Application Note
Pharmaceuticals

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Determining Elemental Impurities in Pharmaceutical Ingredients using ICP-MS

USP/ICH methodology used to measure 24 elemental impurities in raw materials dissolved in DMSO

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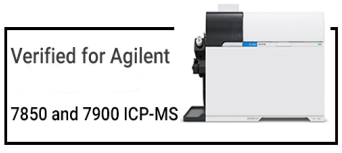

Introduction

The presence of impurities in pharmaceutical ingredients is a concern within the industry. Some contaminants are inherently toxic, while others 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 and in the final dosage form. Raw materials and reagents include water (used for drug manufacturing), intermediates, active pharmaceutical ingredients (APIs), and excipients (stabilizers, fillers, binders, colors, flavors, coatings). Impurities resulting from the production process, such as catalyst residues and contaminants from production process equipment, must also be monitored. The potential for contamination from packaging and container closure systems (CCS) must also be assessed.

The United States Pharmacopeial Convention (USP) has aligned its method for assessing inorganic impurities in pharmaceutical products to harmonize with the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) Q3D guidelines. USP General Chapters <232> (Elemental Impurities-Limits) and <233> (Elemental Impurities-Procedures) specify limits and procedures for measuring elemental impurities in drug products (*1,2*).

Elemental impurity analysis plays an important role in any pharmaceutical development and for quality control (QC) in manufacturing. It is now vital and mandatory for pharmaceutical organizations to demonstrate compliance with the specified levels of elemental impurities in chapter <232> and ICH Q3D (*3*). Table 1 shows the Permitted Daily Exposure (PDE) limits in oral formulations for the list of 24 elements as specified in the USP/ICH methods.

Table 1. Permitted Daily Exposure (PDE) limits for oral formulations.

Element	USP/ICH Class	Oral PDE (µg/day)
Cd	1	5
Pb	1	5
As	1	15
Hg	1	30
Co	2A	50
V	2A	100
Ni	2A	200
Tl	2B	8
Au	2B	100
Pd	2B	100
Ir	2B	100
Os	2B	100
Rh	2B	100
Ru	2B	100
Se	2B	150
Ag	2B	150
Pt	2B	100
Li	3	550
Sb	3	1200
Ba	3	1400
Mo	3	3000
Cu	3	3000
Sn	3	6000
Cr	3	11000

For the analysis of elemental impurities in pharmaceutical materials, USP <233> suggests 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 an 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 in popularity. Advantages of using an organic solvent to dilute samples compared to closed vessel microwave acid digestion include ease of use, less sample ingredient requirements, and higher throughput during sample preparation. Analysis using the Agilent 7800 ICP-MS has shown an excellent capability to handle the organic solvent and deliver accurate and precise results. This study presents a robust solution for the analysis of elemental impurities in pharmaceutical ingredients.

Experimental

Instrumentation

This work was run on a 7800 ICP-MS, but the method is also compatible with the Agilent 7850 or Agilent 7900 ICP-MS models. The ICP-MS was set up using the MicroMist nebulizer, peltier-cooled quartz spray chamber, torch (1.5 mm injector), platinum cones, and 3-bridged, gray/gray tubing. An argon-oxygen mix gas was added as an optional gas to prevent carbon deposition on the cones. Sampling was facilitated using the Agilent SPS 4 autosampler and internal standards were added on-line via the sample delivery peristaltic pump.

The Agilent ICP-MS sample introduction system 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 to +20 °C. This Scott-type double-pass spray chamber enables both aqueous and organic solvents to be run. In this study, the samples were dissolved in DMSO, which has a melting point of 19 °C. Therefore, the spray chamber was set to 17 °C to prevent solidification of the sample during nebulization. The 4th generation ORS^4 collision/reaction cell in the 7800 provides fast cell gas switching and the most effective interference removal in all modes. The ORS^4 is combined with a proven high-performance hyperbolic quadrupole mass filter and the latest generation simultaneous dual-mode discrete dynode detector with 10 orders linear dynamic range.

