

Application News

Inductively Coupled Plasma Mass Spectrometer ICPMS-2050

Analysis of Pharmaceutical Raw Materials Compliant with ICH Q3D Guideline Using ICP-MS with Collision/Reaction Mode

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User Benefits

- ◆ The 24 elements identified in the ICH Q3D guideline can be measured with high sensitivity.
- ◆ Pharmaceutical raw materials that are dissolved in ethanol can be easily analyzed using the Shimadzu ICP-MS organic solvent system.
- ◆ High-sensitivity analysis of Se and the reduction of MoO interference on Cd can be effectively achieved using the hydrogen reaction mode.

■ Introduction

The presence of impurities in pharmaceutical ingredients is a concern within the medical pharmaceutical industry. Therefore, the International Council on Harmonisation of Technical Requirements for Registration for Pharmaceuticals for Human Use requires the management of metallic impurities in pharmaceuticals through guidelines using ICP-MS (ICH Q3D)^{1), 2)}. This standard specifies the Permitted Daily Exposure (PDE) for 24 elements of toxicological concern in oral preparations, injectables, and inhalants.

In the case of oral preparations, only the seven elements of Classes 1 and 2A are considered, except in instances where elements are intentionally added, such as when used as catalysts during synthesis. However, the sources of elemental impurities are diverse and include not only components such as active pharmaceutical ingredients and excipients but also manufacturing equipment and utensils.

ICP-MS has the advantage of being able to analyze various trace elements simultaneously. It is often used for the analysis of elemental impurities in pharmaceuticals. The analyte for ICP-MS is usually a liquid sample, so solid samples require pretreatment.

In this Application News, we measured three types of pharmaceutical raw materials and analyzed the impurities using the Shimadzu ICP-MS organic solvent system. Furthermore, the accuracy, precision, detection limits and specificity of 24 target elements are presented according to USP^{3), 4)} and EP, assuming measurements below the Control Threshold of 30 % of the PDE.

■ Analysis Elements

Class 1: Cd, Pb, As, Hg

Class 2A: Co, V, Ni

Class 2B: Tl, Au, Pd, Ir, Os, Rh, Ru, Se, Ag, Pt

Class 3: Li, Sb, Ba, Mo, Cu, Sn, Cr

■ Control Threshold and Target Limits

A control threshold is defined as 30 % of the specified PDE in the drug. The control threshold can be used to determine if additional controls are required.

Here, the target concentration was set at 30 % of the PDEs. PDEs were converted into target limits using Option 1, which assumes a maximum total daily dose of 10 g of the drug products.

$$\text{Target Limits } (\mu\text{g/g}) = \text{PDE } (\mu\text{g/day}) \times 30\% / 10 \text{ (g/day)}$$

Target limits were converted to target concentrations (J) in the sample solution, where J is determined as:

$$J \text{ } (\mu\text{g/L}) = \frac{\text{Target Limits } (\mu\text{g/g}) \times \text{Sample Digestion Amount (g)}}{\text{Volume (L)}}$$

■ Sample Preparation

1. Eluent: Added 5 mL of HNO₃ and 2.5 mL of HCl into 500 mL ethanol for the electronics industry (FUJIFILM Wako Pure Chemical Corporation).
2. Analysis samples: Weighed 0.1 g of the raw materials (aspirin, salicylic acid and ibuprofen) into a Digi tube and diluted it with eluent to 10 mL (Dilution factor: 100).
3. Calibration solutions: Mixed the Multielement Standard Solution for ICH Q3D Oral Preparation (Cd, Pb, As, Co, V, Ni: FUJIFILM Wako Pure Chemical Corporation), the Multielement Standard Solution for ICH Q3D Oral Preparation (Au, Ir, Os, Pd, Pt, Rh, Ru: FUJIFILM Wako Pure Chemical Corporation), Mercury Standard Solution for ICH Q3D (Hg 30: FUJIFILM Wako Pure Chemical Corporation) and commercially available single standard solution and diluted by the eluent. Solutions containing target analyte elements at concentrations of 0.5 J, 1.0 J, and 1.5 J, as well as a blank solution were prepared. The concentration of each element in the calibration solutions is shown in Table 1.

