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ICPMS-2040/2050 Inductively Coupled Plasma Mass Spectrometer

Application News

Screening Analysis of 24 Elemental Impurity Elements in Drugs Using ICPMS-2040/2050

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User Benefits

- Controlled elements can be verified by a screening analysis of 24 elemental impurity elements.
- Use of the preset method in LabSolutions™ ICPMS makes it possible to begin the analysis simply without laborious study of conditions.
- Study of candidate elements for internal standard correction is possible.

■ Introduction

The ICH Q3D Guideline for Elemental Impurities [1)] establishes permitted daily exposure (PDE) levels for 24 elements of toxicological concern.

The elements that should be considered in risk assessments differ, depending on the administration route of the drug product. For oral preparations, only seven elements of Class 1 and 2A should be considered, except for the intentional addition of elements such as catalyst utilization during synthesis. However, the origins of contamination by elemental impurities are diverse, including not only the components of the drug substance and additives, but also manufacturing equipment and implements.

Therefore, a screening analysis was carried out for all 24 elements, considering potential elemental impurities.

In addition, when internal standard correction is to be used, as in a related article [a], the content of candidate internal standard elements in the specimens must be verified in advance. In this article, a simple concentration analysis of the 24 elements in a drug product as elemental impurities was carried out using the preset method for screening analysis of drug products, which is included in the ICPMS-2040/2050 (Fig. 1). The concentration of the elements used in internal standard correction in the drug was also measured, and it was found that the elements can be used in correction.

Fig. 1 ICPMS-2040/2050 and AS-20 Autosampler

Registration Elements / Mass List

	Elem	Mass	Type	Cond.	Cell Gas
1	Ag	107	QUANT	He1	He
2	As	75	QUANT	He1	He
3	Au	197	QUANT	He1	He
4	Ba	137	QUANT	He1	He
5	Be	9	QUANT	No Gas	OFF
6	Bi	209	QUANT	He1	He
7	Cd	111	QUANT	He1	He
8	Co	59	QUANT	He1	He
9	Cr	52	QUANT	He1	He
10	Cu	63	QUANT	He1	He
11	Ga	71	QUANT	He1	He
12	Hg	202	QUANT	He1	He
13	Ho	165	QUANT	He1	He
14	In	115	QUANT	He1	He
15	Ir	193	QUANT	He1	He
16	Li	7	QUANT	No Gas	OFF

Fig. 2 Analysis Elements/Mass Registration Screen

■ Flow of Analysis

First, a screening analysis of the 24 elemental impurities is conducted with a 2-point calibration curve for a simple determination of the element concentrations. The elements Sc, Ga, In, and Bi, which are frequently used in Internal standardization, were selected as the candidate internal standard elements, and the concentrations of those elements in the sample solution were measured simultaneously with the 24 elements.

A precise quantitative analysis using the selected internal standard elements is carried out for the 7 essential elements of the assessment and the elements narrowed down in the screening analysis [a].

■ Preset Method

The LabSolutions ICPMS software includes a preset method for use in screening analyses of drug products, in which the analysis conditions, measured mass, standard solution concentrations, and other conditions are registered in advance (Fig. 2 and Fig. 3). Therefore, time and trouble necessary in study of the analysis conditions and registration of a large number of measured masses and concentrations are not required.

In this article, the measurements were carried out according to the registered method.

■ Sample

Oral drug products (gastrointestinal drug, orally disintegrating (OD) tablet)

■ Sample Preparation

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

The digestion vessel was cooled to room temperature, and the sample solution was then made up to 50 mL (250-fold dilution).

List of Calibration-Curve Standards(Check ON = Exclude Mass):

	Element	Unit	CAL1 BLK	CAL2 STD
	Ag	ug/L	0.0000000	30.00000
	As	ug/L	0.0000000	15.00000
	Au	ug/L	0.0000000	5.000000
	Ba	ug/L	0.0000000	30.00000
	Be	ug/L	0.0000000	100.0000
	Bi	ug/L	0.0000000	10.00000
	Cd	ug/L	0.0000000	5.000000
	Co	ug/L	0.0000000	30.00000
	Cr	ug/L	0.0000000	30.00000
	Cu	ug/L	0.0000000	30.00000
	Ga	ug/L	0.0000000	100.0000
	Hg	ug/L	0.0000000	5.000000
	Ho	ug/L	0.0000000	10.00000
	In	ug/L	0.0000000	10.00000
	Ir	ug/L	0.0000000	5.000000

Fig. 3 Calibration Sample Registration Screen

■ Adjustment of Standard Solution

Standard solutions containing the 24 elements that were the targets of the analysis and the candidate elements for use in correction of the internal standard, together with a blank solution, were prepared. To reduce the labor required in sample preparation, the following certified mixed standard solutions were used and prepared at the concentration registered in the method, as shown in Fig. 3. The concentrations can be modified as appropriate for the set control target value and the standard solution used.

