SHIMADZU
Excellence in Science

Application News

No. X271

X-Ray Analysis

ICH Q3D Elemental Impurities Analysis of Drug Substances by EDX

The ICH Harmonised Guideline, Guideline for Elemental Impurities (ICH Q3D) of drug products,[1] requires control of the residual amounts of 24 elements whose toxicity is a concern. This requirement was applied to new drug products from June 2016 in the United States and Europe and from April 2017 in Japan. Application to existing drugs began in January 2018 in the United States and in December 2017 in Europe.

Although the recommended analytical methods for elemental impurities are inductively coupled plasma-atomic emission spectrometry (ICP-AES) [2] and ICP-mass spectrometry (ICP-MS), use of appropriate alternative methods is also permitted when such methods exist. Therefore, the appropriateness of X-ray fluorescence spectrometry as an alternative to the above-mentioned methods was verified referring to the United States Pharmacopeia USP <735> [3].

The instrument used was an EDX-7000 and its option, "Pharmaceuticals Impurities Analysis Method Package." Quantitative analysis was done by the calibration curve method with standard sample aqueous solutions using two types of drug substance in powder form as the test materials. The results were satisfactory, confirming the possibility of using EDX in control of elemental impurities of drug products.

T. Nakao, K. Hori

Elements

The Pharmaceuticals Impurities Analysis Method Package enables analysis of the following 12 elements among those specified in ICH Q3D. These elements have high importance for control of elemental impurities.

Class 1 : As, Cd, Hg, Pb

Class 2A : V, Co, Ni

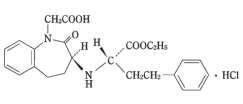
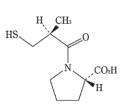
Class 2B : Ru, Rh, Pd, Ir, Pt

Evaluation Samples

The following two types of drug substance powders were used. Table 1 shows the details and the daily amount of drug product of a drug product.

- Benazepril hydrochloride
- Captopril

Table 1 Evaluation Samples and Structural Formulas

Name	Benazepril Hydrochloride	Captopril
Compositional formula	$C_{24}H_{28}N_2O_5 \cdot HCl$	$C_9H_{15}NO_3S$
Atomic weight	460.95	217.29
Structural formula		
Daily amount of drug product	10 mg/day	150 mg/day

Concept of Control Values

(1) Setting of maximum permitted concentration

ICH Q3D stipulates the permitted daily exposure (PDE) for each element. Therefore, when evaluating the elemental impurities in a drug product or its constituent ingredients, the PDE value must be converted to a concentration. The conversion methods in ICH Q3D are Options 1, 2a, 2b, and 3.

In this assessment, the daily amount of drug product was 300 mg, which is higher than the specified value in Table 1, in order to validate the lower concentration range. Values for oral preparations were used as PDE values, and option 2b was used to convert the PDE values.

(2) Setting of spike concentration

Because ICH Q3D defines 30% of the PDE value as the control threshold, 30% of the maximum permitted concentration in (1) was set as the control value. The spike concentration was set at 1/2 of the control value in accordance with USP <735>. Table 2 shows the relationship of the PDE value, maximum permitted concentration, and spike concentration.

Table 2 PDE Values and Spike Concentrations

	PDE Value (A)	Maximum Permitted Concentration (B)=(A)/0.3	Spike Concentration (B)×0.3/2
Element/unit	μg/day	μg/g	μg/g
Pb, Cd	5	16.7	2.5
As	15	50	7.5
Hg	30	100	15
Co	50	167	25
V, Ir, Pt, Ru, Rh, Pd	100	333	50
Ni	200	667	100

Standard Samples

Five standard samples were prepared from each of the following two mixed standard solutions. Table 3 and Table 4 show their concentrations.