Table 1 PDE and the Concentration of the Calibration Solutions

Class	Element	Oral PDE (μg/day)	0.5J (μg/L)	1J (μg/L)	1.5J (μg/L)
1	Cd	5	0.75	1.5	2.25
	Pb	5	0.75	1.5	2.25
	As	15	2.25	4.5	6.75
	Hg	30	4.5	9	13.5
2A	Co	50	7.5	15	22.5
	V	100	15	30	45
	Ni	200	30	60	90
2B	Tl	8	1.2	2.4	3.6
	Au	300	45	90	135
	Pd	100	15	30	45
	Ir	100	15	30	45
	Os	100	15	30	45
	Rh	100	15	30	45
	Ru	100	15	30	45
	Se	150	22.5	45	67.5
	Ag	150	22.5	45	67.5
	Pt	100	15	30	45
	Li	550	82.5	165	247.5
	Sb	1200	180	360	540
3	Ba	1400	210	420	630
	Mo	3000	450	900	1350
	Cu	3000	450	900	1350
	Sn	6000	900	1800	2700
	Cr	11000	1650	3300	4950

4. Internal standards: Mixed the commercially available Be, Bi, Ga, and Y standard solutions and diluted them with the eluent. The concentration of Be, Bi, Ga, and Y in the solution was 0.2 mg/L.
5. Samples for accuracy test: The calibration solutions were spiked to samples. The concentrations of the spiked samples were 0.5J, 1.0J, and 1.5J.

6. Samples for precision test: Spiked the calibration solutions to six independent samples to obtain the target concentrations. This operation was identical to the preparation of the sample with a target concentration of 100 % for accuracy evaluation.

■ Instrument Configurations and Analysis Conditions

Table 2 shows the instrument configuration for ICP-MS. The organic solvent system was used to introduce the ethanol. By using the platinum sampling cone, damage from long-term exposure to organic solvents during analysis can be reduced. To reduce the labor required for sample preparation, the internal standards were added using the Online Internal Standard Kit.

The analysis conditions are shown in Table 3.

These analytical conditions can be easily set from the preset methods registered in LabSolutions™ ICPMS (Version 2.10 and later), thus eliminating the need for complex condition testing.

Table 2 Instrument Configuration of ICPMS-2050

System	: ICPMS-2050
Nebulizer	: Nebulizer, DC04
Chamber	: Cyclone Chamber
Temp. of Chamber	: -5 °C
Torch	: Organic Solvent Torch
Sampling Cone	: Platinum
Skimmer Cone	: Nickel
Autosampler	: AS-20
Internal Standard	: Online Internal Standard Kit (Sample [Solva PVC, I.D. 0.76 mm ^{*1}]: Internal Standard [Solva PVC, I.D. 0.38 mm ^{*2}] = about 4:1)

*1:S018-31558-61, 3 bridges

*2:S018-31558-62, 3 bridges

Table 3 Analysis Conditions of ICPMS-2050

RF Power	: 1.60 kW
Sampling Depth	: 8 mm
Plasma Gas Flowrate	: 20.0 L/min
Auxiliary Gas Flowrate	: 0.50 L/min
Carrier Gas Flowrate	: 0.55 L/min
Dilution Gas Flowrate	: 0.00 L/min
Mix Gas Flowrate	: 0.35 L/min
Peristaltic Pump Speed	: 20 r.p.m
Gas Type	: No Gas
Cell Gas	: - 7.0 mL/min
Cell Voltage	: -50 V
Energy Filter	: - 7 V
	He H ₂ (for Se) H ₂ (for Cd)
	5.0 mL/min 6.5 mL/min
	-30 V -20 V
	7 V 7 V 7 V

