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Inductively Coupled Plasma Mass Spectrometer ICPMS-2040/2050

Application News

Analysis of Elemental Impurities in Oral Drug Products Using ICPMS-2040/2050 —ICH Q3D—

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User Benefits

- Robust quantitative analysis of control thresholds even when Option 1 (ICH Q3D) is used to convert PDEs to concentration limits
- Easily meets acceptance criteria for accuracy and precision for the analytical procedure used to quantify elemental impurities
- Preset methods eliminate the labor needed to establish analytical conditions and allow anyone to perform analysis with ease

■ Introduction

ICH Q3D (R2) Guideline for Elemental Impurities[1] establishes permitted daily exposure (PDE) levels for 24 elements of toxicological concern. The guideline requires that levels of these elements be controlled by appropriate analytical methods.

In response to this guideline, section "2.66 Elemental Impurities" [2] was included in the Japanese Pharmacopoeia (JP), sections "<232> Elemental Impurities—Limits" and "<233> Elemental Impurities—Procedures" [3] were included in the United States Pharmacopeia (USP), sections "5.20 Elemental Impurities" and "2.4.20 Determination of elemental impurities" [4] were included in the European Pharmacopoeia (EP), and inductively coupled plasma mass spectrometry (ICP-MS) was added as an analytical method.

This Application News describes using the ICPMS-2050 (Fig. 1) to analyze commercially available oral drug products (a gastrointestinal drug). Assuming that elemental impurities are measured at concentrations lower than 30 % of the PDE (control threshold), accuracy, precision, and quantitative limits were confirmed in an example analysis performed according to the quantitative procedures described in the JP, USP, and EP.

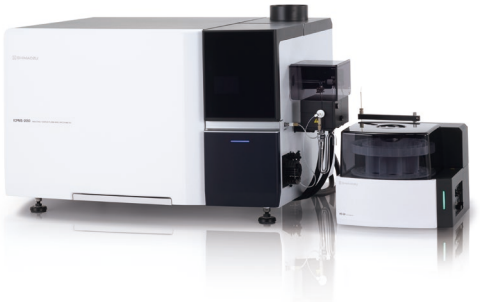


Fig. 1 ICPMS-2050 and AS-20

■ Sample

Test Sample: Oral drug products (gastrointestinal drug, orally disintegrating tablet)

Standard Solutions: Multi-element mixed standard solution for ICH Q3D oral agents (Cd, Pb, As, Co, V, and Ni)
Mercury standard solution for ICH Q3D
Single-element standard solutions of Sc, Ga, In, and Bi

■ Target Elements

The elements targeted in a risk assessment differ depending on the route of administration of the drug products. Quantities of Class 1 and 2A elements were determined as required for a risk assessment of oral drug products.

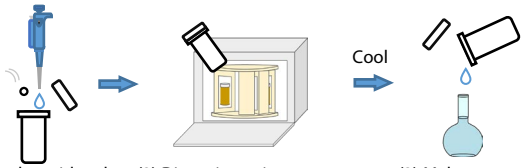
■ Sample Preparation

Test samples were prepared for analysis by the procedure shown in Fig. 2.

Approximately. 0.2 g of the test sample was added 4 mL of pure water, 4 mL of nitric acid, and 0.5 mL of hydrochloric acid, and then digested in a microwave digestion system (200 °C for approximately 60 minutes). Hydrochloric acid was added to improve the stability of Hg and other elements in the solution.

The digestion vessel was cooled to room temperature to avoid vaporization of elements with a low boiling point, and then the sample solution was made up to 50 mL for analysis (250-fold dilution).

A preparation blank solution containing no test sample was also prepared by the same procedure to verify the amounts of each element introduced as contaminants during the digestion process.



(1) Place the acid and test sample in the digestion vessel
(2) Digest in a microwave digestion system
(3) Make up to a fixed volume

Fig. 2 Sample Preparation Procedure

■ Target Limits and Test Solution Concentrations

When evaluating the significance of elemental impurity levels, target limits can be set to 30 % of the PDE (control threshold) divided by the maximum daily dose (Equation 1). PDEs were converted into concentration limits using Option 1, which assumes a maximum total daily dose of 10 g of the drug products.

$$\text{Target Limit [µg/g]} = \frac{\text{PDE [µg/day]} \times 30\ [\%]}{10\ [\text{g/day}]} \quad \ldots[1]$$

Target limits were converted to target concentrations in the sample solution using Equation 2.

$$\text{Target concentration [µg/L]} = \frac{\text{Target Limit [µg/g]} \times \text{Sample Digestion Amount [g]}}{\text{Volume [L]}} \quad \ldots[2]$$

■ Standard Solution

- Standard Solutions
  Standard solutions containing Class 1 and Class 2A elements at 50 %, 100 %, and 150 % of the target concentrations were prepared along with a blank solution. The same volumes of nitric acid and hydrochloric acid as the sample solutions were added to the standard solutions.
- Internal Standard Solution
  Commercially available single-element standard solutions were diluted and mixed to prepare an internal standard solution containing Sc at 2000 µg/L, Ga at 1000 µg/L, and In and Bi at 100 µg/L. The same volumes of nitric acid and hydrochloric acid as the internal standard solutions were added to the sample solutions. To reduce the labor involved in sample preparations, an online internal standard kit was used to automatically add the internal standard solution to a sample at the internal standard ratio of approximately 9:1.