Mixed standard solutions (manufactured by SPEX)

- XSTC-2046
- USP-TXM4

Table 3 Standard Sample Concentrations Using XSTC -2046 [μg/mL]

	Blank	STD1	STD2	STD3	STD4
Dilution ratio	(Ultrapure water)	10	5	2	1
Pb, Cd	0	0.5	1	2.5	5
As	0	1.5	3	7.5	15
Hg	0	3	6	15	30
Co	0	5	10	25	50
V	0	10	20	50	100
Ni	0	20	40	100	200

Table 4 Standard Sample Concentrations Using USP-TXM4 [μg/g]

	Blank	STD1	STD2	STD3	STD4
Dilution ratio	(Ultrapure water)	10	5	2	1
Ir, Pt, Ru, Rh, Pd	0	10	20	50	100

Sample Pretreatment

(1) Preparation of spiked samples

Standard solution for atomic absorption or cellulose powder with high As content was added to the evaluation sample at an added concentration and mixed uniformly to prepare the added sample.

(2) Setting of samples

As shown in Fig. 1, the samples were introduced into a sample container lined with a polypropylene film and then measured.

XSTC-2046 stock solution 8 mL

Captopril drug substance powder 2 g

Fig. 1 Measurement Samples

Validation Results

Validation was conducted for the USP <735> items of Accuracy, Precision, Specificity, Quantitation Limit, Linearity, and Robustness.

Table 5 shows an outline of the USP <735> validation procedure, together with the validation results in this experiment, and Tables 6 to 10 and Fig. 2 show the results for each item.

Table 5 Outline of USP <735> Validation and Validation Results

Item	Method	Acceptance Criterion	Results	Judgment
Accuracy	• Quantitative analysis by calibration curve method • Spike and recovery test	Recovery rate 70.0 to 150.0%	Recovery rate 92 to 108%	Pass
Precision	• Spiked samples: 3 • 3 replicate measurements for 3 samples • Relative standard deviation (RSD) of total of 9 quantitative analysis	RSD ≤ 20.0%	RSD ≤ 5.8%	Pass
Specificity	• Quantitative spectrum is clearly separated and distinguishable from the spectrum of matrix component.	Satisfy Accuracy condition	• Quantitative spectrum was separated from matrix component. • Satisfied Accuracy.	Pass
Quantitation Limit	• Repetition of quantitative analysis 6 replicate measurements for unspiked sample • Estimated value of 10 times the standard deviation	Satisfy max. 50% of control value and Accuracy and Precision conditions.	• Estimated value < 50% of control value (= spike concentration) • Satisfied Accuracy and Precision.	Pass
Linearity	• Standard samples: 5 • Regression line by least squares method.	NLT 0.99	Correlation coefficient R ≥ 0.9941	Pass
Robustness	• Sample quantity shall be used as experimental parameter. • Using 2.0 g as standard value, change to 1.0 g, 0.5 g and 0.3 g.	Change rate of quantitative value after change of experimental parameter shall be within ± 20.0%.	Change rate of quantitative value: -12.0 to +8.3%	Pass

Table 6 Accuracy [μg/g]

Class		Class1				Class2A			Class2B				
Element		As	Hg	Pb	Cd	V	Co	Ni	Ir	Pt	Ru	Rh	Pd
Spike concentration		7.5	15	2.5	2.5	50	25	100	50	50	50	50	50
Benazepril Hydrochloride	Spiked sample	7.2	14.9	2.5	2.6	50.8	25.5	104.2	51.0	49.6	53.0	51.6	50.9
	Unspiked sample	<0.5	<0.3	<0.6	<1.2	<2.9	<1.4	<0.7	<0.5	<0.5	<0.5	<0.5	<0.5
	Recovery rate [%]	96	99	102	104	102	102	104	102	99	106	103	102
Captopril	Spiked sample	7.2	13.8	2.7	2.5	46.2	23.0	94.5	47.9	45.9	52.6	52.4	51.2
	Unspiked sample	<0.5	<0.4	<0.7	<1.2	<3.4	<1.7	<0.8	<0.6	<0.6	<0.4	<0.4	<0.7
	Recovery rate [%]	96	92	108	100	93	92	95	96	92	105	105	102

