

Validation of Analysis Method Using ICPMS-2030 Based on USP <233> ELEMENTAL IMPURITIES - PROCEDURES

■ Introduction

The Guideline for Elemental Impurities ICH Q3D ⁽¹⁾ was setting the Permitted Daily Exposures (PDEs) for 24 elements with toxicity risk issues, and required control of their contents by an appropriate testing method. In the United States Pharmacopeia General Chapters USP <233> ⁽²⁾, inductively coupled plasma-mass spectrometry (ICP-MS) is recommended as the analysis procedures.

In this paper, the validation of the analytical method using a Shimadzu ICPMS-2030 was carried out in accordance with USP <233>. The tested materials were constituent ingredients used in oral formulations. The accuracy, precision, limit of quantitation and specificity of 24 target elements are presented, assuming measurements below the Control Threshold, 30% of the PDE.

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■ Target Elements

The elements that require risk assessment differ depending on the drug administration route. In case of oral administration, risk assessment are required for only 7 elements of Classes 1 and 2A, excluding elements that are intentionally added (e.g., catalysts) during the manufacture of drug substances. Assuming cases of intentional addition, here, the analysis targets were 24 elements included in Classes 2B and 3.

■ Target Concentration

ICH Q3D stipulates that "If the total elemental impurity level from all sources in the drug product is expected to be consistently less than 30% of the PDE, then additional controls are not required, provided the applicant has appropriately assessed the data and demonstrated adequate controls on elemental impurities." Therefore, the control values were set at 10% of the PDE, assuming cases in which the elemental impurity concentration of the test sample is significantly lower than 30% (control threshold) of the established PDE.

Because the daily intake of the sample is 10 g or less, the target concentration was calculated by equation (1) assuming a maximum daily intake of 10 g (Option 1).

$$\text{Target concentration } [\mu\text{g/g}] = \frac{\text{Control value (PDE } [\mu\text{g/day}] \times 0.1)}{\text{Maximum daily amount of drug product [g/day]}} \dots(1)$$

■ Sample

- Test sample : Tosufloxacin Tosylate Monohydrate
- Reference material : • Elemental impurities according to ICH Q3D oral Standard 1 (Sigma-Aldrich)
• Elemental impurities according to ICH Q3D oral Standard 2 (Sigma-Aldrich)
• Ba, Cr, Cu, Li, Mo, Sb, Sn, 1,000 mg/L standard solution (KANTO CHEMICAL)

■ Pretreatment

The test samples were dissolved by using a Multiwave PRO (Anton Paar) as a microwave digestion system. Fig. 1 shows the flow of decomposition treatment. Nitric acid, hydrochloric acid, and ultrapure water were used to decompose 0.2 g of the sample. After decomposition, the decomposition solution was adjusted to a constant volume of 50 mL (dilution rate: 250x). In measurement of Os, a decomposition solution treated under different conditions was used to assure stability.

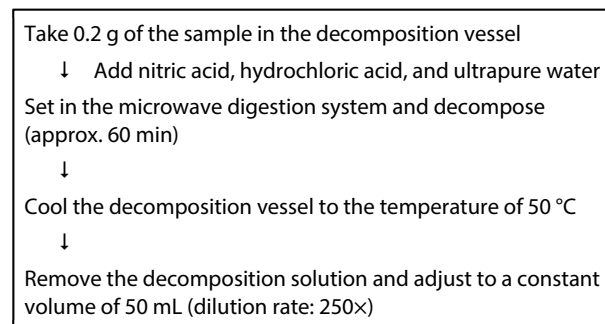


Fig. 1 Flow of Decomposition Treatment

■ Validation Test

A system suitability test of accuracy and precision (repeatability) in quantitative procedures and an evaluation of the quantitative limit and specificity were conducted. It should be noted that the quantitative limit can be demonstrated by meeting the Accuracy requirement.

■ Standard Solutions

Solutions containing the target elements at the three concentration levels of 0.5, 1.0, and 1.5J^{*1} and a blank solution were prepared. Acids were added so that the matrix of the standard solution is identical to that of the sample solution.

■ Sample Preparation

• Accuracy

The reference material was added and prepared to obtain the three target concentrations of 50%, 100%, and 150% before sample decomposition. The concentrations of the added reference material after decomposition were 0.5J, 1.0J, and 1.5J.

• Precision (Repeatability)

Samples were prepared by adding the reference material to 6 independent samples to obtain the target concentrations. This operation was the same as in preparation of the sample with the target concentration of 100% for the accuracy evaluation.