Table 4 IDL of Each Analytical Element

Class	Element	Mass	Condition	IDL (µg/L)
1	Cd	111	H ₂ (for Cd)	0.003
	Pb	208	He	0.004
	As	75	He	0.009
	Hg	202	He	0.009
2A	Co	59	He	0.004
	V	51	He	0.03
	Ni	60	He	0.2
2B	Tl	205	He	0.0007
	Au	197	He	0.004
	Pd	106	He	0.02
	Ir	193	He	0.001
	Os	189	He	0.002
	Rh	103	He	0.001
	Ru	101	He	0.007
	Se	78	H ₂ (for Se)	0.04
	Ag	107	He	0.004
	Pt	195	He	0.004
3	Li	7	No Gas	0.02
	Sb	121	He	0.03
	Ba	138	He	0.03
	Mo	98	He	0.04
	Cu	63	He	0.1
	Sn	120	He	0.06
	Cr	52	He	0.09

■ Detection Limits of Analysis Elements

A calibration curve was prepared using the calibration solutions in Table 1. The instrument detection limit (IDL) was calculated from the standard deviation (SD) of n = 5 consecutive measurements of blank solution. Table 4 shows the IDL of each analytical element.

■ Validation Requirements

1. Accuracy, precision, and limit of quantitation

Accuracy: Spike recovery is 70 %–150 % for the mean of three replicate preparations at each concentration.

Precision (Repeatability): Relative standard deviation (RSD) is not more than 20 % (N = 6) for each target element.

Limit of quantitation: Demonstrated by meeting the accuracy requirement for 50 % of the target concentration.

2. Specificity

The procedure must be able to unequivocally assess each target element in the presence of components that may be expected to be present, including other target elements and matrix components.

■ Accuracy and Precision Validation Results

Measurements were carried out for n = 3 spiked samples with the target concentration of 50 % and 150 %, and n = 6 spiked samples with the target concentration and the blank (unspiked) sample. Spike recovery was calculated by averaging the quantitative values of all samples. Tables 6 to 8 show the measurement results.

Accuracy: Spike recovery of the samples at each of the target concentrations of 50 %, 100 %, and 150 % was in the range of 94 % to 111 %, thereby satisfying the acceptance criterion.

Precision (Repeatability): RSD of the spiked samples with the target concentration ranged from 0.27 % to 3.79 %, satisfying the acceptance criterion.

Limit of quantitation: As accuracy for 50 % of the target concentration satisfied the acceptance criterion, the limit of quantitation could be confirmed.

■ Specificity

ICP-MS analysis often requires evaluation for potential interference by isotopes, polyatomic ions originating from Ar, oxides of coexistent elements and chloride ions. Here, the Cd was assessed.

MoO₃, originating from the Class 3 element Mo, interferes with Cd. Methods such as interference correction (inter-element correction, half-mass correction, and interference correction formula) and collision/reaction cells are sometimes used to reduce these spectral interferences.

In this study, we attempted to remove the interference of MoO₃ on Cd by optimizing the collision and reaction conditions.

A four-point calibration curve for Cd at concentrations of 0–10 µg/L was created, and the Cd concentration derived from MoO₃ interference in a 1 mg/L Mo standard solution was analyzed using He-collision and H₂-reaction cell gas type, with varying cell voltages. The results are shown in Table 5. The optimized conditions (red box) were applied to the analysis.

Table 5 Analytical Results of Cd in the Presence of 1 mg/L Mo in Different Collision / Reaction Conditions

Cell Gas Type	H ₂ Reaction		He Collision
Cell Gas (mL/min)	5.0	6.5	5.0
Cell Voltage (V)	-30	-20	-40
DL of Cd (µg/L)	0.02	0.007	0.02
Conc. of Cd in presence of 1 mg/L Mo (interference from MoO ₃) (µg/L)	1.42	N.D.	1.40