Table 7 Precision [%]

Element		As	Hg	Pb	Cd	V	Co	Ni	Ir	Pt	Ru	Rh	Pd
Benazepril Hydrochloride	RSD	0.5	0.4	4.8	5.8	0.7	0.5	0.3	0.4	0.7	0.8	0.7	0.8
Captopril	RSD	2.3	0.8	4.6	5.5	2.7	1.8	1.1	1.4	0.5	0.6	0.9	0.5

Table 8 Estimated Value of Quantitation Limit [μg/g]

Element	As	Hg	Pb	Cd	V	Co	Ni	Ir	Pt	Ru	Rh	Pd
Benazepril Hydrochloride	0.2	0.4	0.6	1.4	4.3	1.0	0.9	0.5	0.1	0.3	0.6	0.7
Captopril	0.1	0.4	1.0	1.3	4.1	3.3	0.9	0.5	0.4	0.6	0.2	0.5

Table 9 Linearity

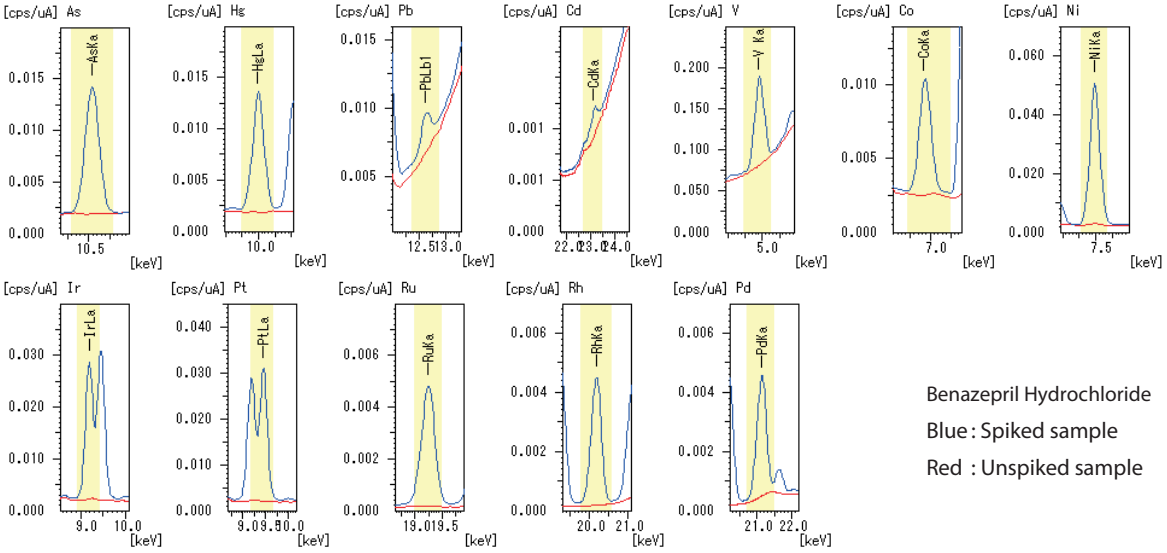
[μg/g]

Element	As	Hg	Pb	Cd	V	Co	Ni	Ir	Pt	Ru	Rh	Pd
Correlation coefficient	0.9998	0.9999	0.9975	0.9941	0.9999	0.9999	0.9999	0.9997	0.9998	0.9999	0.9999	0.9999