*1 J: The concentration (w/v) of the Target element(s) at the Target limit in the test solution. When the test solution is prepared after a sample is degraded, J is obtained by converting the target concentration (µg/g) to the concentration J (µg/L) in the test solution by using equation (2). Table 1 shows the results of conversion from the target concentration to 1.0 J.

$$J [\mu\text{g/L}] = \frac{\text{Target concentration} [\mu\text{g/g}]}{\text{Dilution rate [L/g]}} \dots(2)$$

■ Internal Standard Element Correction

Be, Bi, Ga, Sc, Tb, Te, and Y were used as internal standard elements.

A Shimadzu Automatic Internal Standard Addition Kit was used in addition of these internal standard elements, and the internal standard element solution and sample were mixed at a ratio of 1 : 9.

■ Analysis Conditions

Table 2 ICP-MS Analysis Conditions

Instrument	: ICPMS-2030
RF frequency power	: 1.2 kW
Plasma gas	: 8.0 L/min
Auxiliary gas	: 1.1 L/min
Carrier gas	: 0.7 L/min
Nebulizer	: Nebulizer 07
Pump speed	: 20 rpm
Chamber	: Electronically-cooled cyclonic chamber
Plasma torch	: Mini-torch
Sampling cone/skimmer cone	: Cu
Collision gas	: He
Internal standard element addition	: Automatic addition

Table 1 Results of Conversion from PDE to Target Concentration and J

Class	Element	Oral PDE	Oral 10% PDE	Target concentration Option 1 Maximum daily intake 10 g	1.0J
		µg/day	µg/day	µg/g	µg/L
1	As	15	1.5	0.15	0.6
	Cd	5	0.5	0.05	0.2
	Hg	30	3	0.3	1.2
	Pb	5	0.5	0.05	0.2
2a	Co	50	5	0.5	2
	Ni	200	20	2	8
	V	100	10	1	4
2b ^{*2}	Ag	150	15	1.5	6
	Au	100	10	1	4
	Ir	100	10	1	4
	Os	100	10	1	4
	Pd	100	10	1	4
	Pt	100	10	1	4
	Se	150	15	1.5	6
	Rh	100	10	1	4
	Ru	100	10	1	4
Tl	8	0.8	0.08	0.32	
3 ^{*2}	Ba	1400	140	14	56
	Cr	11000	1100	110	440
	Cu	3000	300	30	120
	Li	550	55	5.5	22
	Mo	3000	300	30	120
	Sb	1200	120	12	48
Sn	600	60	60	240	

*2 For oral, risk assessment is not required for these classes provided the elements are not deliberately added.

■ Validation Results

(1) Accuracy, precision, and limit of quantitation

• Acceptance criteria

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.

• 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 using the average of the quantitative values of all samples. Table 3 shows the measurement results.

Accuracy: Spike recovery of the samples with each of the target concentrations of 50%, 100%, and 150% was in the range of 94% to 105%, and therefore satisfied the acceptance criterion.

Precision (Repeatability): RSD of the spiked samples with the target concentration was 0.5% to 3.9%, 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.

Table 3 Accuracy, Precision, and Limit of Quantitation (µg/L)

Class	Element	m/z	Average of quantitative values of blank (n=6)	50% target concentration spike			100% target concentration spike				150% target concentration spike		
				Spiked concentration	Average of quantitative values (n=3)	Accuracy	Spiked concentration	Average of quantitative values (n=6)	Precision	Accuracy	Spiked concentration	Average of quantitative values (n=3)	Accuracy
									RSD				
1	As	75	0.02	0.3	0.32	99%	0.6	0.59	1.2%	95%	0.9	0.87	95%
	Cd	111	<0.001	0.1	0.099	99%	0.2	0.189	1.5%	95%	0.3	0.286	95%
	Hg	202	0.01	0.6	0.62	103%	1.2	1.22	1.4%	101%	1.8	1.83	101%
	Pb	207	0.02	0.1	0.12	97%	0.2	0.21	0.5%	96%	0.3	0.31	98%
2a	Co	59	<0.005	1	0.985	98%	2	1.93	2.2%	96%	3	2.94	98%
	Ni	60	0.1	4	4.0	98%	8	8.0	1.8%	98%	12	12.1	100%
	V	51	0.02	2	1.89	94%	4	3.86	3.9%	96%	6	5.83	97%
2b	Ag	107	<0.003	3	3.09	103%	6	6.09	0.7%	101%	9	9.16	102%
	Au	197	<0.01	2	2.04	102%	4	3.99	0.5%	100%	6	6.04	101%
	Ir	191	<0.001	2	1.99	100%	4	3.92	0.6%	98%	6	5.91	98%
	Os	188	<0.007	2	1.99	100%	4	3.94	0.9%	99%	6	5.93	99%
	Pd	108	0.14	2	2.12	99%	4	4.06	1.9%	98%	6	6.08	99%
	Pt	194	<0.004	2	2.03	102%	4	3.97	0.5%	99%	6	6.00	100%
	Se	78	<0.03	3	3.06	102%	6	5.96	1.2%	99%	9	9.12	101%
	Rh	103	<0.0009	2	2.00	100%	4	3.88	1.6%	97%	6	5.92	99%
	Ru	101	<0.005	2	1.99	100%	4	3.89	1.8%	97%	6	5.91	98%
Tl	205	<0.003	0.16	0.163	102%	0.32	0.317	0.7%	99%	0.48	0.479	100%	
3	Ba	137	0.06	28	29.1	104%	56	57.4	1.5%	102%	84	85.6	102%
	Cr	52	<0.09	220	220	100%	440	431	1.2%	98%	660	651	99%
	Cu	65	<0.2	60	60.5	101%	120	119	1.5%	99%	180	181	100%
	Li	7	<0.07	11	10.6	96%	22	20.8	1.0%	94%	33	31.3	95%
	Mo	95	0.04	60	59.7	99%	120	117	1.2%	97%	180	177	99%
	Sb	121	<0.01	24	25.2	105%	48	49.9	1.3%	104%	72	74.5	104%
	Sn	118	<0.04	120	124	104%	240	246	0.9%	102%	360	365	101%

