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Application News

No. X273

X-Ray Analysis

ICH Q3D Elemental Impurities Analysis of Tablets by EDX

- Verification Based on USP <233> ELEMENTAL IMPURITIES-PROCEDURES -

In the United States, the United States Pharmacopoeia General Test Chapters USP <232> and <233> have been applied to new drug products since January 1, 2018. ICP-MS and ICP-AES are recommended as the analysis procedures in the chapters. However, if the validation requirements are met, the alternative procedure can be substituted for the recommended analysis procedures[1] [2] [3].

Therefore, the appropriateness of Energy Dispersive X-ray Fluorescence Spectrometer was verified referring to "Limit Procedures" in USP <233>*1.

The used instrument was EDX-7000 and the test was conducted by evaluating of elemental impurities in oral drug (tablets). As the target concentration (allowable concentration), the value obtained by dividing 30% of the PDE *2 value by the maximum daily dose was set.

*1 Since the measurement sample in EDX is "Powder", the "Solution" part described in the test method was replaced with 'powder'
*2 PDE: Permitted Daily Exposure

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Elements

The measurement elements conformed to the method described in ICH Q3D. The seven elements of "Class 1 and Class 2A" are essential for risk assessment. The intentionally added element was assumed to be Pd in "Class 2B".

- Class1 : As, Hg, Pb, Cd
- Class2A : V, Co, Ni
- Class2B : Pd

Samples

Standardization : Cellulose powder spiked with standard solution for ICP

Test sample : as shown in Table 1

Table 1 Sample details under test

Tablets	Oral solid dosage form (Ethical drug)
Active ingredient content	30 mg / 0.5 g
Dosage form	Plain tablet
Daily amount of drug product	0.5 g
Main Component	Hydroxypropylcellulose

Target Concentration

The target concentration was 30% of the PDE values divided by daily amount of drug product. These values for each element are shown in Table 2.

Table 2 PDE Values and Target Concentrations of Oral Preparation

Elements	Unit	As	Hg	Pb,Cd	Co	V,Pd	Ni
PDE Values of Oral Preparation	µg/day	15	30	5	50	100	200
Target Concentrations	µg/g	9	18	3	30	60	120

Sample Preparation

Test samples were crushed into powders. Standardization, Standard powders, and Spiked sample powders 1 and 2 were prepared by spiked standard solutions for ICP. These details are shown in Table 3.

Table 3 Samples Used for Verification

Sample Name	Detail	Spiked Concentration	Number Produced (n)
Standardization	Cellulose Powder	0J, 0.5J, 1.5J	Each 1
Standard Powder	Cellulose Powder	1.0J	3
Spiked Sample Powder 1	Test sample	Target Concentration	3, 6
Spiked Sample Powder 2	Test sample	80% of Target Concentration	3
Unspiked Sample Powder	Test sample	Unspiked	3, 6

Sample Pretreatment

Each samples were introduced into a sample container lined with a polypropylene film. These samples are shown in Fig. 1.

Fig. 1 Standard Powder (Left) ,Spiked Sample Powder1 (Right)

Calibration Curve

The calibration curve was created with 3 points of 0J, 0.5J and 1.5J. Fig. 2 shows the calibration curve and correlation coefficient (R). The correlation coefficient R is 0.999 or more, and good linearity is obtained.

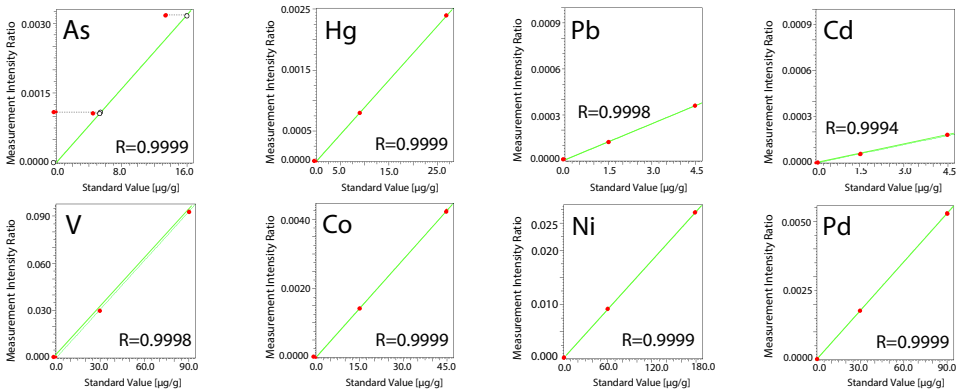

Fig. 2 Calibration Curve and Correlation Coefficient (R)