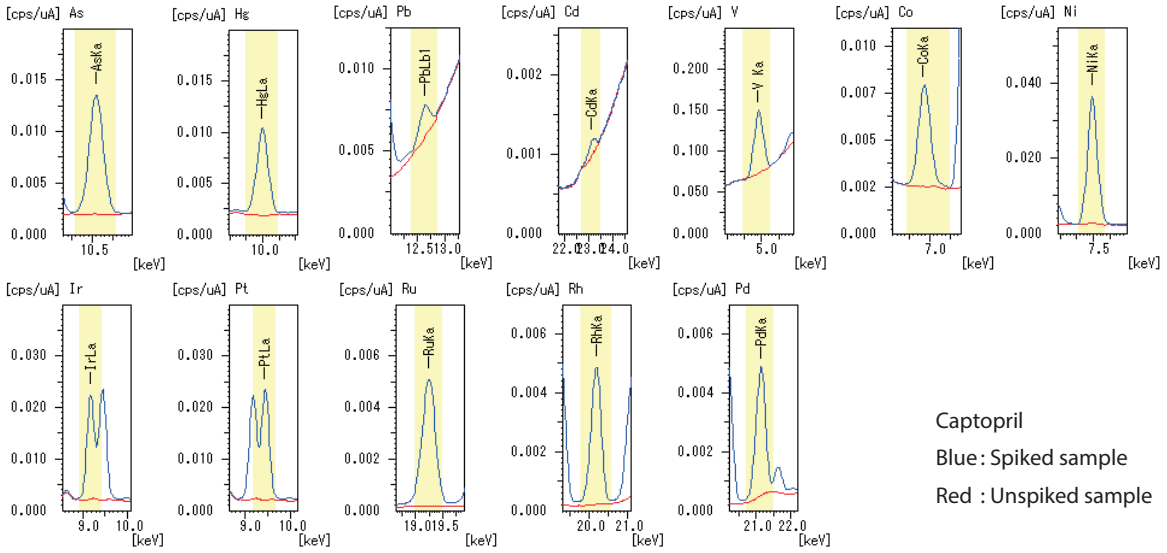
Table 10 Robustness

[μg/g]

Element		As	Hg	Pb	Cd	V	Co	Ni	Ir	Pt	Ru	Rh	Pd
Reprinted from Table 6	2.0 g (standard)	7.2	14.9	2.5	2.6	50.8	25.5	104.2	51.0	49.6	53.0	51.6	50.9
	1.0 g	7.1	15.1	2.4	2.3	51.1	25.7	103.7	51.9	49.8	55.1	53.2	51.3
Benazepril Hydrochloride	0.5 g	6.7	14.9	2.4	2.4	53.2	26.3	104.4	51.7	49.9	53.9	49.3	50.6
	0.3 g	6.6	14.6	2.2	2.4	53.0	26.1	102.1	52.0	49.4	52.2	49.9	50.7
	1.0 g	-1.4	+1.3	-4.0	-11.5	+0.6	+0.8	-0.5	+1.8	+0.4	+4.0	+3.1	+0.8
Change rate [%]	0.5 g	-6.9	0.0	-4.0	-7.7	+4.7	+3.1	+0.2	+1.4	+0.6	+1.7	-4.5	-0.6
	0.3 g	+8.3	-2.0	-12.0	-7.7	+4.3	+2.4	-2.0	+2.0	-0.4	-1.5	-3.3	-0.4
Reprinted from Table 6	2.0 g (standard)	7.2	13.8	2.7	2.5	46.2	23.0	94.5	47.9	45.9	52.6	52.4	51.2
	1.0 g	7.1	13.8	2.6	2.6	45.9	23.1	93.8	48.0	46.0	54.1	53.3	51.1
Captopril	0.5 g	7.3	13.6	2.4	2.4	48.0	23.8	96.3	49.2	46.9	54.7	50.6	51.4
	0.3 g	7.0	13.6	2.4	2.6	47.6	23.7	95.9	47.3	46.5	50.6	49.3	49.8
	1.0 g	-1.4	0.0	-3.7	+4.0	-0.6	+0.4	-0.7	+0.2	+0.2	+2.9	+1.7	-0.2
Change rate [%]	0.5 g	+1.4	-1.4	-11.1	-4.0	+3.9	+3.5	+1.9	+2.7	+2.2	+4.0	-3.4	+0.4
	0.3 g	-2.8	-1.4	-11.1	+4.0	+3.0	+3.0	+1.5	-1.3	+1.3	-3.8	-5.9	-2.7



Benazepril Hydrochloride
Blue : Spiked sample
Red : Unspiked sample



Captopril
Blue : Spiked sample
Red : Unspiked sample

Fig. 2 Specificity

Appropriateness of Spiked Samples and Concentrations

For validation of the appropriateness of the spiked samples and their concentrations, unspiked samples and spiked samples were analyzed with an ICPMS-2030. Part of the sample (powder) was digested with a microwave digestion system and dissolved into a solution. The measurement solutions were diluted by 5,000 times from the solid sample for the Class 1 and Class 2A samples, and by 25,000 times for the Class 2B samples.