- Standard substances
  - Certified mixed standard solutions for ICH Q3D *1 (XSTC-2071A, XSTC-2073)
  - Mercury standard solutions for ICH Q3D*2
  - Single-element standard solutions of Sc, Ga, In, and Bi *2 *3

*1 Manufactured by SPEX CertiPrep
*2 Manufactured by FUJIFILM Wako Pure Chemical Corporation
*3 Manufactured by Kanto Chemical Co., Ltd.

■ Equipment Configuration and Analysis Conditions

Table 1 shows the equipment configuration, and Table 2 shows the analysis conditions.

It should be noted that only He gas is used as the cell gas in the preset method for drug products in order to eliminate spectral interference. However, the gases that can be introduced into the cells of the ICPMS-2040 and ICPMS-2050 are as shown in Table 3. The same analysis as in this article can be carried out with either instrument.

Table 1 Equipment Configuration

Instrument	: ICPMS-2040/2050
Nebulizer	: Nebulizer DC04
Chamber	: Cyclone chamber
Torch	: Mini-torch
Skimmer cone	: Nickel
Autosampler	: AS-20

Table 2 Analysis 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

Table 3 Available Cell Gases

Instrument	He	H_2	3rd gas (option)
ICPMS-2040	○	×	×
ICPMS-2050	○	○	○

■ Measurement Results

The sample solutions were measured using a 2-point calibration curves for the standard solutions and blank. Table 4 shows the measurement results.

It can be understood that the contents of the elemental impurities were substantially lower than the PDE concentration conversion values.

The elements Sc, Ga, In, Bi were all undetected, indicating that they can be used as internal standard elements. The amount of addition of internal standard elements should be a concentration that results in sufficiently small variations, and if the element is detected in the sample, its content should be on a negligible level.

Table 4 Results of Measurements of 24 Elemental Impurity Elements

Class	Element	PDE value for oral drug products (µg/day)	PDE concentration conversion value (µg/g)	Limit of determination in sample (µg/g)	Concentration in sample (µg/g)
1	^{111}Cd	5	0.5	0.005	<
	^{208}Pb	5	0.5	0.0005	0.007
	^{75}As	15	1.5	0.01	<
	^{202}Hg	30	3	0.001	<
2A	^{59}Co	50	5	0.004	<
	^{51}V	100	10	0.02	<
	^{60}Ni	200	20	0.05	<
2B	^{205}Tl	8	0.8	0.0008	<
	^{197}Au	300	30	0.001	0.006
	^{105}Pd	100	10	0.002	<
	^{193}Ir	100	10	0.0005	<
	^{189}Os	100	10	0.002	<
	^{103}Rh	100	10	0.0007	<
	^{101}Ru	100	10	0.003	<
	^{78}Se	150	15	0.2	<
	^{109}Ag	150	15	0.002	<
	^{195}Pt	100	10	0.002	<
3	^{7}Li	550	55	0.02	<
	^{121}Sb	1200	120	0.007	<
	^{137}Ba	1400	140	0.006	0.007
	^{95}Mo	3000	300	0.007	<
	^{63}Cu	3000	300	0.02	<
	^{118}Sn	6000	600	0.006	<
	^{52}Cr	11000	1100	0.01	0.07

PDE concentration conversion value: Option 1 was selected (maximum daily dose: 10 g).
Limit of determination (quantitative limit): 10 × σ (standard deviation of calibration curve blank) × Slope of calibration curve.
< : Below limit of determination (quantitative limit)

■ Conclusion

In this article, a simultaneous screening analysis of 24 elemental impurity elements in an oral drug product and candidate elements for internal standard correction was carried out using an ICPMS-2040/2050.

The time and work necessary in study and registration of the analysis conditions and measured masses of the large number of elements in this experiment can be greatly reduced by using the preset method of the LabSolutions ICPMS software.

<References>

1) ICH HARMONISED GUIDELINE FOR ELEMENTAL IMPURITIES Q3D(R2)

<Related Applications>

a. Application News 01-00577, Analysis of Elemental Impurities in Oral Drug Products Using ICPMS-2040/2050 –ICH Q3D–
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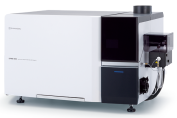

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