■ Quantitative Method

The accuracy and precision of the quantitative method were assessed by analyzing a sample solution spiked with target elements at 50 %, 100 %, and 150 % of the target concentration.

Accuracy was verified based on recovery rates from a spike and recovery test; precision was verified based on the relative standard deviation (RSD) when concentration levels were measured six times in a sample spiked with 100 % of the target concentration; and quantitative limits were verified based on spike recovery after spiking to 50 % of the target concentration.

■ Equipment Configuration and Analytical Conditions

The equipment setup is shown in Table 1, and the analytical conditions used are shown in Table 2. The analytical conditions and mass measurements were taken from a preset method available in LabSolutions™ ICPMS.

Collision mode (He gas) was used to eliminate spectral interference. The same analysis can also be performed using the ICPMS-2040, which is a dedicated collision mode system.

Table 1 Equipment Configuration

Instrument:	ICPMS-2050
Nebulizer:	Nebulizer DC04
Chamber:	Cyclone Chamber
Torch:	Mini-Torch
Skimmer Cone:	Nickel
Autosampler:	AS-20
Internal Standard Elements:	Online Internal Standard Kit (sample: internal standard = about 9 : 1)

Table 2 Analytical Conditions

RF Power:	1.20 kW
Plasma Gas Flowrate:	9.0 L/min
Auxiliary Gas Flowrate:	1.10 L/min
Carrier Gas Flowrate:	0.85 L/min
Cell Gas:	He

■ Results

The results are shown in Table 3. The concentrations in the solid test sample were calculated by subtracting the concentrations in the preparation blank from the concentrations in the sample solution and then multiplying by the dilution factor.

The concentrations of all elements in the sample solution were less than the target concentrations.

The acceptance criteria for the accuracy and precision of the JP, USP, and EP quantitative procedures are spike recoveries between 70 % and 150 % (accuracy) and RSDs of 20 % or below (precision). Each pharmacopoeia lists different quantitative limits, the most stringent of which require that the accuracy acceptance criteria are met at no more than 50 % of the target concentration. In this case, spike recovery rates between 94 % and 104 % and RSD results of 3 % or below met the acceptance criteria with sufficient margins.

Instrument detection limits (IDLs) were also verified to be sufficiently low at no more than 1/10 of 50 % of the target concentrations.

■ Conclusion

This Application News used the ICPMS-2050 to analyze oral drug products.

The ICPMS-2050 was shown to offer performance that easily meets the acceptance criteria for the accuracy, precision, and quantitative limits of the quantitative procedures described in the JP, EP, and USP.

Investigating analytical conditions and which masses to measure is time-consuming and labor-intensive; in this example analysis, such time-consuming work was avoided by using a preset method from LabSolutions ICPMS.

Based on the above, the ICPMS-2050 is an effective tool for analyzing elemental impurities in oral drug products.

< References >

1) ICH Q3D (R2) GUIDELINE FOR ELEMENTAL IMPURITIES
2) Japanese Pharmacopoeia: 2.66 Elemental Impurities
3) United States Pharmacopeia
<232> ELEMENTAL IMPURITIES-LIMITS
<233> ELEMENTAL IMPURITIES-PROCEDURES
4) European Pharmacopoeia
5.20 Elemental Impurities
2.4.20 Determination of Elemental Impurities

Table 3 Quantitative Results

Class	Element	IDL [µg/L]	Preparation Blank Concentration [µg/L]	Sample Solution Concentration [µg/L]	Concentration in Solid Sample [µg/g]	Spiked to 50 % of the Target Concentration		Spiked to 100 % of the Target Concentration			Spiked to 150 % of the Target Concentration	
						Spiked Concentration [µg/L]	Recovery [%]	Spiked Concentration [µg/L]	Recovery [%]	RSD [%]	Spiked Concentration [µg/L]	Recovery [%]
1	^{111}Cd	0.006	N.D.	N.D.	N.D.	0.3	94	0.6	97	2.2	0.9	96
	^{208}Pb	0.001	0.005	0.029	0.006	0.3	102	0.6	103	0.95	0.9	103
	^{75}As	0.01	N.D.	N.D.	N.D.	0.9	103	1.8	100	0.74	2.7	99
	^{202}Hg	0.003	N.D.	N.D.	N.D.	1.8	96	3.6	96	0.94	5.4	97
2A	^{59}Co	0.003	N.D.	N.D.	N.D.	3	100	6	100	0.73	9	100
	^{51}V	0.02	N.D.	N.D.	N.D.	6	103	12	104	0.93	18	104
	^{60}Ni	0.1	N.D.	0.2	0.05	12	104	24	104	0.60	36	104

IDL = Standard deviation upon repeated analysis of the blank solution × 3 × Calibration curve slope
N.D. = Not Detected

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