N.D.: <DL

Table 6 Analytical Result of Aspirin

Element	Conc. in Solution (µg/L)	Conc. in Raw material (µg/g)	50 % Spike of Target Conc.			100 % Spike of Target Conc.				150 % Spike of Target Conc.		
			Spike Conc. (µg/L)	Conc. of Spiked Sample (µg/L)	Accuracy (Recovery)	Spike Conc. (µg/L)	Conc. of Spiked Sample (µg/L)	Accuracy (Recovery)	%RSD	Spike Conc. (µg/L)	Conc. of Spiked Sample (µg/L)	Accuracy (Recovery)
Cd	N.D.	N.D.	0.75	0.706	94 %	1.5	1.48	99 %	3.79	2.25	2.46	109 %
Pb	N.D.	N.D.	0.75	0.746	99 %	1.5	1.49	99 %	2.53	2.25	2.31	103 %
As	N.D.	N.D.	2.25	2.29	102 %	4.5	4.48	100 %	2.26	6.75	6.95	103 %
Hg	N.D.	N.D.	4.5	4.65	103 %	9	9.52	106 %	2.08	13.5	15.0	111 %
Co	0.052	0.0052	7.5	7.31	97 %	15	14.58	97 %	2.10	22.5	22.8	101 %
V	0.25	0.025	15	15.3	100 %	30	30.5	101 %	2.05	45	46	102 %
Ni	0.4	0.04	30	30.3	100 %	60	59.6	99 %	1.94	90	92.9	103 %
Tl	N.D.	N.D.	1.2	1.18	98 %	2.4	2.47	103 %	1.10	3.6	3.75	104 %
Au	0.042	0.0042	45	45.7	101 %	90	92.9	103 %	2.26	135	146	108 %
Pd	N.D.	N.D.	15	14.7	98 %	30	30.8	103 %	2.34	45	47.9	106 %
Ir	0.002	0.0002	15	15.0	100 %	30	30.9	103 %	2.16	45	48.6	108 %
Os	0.005	0.0005	15	15	100 %	30	30.5	102 %	2.30	45	47.9	106 %
Rh	0.001	0.0001	15	14.7	98 %	30	30.6	102 %	2.31	45	47.8	106 %
Ru	N.D.	N.D.	15	14.6	97 %	30	30.4	101 %	2.39	45	48.0	107 %
Se	N.D.	N.D.	22.5	22.0	98 %	45	46.6	104 %	1.53	67.5	71.8	106 %
Ag	0.054	0.0054	22.5	22.0	98 %	45	44.8	106 %	1.26	67.5	72.1	107 %
Pt	N.D.	N.D.	15	15.1	101 %	30	31.0	103 %	2.44	45	49.0	109 %
Li	0.91	0.091	82.5	82.5	99 %	165	170	102 %	1.55	247.5	270	109 %
Sb	2.65	0.265	180	185	101 %	360	372	103 %	2.39	540	577	106 %
Ba	0.28	0.028	210	207	98 %	420	419	100 %	2.40	630	653	104 %
Mo	0.06	0.006	450	444	99 %	900	914	102 %	2.32	1350	1430	106 %
Cu	0.1	0.01	450	443	98 %	900	890	99 %	2.07	1350	1380	102 %
Sn	0.16	0.016	900	898	100 %	1800	1803	100 %	2.42	2700	2830	105 %
Cr	0.42	0.042	1650	1650	100 %	330	3210	97 %	2.22	4950	5080	103 %