The Agilent ICP-MS MassHunter software is easy to set up and operate, with preset methods providing simple implementation for the USP/ICH chapters. ICP-MS operating conditions used are listed in Table 2.

Table 2. ICP-MS operating conditions.

Parameter	Setting
Preset Plasma Mode	General Purpose
RF Power (W)	1550
Nebulizer Gas (L/min)	0.99
Optional Gas (%)	10
Sample Depth (mm)	8.0
Spray Chamber Temp (°C)	17
Helium Cell Gas Flow Rate (mL/min)	4
Energy Discrimination (V)	3

Sample and standard preparation

The calibration standards were prepared using NIST traceable standards diluted in DMSO. Three active pharmaceutical ingredients (APIs) in powder form were prepared for analysis. 100 mg of each API sample was accurately weighed into a 50 mL Falcon tube with 5 mL of DMSO. The tubes were 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 together with the unspiked solutions. The internal standard was added on-line. Figure 1 shows the flow diagram for sample preparation and analysis.

Results and discussion

Calibration

USP/ICH analytes in Class 1 (Cd, Pb, As, and Hg) and Class 2A (Co, V, and Ni) must be included in the risk assessment for all pharmaceutical products. The calibration graphs for As, Hg, Cd, and Pb, measured in DMSO by ICP-MS, are shown in Figure 2.

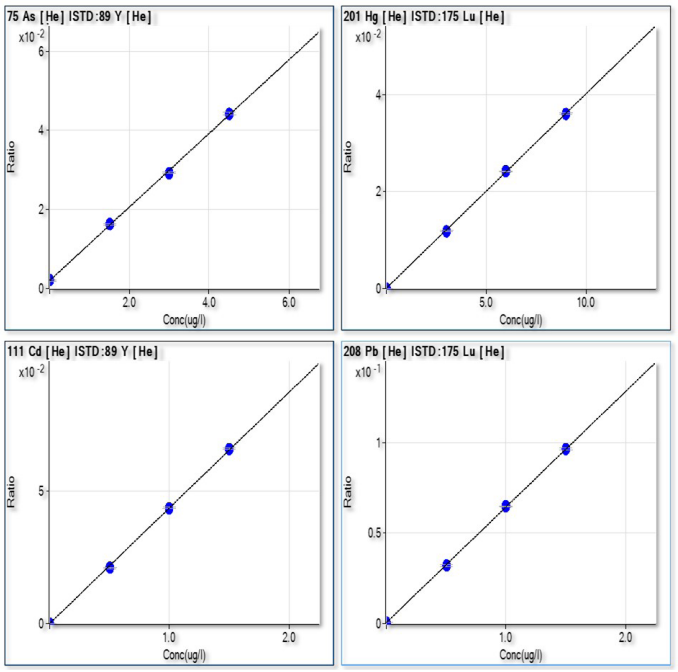

Figure 2. Calibration graphs for As, Cd, Hg, and Pb.

