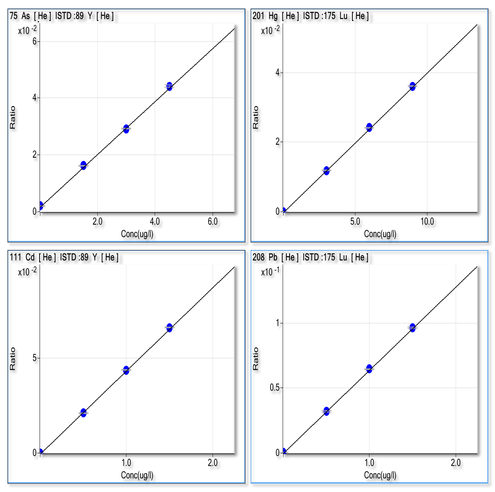
The calibration standards were prepared using NIST traceable standards in DMSO (Dimethyl sulfoxide). 100 mg of active pharmaceutical ingredient (API) sample was accurately weighed into a 50 mL falcon tube with 5 mL of DMSO. The tubes was then sonicated for 15 min for complete sample dissolution and made up to 50 mL with DMSO. The samples were prepared in multiple replicates. Spiked samples were prepared simultaneously. The internal standard was added online. Below Figure shows the flow diagram for sample preparation and analysis.




## Results and Discussion

**Calibration:**

The calibration graphs for As, Hg, Cd and Pb are shown in below figure.




| Element | R Value | DL (ug/L) |
|---|---|---|
| Cd | 0.9998 | 0.002 |
| Pb | 1.0000 | 0.002 |
| As | 0.9997 | 0.072 |
| Hg | 1.0000 | 0.014 |
| Co | 1.0000 | 0.001 |
| V | 1.0000 | 0.001 |
| Ni | 0.9999 | 0.007 |
| Tl | 0.9997 | 0.001 |
| Au | 0.9953 | 0.001 |
| Pd | 1.0000 | 0.018 |
| Ir | 1.0000 | 0.002 |
| Os | 0.9998 | 0.007 |
| Ru | 1.0000 | 0.001 |
| Rh | 0.9998 | 0.002 |
| Se | 0.9999 | 0.001 |
| Ag | 0.9983 | 0.001 |
| Pt | 1.0000 | 0.002 |
| Li | 0.9999 | 0.119 |
| Sb | 1.0000 | 0.001 |
| Ba | 0.9999 | 0.016 |
| Mo | 1.0000 | 0.008 |
| Cu | 1.0000 | 0.033 |
| Sn | 1.0000 | 0.010 |
| Cr | 0.9999 | 0.007 |

Above is the lists the elements, along with their calibration coefficients (R value) and detection limits (DL). The system demonstrates good sensitivity in DMSO, with detection limits at µg/L levels for all elements

**System Suitability:**

As per USP general chapters <232> and <233>, the system suitability is established by comparing the results obtained from standardization solution 1 (1.5J) before and after the analysis of the sample solution, with suitability criteria for drift of not more than (NMT) 20% for each target element [2]. Below table shows the system suitability results, with % drift well within the suitability criteria.

| Element | J value (µg/L) | Standardization solution 1 (1.5J) before the analysis (n=6) | Standardization solution 1 (1.5J) after the analysis (n=6) | % Drift n=6 |
|---|---|---|---|---|
| Li | 110 | 161 | 166 | 2.8 |
| V | 20 | 30 | 30 | 0.3 |
| Cr | 2200 | 3320 | 3317 | -0.1 |
| Co | 10 | 15 | 15 | 0.1 |
| Ni | 40 | 60 | 60 | 0.3 |
| Cu | 600 | 899 | 902 | 0.2 |
| As | 3 | 4.5 | 4.5 | 0.1 |
| Se | 1 | 1.5 | 1.5 | 0.1 |
| Mo | 600 | 904 | 899 | -0.6 |
| Ru | 20 | 30 | 30 | 0.3 |
| Rh | 20 | 30 | 30 | 0.1 |
| Pd | 20 | 30 | 30 | 0.0 |
| Ag | 30 | 42 | 45 | 8.0 |
| Cd | 1 | 1.5 | 1.5 | 0.1 |
| Sn | 1200 | 1819 | 1802 | -0.9 |
| Sb | 240 | 363 | 359 | -1.2 |
| Ba | 280 | 413 | 418 | 1.2 |
| Os | 20 | 29 | 30 | 4.5 |
| Ir | 20 | 30 | 30 | 0.7 |
| Pt | 20 | 30 | 30 | 1.0 |
| Au | 20 | 30 | 31 | 2.3 |
| Hg | 6 | 9 | 9 | 0.1 |
| Tl | 1.6 | 2.4 | 2.4 | 0.1 |
| Pb | 1 | 1.5 | 1.5 | 0.1 |

## Results and Discussion

**Accuracy studies at 100% J value**

The tested active pharmaceutical ingredients were spiked before the sample preparation step at concentrations of 100% J value for each target element as per the requirement of chapters <232> and <233>. The acceptance criteria for spike and recovery is 70 –150% for the mean of the replicates at each concentration [1]. Below table shows the accuracy study results at 100% J value. The obtained results demonstrate excellent %RSD, with all results within the acceptable recovery range.