Table 11 shows the ICP-MS analysis results.

Because both of the two types of drug substance samples were close to the spike concentrations, it is thought that the spiking and homogenization of the evaluation samples were conducted properly. In addition, the appropriateness of the measurement results was also conformed for the unspiked samples.

Table 11 ICPMS-2030 Analysis Results (Average Value for n =2) [μg/g]

Class		Class1				Class2A			Class2B				
Element		As	Hg	Pb	Cd	V	Co	Ni	Ir	Pt	Ru	Rh	Pd
Spike concentration		7.5	15	2.5	2.5	50	25	100	50	50	50	50	50
Benazepril Hydrochloride	Spiked sample	7.1	14.9	2.58	2.42	48.6	24.1	99.0	52.1	49.9	50.0	50.3	49.5
	Unspiked sample	<0.2	<0.1	0.03	<0.02	<0.7	<0.02	0.3	<0.05	<0.2	<0.05	<0.07	<0.1
Captopril	Spiked sample	7.3	15.0	2.62	2.43	50.5	24.8	99.8	51.8	49.5	49.4	50.7	50.1
	Unspiked sample	<0.2	<0.1	0.03	<0.02	<0.7	<0.02	<0.2	<0.05	<0.2	<0.05	<0.07	<0.1

< : Indicates that the value was less than the conversion lower limit of determination (10 σ) for the drug substance (unspiked) powder.
Less than the conversion lower limit of determination (10 σ): Lower limit of determination (10 σ) in measurement solution × Dilution rate (Class 1, 2A: 5,000×, Class 2B 25,000×)

Conclusion

This experiment demonstrated the effectiveness of EDX as an alternative to ICP-AES/ICP-MS in ICH Q3D elemental impurities analysis of drug substance samples. Validation and verification results were also satisfactory even for Captopril, which has a high sulfur content of approximately 15%. The effectiveness of this method package, which produces calibration curves using standard aqueous solution samples, was also confirmed. Based on these results, it is considered possible to apply this method to control of various types of drug substances and drug products.

Because there are cases in which the limit concentration for analysis by EDX is on the order of a daily amount of drug product of 1 g, selective combined operation with EDX, corresponding to the type of drug substance and intake amount, is considered useful for efficiency and cost reduction.

Table 12 EDX Measurement Conditions (Pharmaceuticals Impurities Analysis Method Package)

Instrument	: EDX-7000
Elements	: As, Hg, Pb, Cd, V, Co, Ni, Ir, Pt, Ru, Rh, Pd
Analysis group	: Quantitative
Detector	: SDD
X-ray tube	: Rh target
Tube voltage	: 50 [kV]
Tube current	: Auto [μA]
Collimator	: 10 [mmφ]
Primary filter	: #1 (Cd, Ru, Rh, Pd), #2 (V) #4 (As, Hg, Pb, Co, Ni, Ir, Pt)
Atmosphere	: Air
Integral time	: 1,800 [s] × 3 (#1, #2, #4)
Dead time	: Max. 30 [%]

<References>
(1) ICH HARMONISED GUIDELINE, GUIDELINE FOR ELEMENTAL IMPURITIES Q3D (R1) (Final version Adopted on 22 March 2019)
(2) USP <233> Elemental Impurities – Procedures
(3) USP <735> X-Ray Fluorescence Spectrometry (May 2015)

First Edition: Oct. 2019

Shimadzu Corporation
www.shimadzu.com/an/