N.D.: <IDL

Table 7 Analytical Result of Salicylic Acid

Element	Conc. in Solution (µg/L)	Conc. in Raw material (µg/g)	50 % Spike of Target Conc.			100 % Spike of Target Conc.				150 % Spike of Target Conc.		
			Spike Conc. (µg/L)	Conc. of Spiked Sample (µg/L)	Accuracy (Recovery)	Spike Conc. (µg/L)	Conc. of Spiked Sample (µg/L)	Accuracy (Recovery)	%RSD	Spike Conc. (µg/L)	Conc. of Spiked Sample (µg/L)	Accuracy (Recovery)
Cd	0.004	0.0004	0.75	0.716	95 %	1.5	1.44	95 %	3.26	2.25	2.20	98 %
Pb	N.D.	N.D.	0.75	0.710	95 %	1.5	1.42	94 %	1.66	2.25	2.28	101 %
As	N.D.	N.D.	2.25	2.32	103 %	4.5	4.39	97 %	1.60	6.75	6.93	103 %
Hg	0.013	0.0013	4.5	4.40	97 %	9	9.11	101 %	1.74	13.5	14.8	110 %
Co	0.007	0.0007	7.5	7.37	98 %	15	14.1	94 %	2.01	22.5	22.7	101 %
V	0.19	0.019	15	15.4	101 %	30	30.1	100 %	1.16	45	47.2	104 %
Ni	0.3	0.03	30	29.4	97 %	60	57.3	95 %	1.50	90	92.9	103 %
Tl	N.D.	N.D.	1.2	1.18	98 %	2.4	2.34	98 %	1.16	3.6	3.67	102 %
Au	0.027	0.0027	45	44.3	98 %	90	88.8	99 %	1.71	135	145	107 %
Pd	N.D.	N.D.	15	14.5	97 %	30	29.3	98 %	1.53	45	47.1	105 %
Ir	0.003	0.0003	15	14.8	99 %	30	29.4	98 %	1.73	45	47.7	106 %
Os	0.04	0.004	15	14.7	98 %	30	29.2	97 %	1.63	45	47.2	105 %
Rh	0.001	0.0001	15	14.5	97 %	30	29.2	97 %	1.10	45	46.6	104 %
Ru	N.D.	N.D.	15	14.6	97 %	30	29.0	97 %	1.10	45	46.6	104 %
Se	N.D.	N.D.	22.5	22.2	99 %	45	45.7	101 %	1.21	67.5	71.9	107 %
Ag	0.035	0.0035	22.5	21.8	97 %	45	45.4	101 %	1.06	67.5	70.4	104 %
Pt	N.D.	N.D.	15	14.7	98 %	30	29.6	99 %	1.46	45	48.2	107 %
Li	0.90	0.09	82.5	79.7	96 %	165	162	98 %	1.68	247.5	257	103 %
Sb	2.03	0.203	180	180	99 %	360	354	98 %	1.36	540	553	102 %
Ba	0.04	0.004	210	203	97 %	420	394	94 %	2.90	630	623	99 %
Mo	0.04	0.004	450	440	98 %	900	870	97 %	1.05	1350	1390	103 %
Cu	0.1	0.01	450	441	98 %	900	859	95 %	1.16	1350	1380	102 %
Sn	0.09	0.009	900	883	98 %	1800	1727	96 %	1.14	2700	2750	102 %
Cr	0.27	0.027	1650	1620	98 %	330	3102	94 %	1.57	4950	5080	103 %