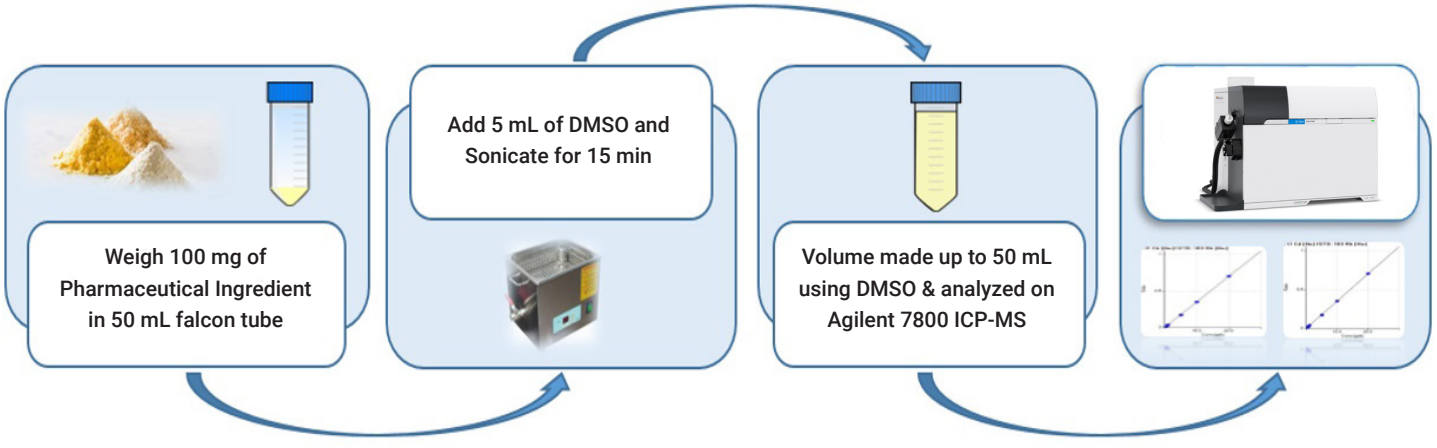

Figure 1. Flow diagram for sample preparation and analysis using the Agilent ICP-MS.

Table 3 lists the USP/ICH target elements together with the Agilent 7800 calibration coefficients (R value) and detection limits (DL). The system demonstrates good sensitivity in DMSO, with detection limits at low ng/L (ppt) levels for all elements.

Table 3. Agilent 7800 ICP-MS calibration curve correlation coefficients and detection limits of elements in DMSO solution.

Element	R Value	DL (µg/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

System suitability

According to USP general chapter <233>, the system suitability is established by performing a series of accuracy, stability, and spike recovery tests. The drift performance test involves comparing the results obtained from standardization solution 1 (1.5 J) before and after the analysis of the sample solutions. To meet the suitability criteria, drift should be not more than (NMT) 20% for each target element (*2*). Table 4 shows the system suitability results for the 7800, with % drift well within the suitability criteria. The sample analysis time between the two measurements was approximately four hours.

Table 4. System suitability results of 1.5 J for each target element.

Element	J Value (µg/L)	Standardization solution 1 (1.5 J) before the analysis (n=6)	Standardization solution 1 (1.5 J) after the analysis (n=6)	% Drift
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

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 per the requirements of USP chapter <233>. The acceptance spike recovery range is 70 to 150% for the mean of the replicates at each concentration (*1*). Table 5 shows the 7800 ICP-MS accuracy study results at 100% J value. The obtained results demonstrate excellent accuracy and precision (%RSD), with all results within the acceptable recovery range.

Table 5. Accuracy results for spike recoveries at 100% J for each target element.

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 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. Table 6 shows the intermediate precision results obtained on the 7800 for all three API samples.

Table 6. Intermediate precision results.

Element	J Value (µg/L)	Intermediate precision at 100% J (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 provided complete solubilization and good stability of the USP/ICH analytes in all three API samples. No matrix effects (suppression or drift) were observed during the analysis. The methodology for the preparation and analysis of pharmaceutical samples in DMSO meets the requirements of ICH Q3D and USP <232> and <233>. The method is easy-to-operate for pharmaceutical laboratories wishing to update their methodology and instrumentation.

Conclusion

The Agilent 7800 ICP-MS, along with the organic solvent preparation method, proved to be ideal for the determination of elemental impurities in pharmaceutical ingredients, per ICH Q3D and USP chapters <232> and <233>. The 7800 produced excellent results in terms of sensitivity, stability, robustness, recovery, and detection limits for all the required elements. The main advantage of the method is that it avoids a time-consuming acid digestion methodology, enabling higher sample throughput and increased productivity.

References

1. USP Chapter <232> Elemental Impurities- Limits, Pharmacopeial Forum, 42(2), Mar-April 2016.
2. USP Chapter <233> Elemental Impurities- Procedures, USP 38–NF 33, Second Supplement
3. ICH Guideline Q3D on Elemental Impurities, EMA/CHMP/ICH/353369/2013, July 2016.

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