SHIMADZU
Excellence in Science

Inductively Coupled Plasma Mass Spectrometer ICPMS-2030

Application News

Analysis of Elemental Impurities in Medium-chain Triglycerides According to USP

Yeeun Han
Shimadzu Scientific Korea

User Benefits

- A sensitive and reliable method to determine elemental impurities in MCT, using ICPMS-2030 with collision cell technology.
- Validation requirements for the USP<233> elemental impurity test method could be achieved.

■ Introduction

Since 2020, regulations on elemental impurities in medicines have been in full swing in ICH member countries. As a result, in USP and EP, heavy metal test methods using atomic absorption spectroscopy (AAS) are being deleted or replaced by ICP-AES and ICP-MS methods.

In heavy metal analyses, graphite-AAS atomic absorption spectroscopy (GF-AAS) has been mainly used for trace analysis. But they are being replaced by analytical methods using ICP-MS for securing higher accuracy and precision.

As an example, analysis of five heavy metals (Pb, Cr, Cu, Ni, Sn) in medium-chain triglycerides (MCT), which are used as carrier oil for several oral drugs and vitamins due to their fast absorption properties into the human body, have been carried out by using GF-AAS after pretreatment by organic solvents. But it is recently revised to use ICP-MS as an analytical tool.

In USP, analysis of five heavy metals, within the same allowable value as before, is revised to use ICP-MS after decomposing the MCT sample with wet digestion by sulfuric acid. Meanwhile, EP deleted the list of elements for heavy metal analysis and revised it to apply the analysis method of usual elemental impurity, if applicable. [1], [2]

Therefore, this newsletter is attempted to analyze harmful heavy metals in MCTs by using ICP-MS and confirm the validity of results based on the revised USP Individual Test method and USP<233> Metal Impurities Test method.

■ Experimental

1. USP Individual Test method (MCT)

The sample pretreatment was carried out by wet digestion as shown in <Figure 1>. The standard solution for construction of calibration curve was diluted with a 6.5 % aqueous nitric acid for Cr, Cu, Pb, Ni and 7.5 % aqueous hydrochloric acid for Sn to prepare 1 µg/L or 5 µg/L of each standard solution to the test method, respectively.

The allowable concentration and the mass number for each element for ICP-MS analysis are shown in Table 1.

2. USP<233> Elemental impurities

In EP, the elemental impurity test method was not specifically defined, so USP <233> elemental impurity test method was applied.[3] The maximum daily dose was set to 10 g/day, and *J*-value was calculated based on the decomposition of MCTs using a microwave. They are listed in <Table 2>. The test was conducted on a total of 10 elements by adding Cr, Cu, and Sn as included in the USP criteria along with 7 elements corresponding to ICH Q3D Class 1 and 2. The allowable concentrations in <Table 1> were applied to the 5 elements prescribed by the USP. For other elements, the allowable concentration was calculated based on the oral permitted daily exposure (PDE) of ICH Q3D. [4]

The standard solution for preparing the calibration curve was prepared to have a concentration within 50 % to 150 %, respectively based on *J*-value. The concentration of the reagent added to the standard solution was the same amount as that of the sample solution. The calculated *J*-value and analytical parameters are shown in <Table 2>.

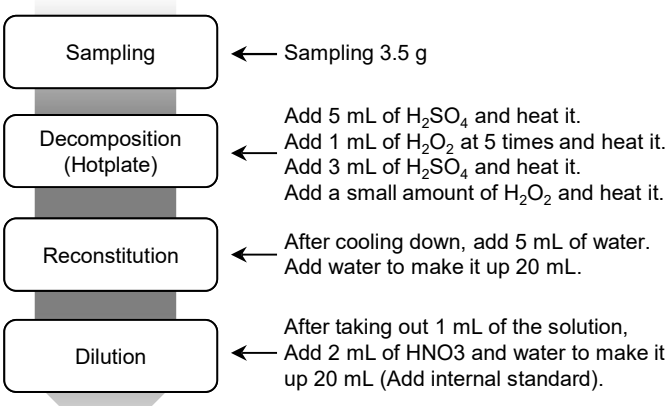

Fig. 1 Figure 1. Sample pretreatment
: USP Individual Test method(MCT)

