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ICP-MS ICPMS -2030

Application News

Elemental Impurity Analysis in Cutaneous and Transcutaneous Drug Products Using ICP-MS Based on ICHQ3D (R2)

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User Benefits

- Even if Option 1 is used to convert the PDE to the target concentration, the control value can be set at 10 % of the PDE.
- The acceptance criteria for accuracy and precision in Quantitative Tests of 2.66 Elemental Impurities in the Japanese Pharmacopoeia 18th Edition can be easily achieved.

■ Introduction

The ICH Q3D Guideline for Elemental Impurities specifies the Permitted Daily Exposure (PDE) of 24 toxic elements for oral, parenteral, and inhalation routes. In Japan, since the Japanese Pharmacopoeia 18,[1)] which describes analytical methods, was announced on June 7, 2021, elemental impurity control must be performed for the drug products specified in the Japanese Pharmacopoeia within a three-year grace period.

In addition, the ICH Q3D guideline has been updated to Q3D (R2)[2)] and new PDE values have been established for cutaneous and transcutaneous drug products (cutaneous products). After an international agreement on Q3D (R2) has been reached, elemental impurity control should also be considered for cutaneous and transcutaneous routes, as these routes will be listed in each country's pharmacopeia.

In this Application News, white petrolatum and heparinoid oil-based cream, which are in high demand for cutaneous and transcutaneous drug products, were used as test samples and analyzed for class 1 and 2A of elements which require a risk assessment.

■ Setting of Target Concentration

For cutaneous products, the cutaneous and transcutaneous concentration limits (CTCL) have been established for Ni and Co, and the concentration limits calculated from both the PDE and CTCL must be met. In this study, Option 1, where the daily dose of a drug product is 10 g, was chosen as the conversion to target concentration method. Since the concentration limits calculated from the PDE values were below the CTCL,*1 these values were used for Ni and Co.

ICHQ3D does not require additional controls if the total elemental impurity level from all sources in the drug product is less than 30 % of the PDE (and CTCL for Ni and Co). In this study, the target concentration was set at 10 % of the PDE to demonstrate that the elemental impurities in the test sample were well below the control threshold.

*1 CTCL may be used when the maximum daily dose is low. For example, if the maximum daily dose is 1 g, the concentration limit for Co is 50 µg/g, which is above the CTCL of 35 µg/g, so CTCL is used.

■ Samples

Test samples: white petrolatum, heparinoid oil-based cream

Reference materials:

< Standard Solutions >

Cd, Pb, As, Hg, Co, V, Ni 1000 mg/L standard solution (KANTO CHEMICAL)

< Internal standard solutions >

Ga, Te, Y, Tl 1000 mg/L standard solution (KANTO CHEMICAL)

■ Pretreatment

The test samples were dissolved using an Anton Paar Multiwave 5000 Microwave Digestion Platform. Fig. 1 shows the flow of decomposition treatment.

Collect 0.2 g of the sample into the decomposition vessel
↓ Add 2 mL of ultrapure water, 5 mL of nitric acid and 0.25 mL of hydrochloric acid.
Set vessel in the microwave digestion system and decompose (approx. 70 min)
↓
Cool the decomposition vessel to 60 °C
↓
Remove the decomposition solution, and dilute to 50 mL (dilution rate: 250 ×)

Fig.1 Flow of Decomposition Treatment

■ Standard Solution

Solutions containing the target elements at three concentration levels, 0.5, 1.0, and 1.5J*2 and a blank solution were prepared. Acid was added to make the standard solution matrix identical to that of the sample solution.

*2 J: concentration of the element in the measurement solution calculated from the target concentration (w/v)

Table 1 Conversion of PDE Values to Target Concentration and J

Class	Element	Cutaneous and transcutaneous PDE	Option 1 Maximum daily intake 10 g concentration limits	CTC	Target concentration 10 % PDE	1.0 J
		µg/day	µg/g	µg/g	µg/g	µg/L
1	Cd	20	2	-	0.2	0.8
	Pb	50	5	-	0.5	2.0
	As	30	3	-	0.3	1.2
	Hg	30	3	-	0.3	1.2
2A	Co	50	5	35	0.5	2.0
	V	100	10	-	1	4.0
	Ni	200	20	35	2	8.0

■ Preparation of Samples to Confirm Precision and Accuracy

To verify the precision and accuracy of the measurements, 0.5 J and 1.0 J of the reference materials were added to the test substance and analyzed.

■ Internal Standard Element Correction

Ga, Te, Y, and Tl were used as internal standard elements. In order to add these internal standard elements, the internal standard element solution and the sample were mixed at a ratio of 1:9 using the Shimadzu Automatic Internal Standard Addition Kit.