N.D.: <IDL

Table 8 Analytical Result of Ibuprofen

Element	Conc. in Solution (µg/L)	Conc. in Raw material (µg/g)	50 % Spike of Target Conc.			100 % Spike of Target Conc.				150 % Spike of Target Conc.		
			Spike Conc. (µg/L)	Conc. of Spiked Sample (µg/L)	Accuracy (Recovery)	Spike Conc. (µg/L)	Conc. of Spiked Sample (µg/L)	Accuracy (Recovery)	%RSD	Spike Conc. (µg/L)	Conc. of Spiked Sample (µg/L)	Accuracy (Recovery)
Cd	0.004	0.0004	0.75	0.729	97 %	1.5	1.44	96 %	3.03	2.25	2.28	101 %
Pb	0.009	0.0009	0.75	0.735	97 %	1.5	1.47	97 %	0.57	2.25	2.26	100 %
As	N.D.	N.D.	2.25	2.16	96 %	4.5	4.44	99 %	0.67	6.75	6.78	100 %
Hg	0.011	0.0011	4.5	4.37	97 %	9	8.74	97 %	1.19	13.5	13.9	103 %
Co	0.014	0.0014	7.5	7.35	98 %	15	14.8	98 %	0.57	22.5	22.1	98 %
V	0.16	0.016	15	15.0	99 %	30	30.1	100 %	1.42	45	45.6	101 %
Ni	0.2	0.02	30	29.8	99 %	60	59.6	99 %	0.81	90	89.1	99 %
Tl	N.D.	N.D.	1.2	1.17	98 %	2.4	2.33	97 %	0.32	3.6	3.6	100 %
Au	0.024	0.0024	45	43.2	96 %	90	87.3	97 %	0.56	135	136	101 %
Pd	N.D.	N.D.	15	14.9	99 %	30	29.9	100 %	0.62	45	46.6	104 %
Ir	0.002	0.0002	15	14.6	97 %	30	29.3	98 %	0.26	45	45.6	101 %
Os	0.002	0.0002	15	14.6	97 %	30	29.3	98 %	0.41	45	45.4	101 %
Rh	N.D.	N.D.	15	15.0	100 %	30	29.8	99 %	0.39	45	46.1	102 %
Ru	N.D.	N.D.	15	15.1	101 %	30	29.7	99 %	0.69	45	46.1	102 %
Se	N.D.	N.D.	22.5	21.8	97 %	45	43.6	97 %	0.57	67.5	67.5	100 %
Ag	0.020	0.002	22.5	22.6	100 %	45	44.4	99 %	0.59	67.5	69.9	104 %
Pt	N.D.	N.D.	15	14.4	96 %	30	29.2	97 %	0.47	45	45.8	102 %
Li	0.76	0.076	82.5	85.2	102 %	165	167	101 %	1.00	247.5	258	104 %
Sb	0.91	0.091	180	185	102 %	360	360	100 %	0.67	540	551	102 %
Ba	0.07	0.007	210	221	100 %	420	410	98 %	0.55	630	636	101 %
Mo	0.05	0.005	450	449	100 %	900	889	99 %	0.27	1350	1370	101 %
Cu	0.1	0.01	450	449	100 %	900	899	100 %	0.47	1350	1350	100 %
Sn	0.06	0.006	900	915	102 %	1800	1760	98 %	0.62	2700	2760	102 %
Cr	5.76	0.576	1650	1630	98 %	330	3275	99 %	1.55	4950	4930	99 %

N.D.: <IDL

Conclusion

In this Application News, we measured three types of pharmaceutical raw materials and analyzed 24 elements indicated in the ICH Q3D guideline using the Shimadzu ICP-MS organic solvent system.

In accordance with the pharmacopeias (USP, EP), the accuracy, precision, quantification limit, and specificity were confirmed. The results of the validation demonstrated that the performance meets the acceptance criteria with a sufficient margin.

Based on the above, it was determined that the Shimadzu ICPMS-2050 is an effective analytical method for the 24-element analysis of pharmaceutical raw materials that can be dissolved in ethanol.

The analytical conditions can be easily registered from preset methods, allowing for analysis without the need to consider complex analytical conditions for organic solvents.

<References>

- 1) [GUIDELINE FOR ELEMENTAL IMPURITIES Q3D \(2014.12.16\)](#)
- 2) [GUIDELINE FOR ELEMENTAL IMPURITIES Q3D\(R2\) \(2022.04.26\)](#)
- 3) [USP <232> Elemental Impurities-Limits](#)
- 4) [USP <233> Elemental Impurities-Procedures](#)

<Related Applications>

1. Analysis of Elemental Impurities in Oral Drug Products Using ICPMS-2040/2050 –ICH Q3D [Application News 01-00577](#)
2. Screening Analysis of 24 Elemental Impurity Elements in Drugs Using ICPMS-2040/2050 [Application News 01-00718](#)

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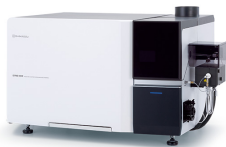
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