< : Less than detection limit (3 σ)

σ : Standard deviation of n=10 consecutive measurements of blank solution

(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. In ICP-MS, evaluation for interference by isobars, polyatomic ions originating from Ar, oxides of coexistent elements, and chloride ions is necessary. Here, the two elements As and Cd were assessed.

1. As

In the case of As, the polyatomic ion ArCl originating from Ar and Cl causes interference. Because the test samples contain 0.5% hydrochloric acid, which is used in decomposition, interference has a large effect. Fig. 2 shows the As ($m/z=75$) spectrum when a 0.5% HCl solution was measured. It can be understood the interference by ArCl is greatly reduced by using a collision gas. A quantitative analysis of As was also done for a 0.5% HCl solution. Table 4 shows the results. Without use of the collision gas, the value of As is abnormally high due to interference, but As is below the lower limit of detection when the collision gas is used. This result confirmed that quantitation is possible without interference of ArCl, even when hydrochloric acid is used in decomposition of the sample.

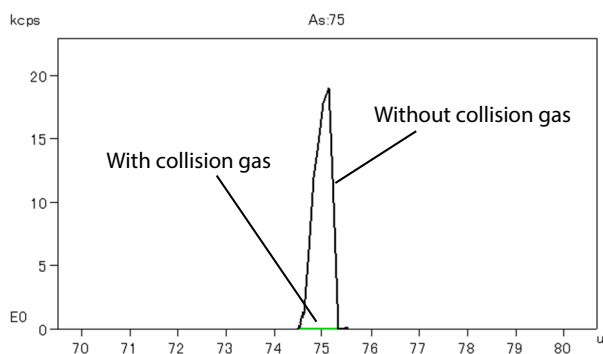


Fig. 2 Profiles of As for 0.5% HCl Solution

Table 4 Results of Quantitation of As for 0.5% HCl Solution ($\mu\text{g/L}$)

Element (m/z)	Without collision gas	With collision gas
As (75)	2.6	<0.009

2. Cd

MoO originating from the Class 3 element Mo causes interference with Cd. A 180 $\mu\text{g/L}$ Mo solution (concentration equivalent to 1.5J) was analyzed, and the amount of interference with Cd was measured. Here, in addition to using a collision gas, interelement correction was also conducted. Table 5 shows the results.

When the collision gas was used without interelement correction, interference by MoO was reduced but not completely eliminated. However, the quantitative value was below the lower limit of detection when the collision gas was used in combination with interelement correction. This result confirmed that use of interelement correction together with a collision gas enables appropriate correction of interference, which could not be eliminated by the collision gas alone.

Correction of interference originating from divalent ions and isobars ions is also possible by using interelement correction, and measurements can be conducted without using a reaction cell.

Table 5 Results of Quantitation of Cd for 180 $\mu\text{g/L}$ Mo Solution ($\mu\text{g/L}$)

Element (m/z)	With collision gas without interelement correction	With collision gas and interelement correction
Cd (111)	0.056	<0.001

Conclusion

By using this analytical procedure, the results satisfied the acceptance criteria for accuracy and reproducibility, even when the control value was set to a lower concentration level than the control threshold. Use of a collision gas in combination with interelement correction enables analysis of target elements with no problems, even when hydrochloric acid was added in the pretreatment process or the other target elements were present.

As described above, the ICPMS-2030 is effective for measurement of elemental impurities conforming to USP <233> Elemental Impurities-Procedures.

<Acknowledgement>

We wish to express our deep gratitude to Anton Paar Japan K.K. for its advice and cooperation in the use of the Multiwave PRO microwave reaction system sample pretreatment device.

<References>

- (1) Guideline for Elemental Impurities Q3D (R1)
- (2) USP <233> Elemental Impurities-Procedures

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