Table 4 Validation Requirements, Acceptance Criteria, and Results

Validation Requirements	Procedure		Acceptance Criteria	Results	Judgment
Detectability	(1)	Standard powder: n = 3 measured 3 times each Spiked sample powder 1: n = 3 measured 3 times each	The average value of Spiked sample powder1 should be within ± 15% of the average value of Standard powder	【Table 5 Results (1)】	Pass
	(2)	Spiked sample powder 2: n = 3 measured 3 times each	Average value of Spiked sample powder 2 < Average value of Standard powder	【Table 5 Results (2)】	Pass
Specificity	- Comparison with Unspiked samples - Spectrum confirmation - Matrix components and coexisting elements: removal and correction of overlapping effects by them		Specific detection for matrix components and coexisting elements (Meeting detection sensitivity requirements)	【Fig. 3】 - Applying overlap correction for [As] for [Pb], and [Co] for [Fe] - Compared with Unspiked sample, each element spectral peak of added sample 1 is clear	Pass
Repeatability	Measure 6 of Spiked sample powder 1		Relative standard deviation (RSD) ≦20%	【Table 6】	Pass

Table 5 Detectability

[µg/g]

Elements Spiked Concentration	As 9.0	Hg 18.0	Pb 3.0	Cd 3.0	V 60	Co 30	Ni 120	Pd 60	Judgment
(A) Standard Powder 1.0J	9.0	18.2	3.0	2.9	58.5	29.9	120.5	59.1	Pass
(B) Unspiked Sample Powder	<0.47	<0.26	<0.63	<1.15	<2.25	<1.17	<0.52	<0.63	
(C) Spiked Sample Powder 1 (Target Concentration)	9.3	17.8	3.1	2.9	56.7	29.3	117.9	59.5	
Results(1) [(C)/(A) -1] ×100 [%]	+3.6	-2.2	+2.6	0.0	-3.1	-2.0	-2.2	+0.7	
Spiked Concentration	7.2	14.4	2.4	2.4	48	24	96	48	Pass
(D) Spiked Sample Powder 2 (80% of Target Concentration)	7.5	13.9	2.4	2.1	45.9	23.3	95.1	48.2	
Results(2) Relationship of (D)<(A)	<	<	<	<	<	<	<	<	

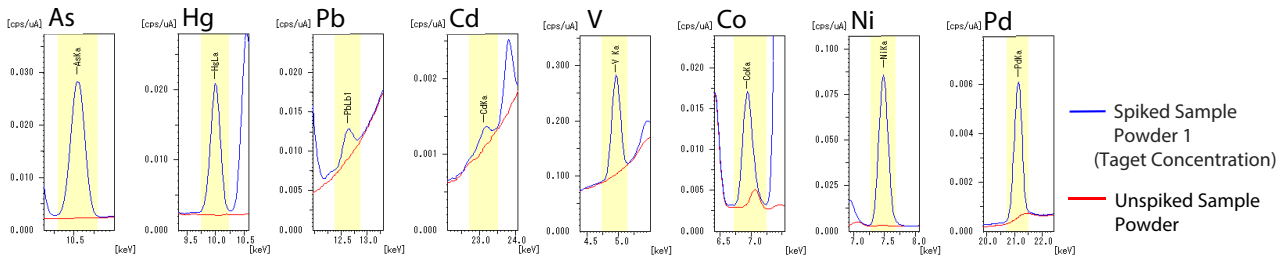

Fig. 3 Specificity

Table 6 Repeatability

[µg/g]

Elements	As	Hg	Pb	Cd	V	Co	Ni	Pd	Judgment
Average of quantitative values by continuous repeated measurement	9.3	17.5	3.0	2.9	56.1	28.9	119.0	60.4	Pass
Standard Deviation	0.09	0.09	0.06	0.19	0.83	0.22	0.76	0.32	
RSD [%]	0.9	0.5	1.9	6.6	1.5	0.8	0.6	0.5	

Validation Results

Validation requirements, procedure, acceptance criteria, and results are shown in Table 4. Each result's details are shown in Table 5 and 6, and Fig. 3.

Conclusion

EDX-7000 was verified as the alternative procedure referring to “Limit Procedures” in USP <233>. It can be applied to the management of formulations and drug substances with similar compositions.

Along with the recommended ICP-MS and ICP-AES, cost reduction can be expected by using EDX according to the type and dosage of the drug product.

Table 7 Measurement Condition

Instrument	: EDX-7000, Sample Turret (option)
Elements	: As, Hg, Pb, Cd, V, Co, Ni, 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, Pd), #2(V), #4 (As, Hg, Pb, Co, Ni)
Atmosphere	: Air
Integral time	: 1,800 [s] × 3 (#1, #2, #4)
Dead time	: Max.30 [%]

References
(1) <232> Elemental Impurities-Limits
(2) <233> Elemental Impurities-Procedures
(3) Application News No.X271
ICH Q3D Elemental Impurities Analysis of Durg Substances by EDX
(4) ICH HARMONISED GUIDELINE,GUIDELINE FOR ELEMENTAL IMPURITIES Q3D(R1) (Final version Adopted on 22 March 2019)

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