| Element | J Value (µg/L) | API-1 % Recovery (n=6) | % RSD | API-2 % Recovery (n=6) | % RSD | API-3 % Recovery (n=6) | % RSD |
|---|---|---|---|---|---|---|---|
| Li | 110 | 107.1 | 3.0 | 102.4 | 3.2 | 103.0 | 1.5 |
| V | 20 | 101.7 | 2.7 | 97.5 | 1.1 | 98.7 | 1.2 |
| Cr | 2200 | 106.1 | 2.7 | 102.2 | 0.9 | 103.0 | 1.1 |
| Co | 10 | 104.4 | 2.7 | 100.4 | 1.3 | 101.0 | 1.1 |
| Ni | 40 | 104.4 | 2.8 | 100.4 | 1.4 | 101.1 | 1.0 |
| Cu | 600 | 109.8 | 2.8 | 105.5 | 1.9 | 106.4 | 1.0 |
| As | 3 | 90.9 | 3.1 | 90.6 | 4.9 | 96.6 | 2.0 |
| Se | 1 | 95.0 | 7.1 | 86.5 | 4.6 | 92.9 | 1.4 |
| Mo | 600 | 105.2 | 2.8 | 101.4 | 1.2 | 102.0 | 0.7 |
| Ru | 20 | 101.8 | 2.6 | 97.9 | 1.4 | 98.2 | 0.5 |
| Rh | 20 | 102.1 | 2.5 | 98.2 | 1.3 | 98.6 | 0.4 |
| Pd | 20 | 104.1 | 2.2 | 100.0 | 1.2 | 100.5 | 0.6 |
| Ag | 30 | 91.3 | 2.0 | 97.8 | 2.9 | 94.6 | 2.2 |
| Cd | 1 | 103.2 | 2.6 | 98.7 | 2.1 | 100.0 | 1.5 |
| Sn | 1200 | 106.9 | 2.2 | 102.5 | 1.3 | 102.8 | 0.6 |
| Sb | 240 | 110.5 | 2.3 | 107.2 | 1.7 | 108.0 | 0.6 |
| Ba | 280 | 93.7 | 2.1 | 90.5 | 1.0 | 91.3 | 0.5 |
| Os | 20 | 91.8 | 2.9 | 87.4 | 0.6 | 88.1 | 0.4 |
| Ir | 20 | 103.5 | 2.4 | 98.4 | 0.9 | 99.0 | 0.4 |
| Pt | 20 | 106.7 | 2.3 | 101.4 | 1.0 | 102.2 | 0.2 |
| Au | 20 | 98.6 | 2.7 | 95.6 | 3.0 | 94.1 | 2.8 |
| Hg | 6 | 108.2 | 3.4 | 102.3 | 0.9 | 103.2 | 0.6 |
| Tl | 1.6 | 102.9 | 2.7 | 97.6 | 0.3 | 98.8 | 0.7 |
| Pb | 1 | 101.7 | 3.1 | 96.6 | 0.4 | 97.1 | 0.5 |

**Intermediate Precision:**

The intermediate precision (ruggedness) is determined by performing the repeatability analysis again, either on a different day, with a different instrument or with a different analyst, or a combination of the above. The acceptance criteria for relative standard deviation should be NMT 25% for each target element [2]. For each API sample, six replicates were spiked at the target concentration and analyzed on two separate days. Below table shows the intermediate precision results for all 3 API samples.

| Element | J Value (µg/L) | Intermediate precision at 100% (n=12) | | |
|---|---|---|---|---|
| | | API-1 | API-2 | API-3 |
| Li | 110 | 4.2 | 2.8 | 2.1 |
| V | 20 | 3.7 | 2.7 | 1.8 |
| Cr | 2200 | 4.2 | 3.1 | 1.9 |
| Co | 10 | 4.1 | 2.9 | 1.8 |
| Ni | 40 | 3.5 | 2.6 | 2.1 |
| Cu | 600 | 8.3 | 9.2 | 1.2 |
| As | 3 | 4.2 | 7.2 | 9.5 |
| Se | 1 | 4.2 | 3.0 | 1.7 |
| Mo | 600 | 3.1 | 2.9 | 2.4 |
| Ru | 20 | 4.1 | 2.8 | 1.8 |
| Rh | 20 | 3.4 | 2.5 | 1.6 |
| Pd | 20 | 4.7 | 4.8 | 3.3 |
| Ag | 30 | 3.5 | 2.9 | 3.8 |
| Cd | 1 | 3.7 | 3.0 | 1.5 |
| Sn | 1200 | 2.1 | 1.4 | 1.2 |
| Sb | 240 | 4.1 | 2.9 | 1.9 |
| Ba | 280 | 3.6 | 2.8 | 1.8 |
| Os | 20 | 3.3 | 2.5 | 1.6 |
| Ir | 20 | 3.2 | 2.6 | 1.5 |
| Pt | 20 | 6.3 | 3.5 | 1.7 |
| Au | 20 | 3.5 | 2.5 | 1.4 |
| Hg | 6 | 3.9 | 2.6 | 1.7 |
| Tl | 1.6 | 3.5 | 2.9 | 1.8 |
| Pb | 1 | 4.2 | 2.8 | 2.1 |

This optimized organic solvent preparation method does not show the presence of any significant elements in any of the three API samples and no matrix effects were observed during analysis. So this new methodology for the preparation and analysis of pharmaceutical samples, as described in USP <232> and <233>, provides an opportunity for pharmaceutical laboratories to update their methodology and instrumentation

## Conclusions

The Agilent 7800 ICP-MS, along with the optimized organic solvent preparation method for the determination of elemental impurities in pharmaceutical ingredients, as per USP chapters <232> and <233>, provides a complete solution, with excellent results obtained in terms of sensitivity, stability, robustness, recovery and detection limits for all the required elements. The main advantage being that it replaces the tedious acid digestion methodology, enabling higher sample throughput and increasing productivity

**References:**

[1] USP Chapter <232> Elemental Impurities- Limits, Pharmacopeial Forum, 2011, 42(2).
[2] USP Chapter <233> Elemental Impurities-Procedure, USP 38–NF 33, Second Supplement.