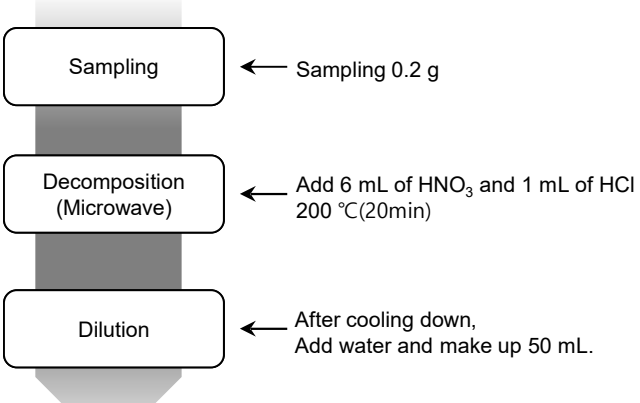

Fig. 2 Sample pretreatment
: USP<233> Elemental impurities

Table 1 The mass number of each element and the allowable criteria according to USP

Element	Isotope (amu)	Acceptance criteria, NMT* (μg/g)
Chromium (Cr)	52	0.05
Copper (Cu)	63	0.1
Lead (Pb)	206	0.1
Nickel (Ni)	58	0.1
Tin (Sn)	118	0.1

* NMT: Not more than.

Table 2 The analytical conditions for each element to analyze elemental impurities

Element	Oral PDE (μg/day)	Target concentration of drug* (μg/g)	*J* value** (μg/L)	Internal standard
^{52}Cr		.0.05	0.2	^{71}Ga
^{63}Cu		0.10	0.4	^{71}Ga
^{60}Ni	regardless	0.10	0.4	^{71}Ga
^{208}Pb		0.10	0.4	^{205}Tl
^{118}Sn		0.10	0.4	^{115}In
^{111}Cd	5	0.25	1.0	^{115}In
^{75}As	15	0.75	3.0	^{71}Ga
^{202}Hg	30	1.50	6.0	^{205}Tl
^{59}Co	50	2.50	10.0	^{71}Ga
^{51}V	100	5.00	20.0	^{71}Ga

* Target concentration: For Cr, Cu, Ni, Pb, and Sn, the allowable concentration values of the USP test method were applied, and other elements were calculated by assuming the maximum daily dose of 10 g from the PDE of ICH Q3D.
** *J* value: Reference concentration of the test solution prepared by pretreating 0.2 g of the sample and diluting it with 50 mL.

■ Analytical conditions

ICP-MS (Figure 3) was used for sample analysis with instrumental parameters in Table 3. For Ga, In and Tl, internal standard elements were matched as indicated in the test method of each element.

The validity of each test method was confirmed through checking recovery rates from additional method following published method, and accuracy and repeatability were confirmed.

Table 3 Analytical conditions

RF power	1.20 kW
Sampling depth	5.0 mm
Plasma gas flow	8.0 L/min
Auxiliary gas flow	1.10 L/min
Carrier gas flow	0.70 L/min
Cell gas (He) flow	6.0 mL/min
Torch type	Mini torch
Sampling & Skimmer cone	Nickel
Quantification method	Internal Standard Correction Method

Fig 3 ICPMS-2030 system

■ Results

The results for the USP individual test method showed a good recovery rate of 80 % - 120 %, as shown in <Table 4>, and the results for the USP<233> elemental impurity test method also showed satisfactory results to validation requirements as shown in <Table 5>.