■ Analytical Conditions

Table 2 ICP-MS Analytical Conditions

Instrument	: ICPMS -2030
RF Frequency Power	: 1.2 kW
Plasma Gas	: 9.0 L/min
Auxiliary Gas	: 1.1 L/min
Carrier Gas	: 0.7 L/min
Nebulizer	: Nebulizer 07UES
Pump Speed	: 20 rpm
Chamber	: Electronically-cooled cyclone chamber
Plasma Torch	: Mini-torch
Sampling Cone/ Skimmer Cone	: Cu
Collision Gas	: He
Internal Standard Element Addition	: Automatic addition

■ Measurement Results

The measurement results are shown in Tables 3 and 4. The accuracy and precision were confirmed by measuring the 0.5 J and 1.0 J spikes. The accuracy is indicated by the spike test recovery rate and the precision by the RSD of n = 6 measurements.

■ Conclusion

The measurement results showed that all the elements analyzed in the two samples were below the detection limit.

Even when Option 1, which has a large maximum daily dose, was used for the concentration conversion method, and the target concentration was 10 % of the PDE value, the detection limit was well below 1.0 J. Furthermore, the accuracy and precision of the test results were 98 to 106 % for the addition recovery rate of 70 to 150 % and 2.6 % or less for the relative standard deviation of 20 % or less, compared with the compliance acceptance criteria specified in the 18th edition of the Japanese Pharmacopoeia. The ICPMS-2030 is sensitive enough to meet such strict target concentrations and can easily meet the Japanese Pharmacopoeia compliance standards. The above results confirm the effectiveness of the ICPMS-2030 for elemental impurity analysis of cutaneous and transcutaneous drug products.

Acknowledgments
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Reference
1) Japanese Pharmacopoeia 18th Edition (the Ministry of Health, Labour and Welfare Notification No. 220 of June 7, 2021)
2) Guideline for Elemental Impurities Q3D (R2) Draft version

Table 3 White Petrolatum Measurement Results (µg/L)

Class	Element	*m/z*	Average of quantitative values of unspiked sample	0.5 J spike				1.0 J spike			
				Spiked concentration	Average of quantitative value (n = 6)	Precision RSD	Accuracy Spike recovery	Spiked concentration	Average of quantitative value (n = 6)	Precision RSD	Accuracy Spike recovery
1	Cd	111	< 0.0005	0.4	0.41	0.8 %	103 %	0.8	0.81	0.7 %	102 %
	Pb	208	< 0.0009	1	1.01	0.7 %	101 %	2	2.00	0.4 %	100 %
	As	75	< 0.006	0.6	0.59	1.4 %	98 %	1.2	1.21	1.6 %	101 %
	Hg	200	< 0.009	0.6	0.59	2.6 %	98 %	1.2	1.21	1.1 %	100 %
2A	Co	59	< 0.001	1	1.01	1.5 %	101 %	2	1.98	0.5 %	99 %
	V	51	< 0.02	2	2.07	2.1 %	104 %	4	4.10	1.2 %	102 %
	Ni	60	< 0.02	4	4.09	0.9 %	102 %	8	8.03	0.7 %	100 %

Table 4 Heparinoid Oil-Based Cream Measurement Results (µg/L)

Class	Element	*m/z*	Average of quantitative values of unspiked sample	0.5 J Spike				1.0 J Spike			
				Spiked concentration	Average of quantitative value (n = 6)	Precision RSD	Accuracy Spike recovery	Spiked concentration	Average of quantitative value (n = 6)	Precision RSD	Accuracy Spike recovery
1	Cd	111	< 0.0005	0.4	0.41	1.2 %	103 %	0.8	0.81	1.0 %	101 %
	Pb	208	< 0.0009	1	1.03	0.8 %	103 %	2	2.00	0.7 %	100 %
	As	75	< 0.006	0.6	0.59	1.2 %	99 %	1.2	1.15	1.1 %	96 %
	Hg	200	< 0.009	0.6	0.60	1.8 %	100 %	1.2	1.19	1.0 %	99 %
2A	Co	59	< 0.001	1	1.01	1.0 %	101 %	2	1.97	0.8 %	98 %
	V	51	< 0.02	2	2.12	2.4 %	106 %	4	4.10	2.1 %	102 %
	Ni	60	< 0.02	4	4.11	0.8 %	103 %	8	8.05	0.5 %	101 %

<: Less than detection limit (3σ)
σ: Standard deviation of n = 10 consecutive measurements of blank solution

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