Table 4. Test result (Individual Test method: MCT)

Element	Non-spiked sample (*n* = 3)		Spike recovery test						
			Test 1 (*n* = 3)			Test 2 (*n* = 6)			
	Raw data (μg/L)	Result (μg/g)	Spiked conc. (μg/L)	Raw data (μg/L)	Accuracy (Recovery)	Spiked conc. (μg/L)	Raw data (μg/L)	Accuracy (Recovery)	Precision (RSD)
^{52}Cr	0.064	0.007	0.5	0.640	115 %	1.0	1.265	120 %	5.0 %
^{63}Cu	ND	ND	0.5	0.476	95 %	1.0	0.976	98 %	1.3 %
^{58}Ni	ND	ND	0.5	0.399	80 %	1.0	0.874	87 %	2.1 %
^{206}Pb	ND	ND	0.5	0.491	98 %	1.0	0.983	98 %	1.2 %
^{118}Sn	0.021	0.002	0.5	0.480	92 %	1.0	0.982	96 %	1.1 %

- ND(Not Detected): Below the detection limit calculated from the standard deviation on 10 repeat measurements of calibration curve blank .

Table 5 Test result (USP<233> elemental impurities)

Element	Non-spiked sample (*n* = 3)		Spike recovery test									
			50 % of *J* value (*n* = 3)			100 % of *J* value (*n* = 6)				150 % of *J* value (*n* = 3)		
	Raw data (µg/L)	Result (µg/g)	Spiked conc. (µg/L)	Raw data (µg/L)	Accuracy (Recovery)	Spiked conc. (µg/L)	Raw data (µg/L)	Accuracy (Recovery)	Precision (%RSD)	Spiked conc. (µg/L)	Raw data (µg/L)	Accuracy (Recovery)
^{52}Cr	ND	ND	0.1	0.088	88 %	0.2	0.179	90 %	1.0 %	0.3	0.283	94 %
^{63}Cu	0.075	0.019	0.2	0.254	89 %	0.4	0.437	90 %	3.2 %	0.6	0.642	94 %
^{60}Ni	ND	ND	0.2	0.191	95 %	0.4	0.381	95 %	3.1 %	0.6	0.589	98 %
^{208}Pb	ND	ND	0.2	0.198	99 %	0.4	0.398	99 %	0.7 %	0.6	0.622	104 %
^{118}Sn	ND	ND	0.2	0.179	89 %	0.4	0.369	92 %	2.9 %	0.6	0.574	96 %
^{111}Cd	ND	ND	0.5	0.454	91 %	1.0	0.932	93 %	1.2 %	1.5	1.444	96 %
^{75}As	ND	ND	1.5	1.592	106 %	3.0	3.206	107 %	1.7 %	4.5	4.926	109 %
^{202}Hg	ND	ND	3.0	2.973	99 %	6.0	6.088	101 %	0.6 %	9.0	9.583	106 %
^{59}Co	ND	ND	5.0	4.951	99 %	10.0	9.956	100 %	1.1 %	15.0	15.301	102 %
^{51}V	ND	ND	10.0	9.995	100 %	20.0	20.079	100 %	1.1 %	30.0	30.929	103 %

* ND(Not Detected): Below the detection limit calculated from the standard deviation on 10 repeat measurements of calibration curve blank .

■ Conclusion

In the ICH Q3D guide for analyzing trace metal elemental impurities in medicines, the test method is shifting from using AAS to ICP-AES or ICP-MS to secure accuracy, precision and convenience. This newsletter is intended to compare and evaluate analytical results obtained by using ICP-MS based on the revised USP individual test method for MCT and USP<233> elemental impurity test method.

■ References

1. Medium-Chain Triglycerides, USP43-NF38, 2020.11.01

2. Triglycerides, Medium-Chain, 01/2020:0868, European Pharmacopoeia (Ph. Eur.) 10th Edition, 2019. 07

3. USP43-NF38 <232> ELEMENTAL IMPURITIES—LIMITS, <233> ELEMENTAL IMPURITIES—PROCEDURES, 2020.11.01

4. ICH(*The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use*) Q3D(R1) Guideline for Elemental Impurities, Step 4, 2019. 03.22

09-SSK-009-EN First Edition: Mar. 2022

Shimadzu Corporation
www.shimadzu.com/an/

Shimadzu Scientific Korea
www.shimadzu.co.kr