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Elemental Analysis: ICPMS-2030

Validation of quantitative method for determination of elemental impurities in pharmaceutical products following USP 232/233 on ICPMS-2030

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Overview

The 24 elemental impurities defined in USP<232> in three generic drug products were quantitatively determined on ICPMS-2030. A simple ICP-MS method that employs a single collision mode for all targeted elements is optimised and used. The sample preparation and method validation follow the USP<233> procedure strictly including both limit procedures and quantitative procedures.

1. Introduction

Elemental impurities in pharmaceutical products are of great concerns for both manufactures and consumers due to their impact on patient safety, drug shelf life and thus drug efficacy. In January 2018, new USP guidelines for elemental impurities was implemented to replace USP <231> - Heavy Metal Limit Test. The over 100-year-old colorimetric method is considered not quantitative and inadequate to determine the toxicity of individual metal contaminations [3]. After being harmonized to ICH Q3D, USP<232> defines 24 targeted elements and the Permitted Daily Exposure (PDE) based on each impurity's toxicity and their possibility of contamination in drug manufacturing process [1]. The new USP<233> specifies ICPOES and ICPMS as the recommended measuring techniques [2]. For samples required strong acid digestion, USP<233> recommends to use closed vessel to minimize the loss of volatile impurities such as mercury and lead in sample preparation.

2. Experimental

2.1 Sample Preparation

Three pharmaceutical products in various forms are obtained in their original packaging.

Drug 1 Capsule, Antibacterial

Drug 2 Tablet, Pain and fever treatment

Drug 3 Liquid, Cough suppressant

Weighted sample (approximately 0.4g) was transferred into the vessel of microwave digestion system (Milestone Ethos Easy). Concentrated strong acids, hydrogen dioxide in ultrapure grade and DI water were added into each vessel shown in Table 2.

Figure 1. ICPMS-2030

Parameter	Setting
RF Frequency Power	1.20 kW
Sampling Depth	5.0 mm
Plasma Gas	Ar 8.0 L/min
Auxiliary Gas	Ar 1.10 L/min
Carrier Gas	Ar 0.70 L/min
Torch	Mini-Torch, ICPMS
Nebulizer	Nebulizer, 07UES
Chamber	Cyclone Chamber
Chamber Temperature	5°C
No. of Scans	10 times
Cell Gas (He)	6.0 mL/min
Cell Voltage	-21.0 V
Energy Filter	7.0 V
Solvent Rinse Time	10 sec (Low), 30 sec (High)
Sample Rinse Time	30 sec (Low), 40 sec (High)

Table 1. Analytical conditions and parameters of ICPMS-2030

Microwave Oven	
Model	Milestone Ethos Easy
Mixed Acid Recipe	
Acid	Volume (mL)
HNO_3	2
HCl	0.5
H_2O_2	0.5
DI Water	3
Digestion Program	
Step	Time (min)
Ramp to 220°C	20
Hold at 220°C	20
Cool down to room Temperature	30

Table 2. Microwave digestion protocol

Closed vessel microwave digestion is regarded as a universal digestion method that can prevent sample loss of volatile elements. Digested samples were diluted to 100mL with ultrapure DI water to give a dilution factor of 250x. All samples were in a matrix of 2% HNO_3 and 0.5% HCl. Sc, Y and Bi were added as internal standards at a final concentration of 100 µg/L each with internal standards online addition kit.

2.2 Analytical conditions

An Shimadzu ICPMS-2030 (Figure 1) coupled with autosampler AS-10 was used. A universal He collision mode on ICPMS-2030 was used to reduce or eliminate polyatomic interferences. The detailed instrument configurations and the optimized operating parameters are summarized in Table 1.

2.3 Calibration standards

Calibration standards were prepared in accordance with USP<233> with the calibration standard at 0.5J, 1.0J and 2.0J in Table 3. J value is the concentration (target limit) of element(s) and is calculated from PDE for oral administration defined in USP<232>. The diluted drug samples were measured using an external calibration approach against calibration solutions with the same matrix (in 2% HNO3 and 0.5% HCl) as the prepared samples.

Element	USP/ICH Class	Isotope used	*PDE (Oral) (µg/day)	0.5J^ value (µg/L)	1.0J value (µg/L)	2.0J value (µg/L)	r
Cd	1	111	5	2.5	5	10	1.00000
Pb	1	206	5	2.5	5	10	0.99999
As (Inorg.)	1	75	15	7.5	15	30	0.99998
Hg (Inorg.)	1	202	30	15	30	60	0.99995
Co	2A	59	50	25	50	100	0.99999
V	2A	51	100	50	100	200	1.00000
Ni	2A	62	200	100	200	400	0.99999
Tl	2B	205	8	4	8	16	0.99995
Au	2B	197	100	50	100	200	0.99993
Pd	2B	105	100	50	100	200	0.99980
Ir	2B	193	100	50	100	200	0.99996
Os	2B	188	100	50	100	200	0.99965
Rh	2B	103	100	50	100	200	0.99999
Ru	2B	101	100	50	100	200	0.99991
Pt	2B	194	100	50	100	200	0.99943
Se	2B	78	150	75	150	300	0.99997
Ag	2B	107	150	75	150	300	0.99963
Li	3	7	550	275	550	1100	0.99940
Sb	3	121	1200	600	1200	2400	1.00000
Ba	3	137	1400	700	1400	2800	0.99904
Mo	3	97	3000	1500	3000	6000	0.99997
Cu	3	63	3000	1500	3000	6000	0.99999
Sn	3	118	6000	3000	6000	12000	1.00000
Cr	3	52	11000	5500	11000	22000	0.99998

* ***PDE (Oral)*** *is Permitted Daily Exposure limit for oral administration drugs defined in USP<232>*

^ ***J value*** *is calculated from J=PDE/(Dilution Factor*Max. Daily Dose) assuming maximum daily dose is 4g per day and DF is 250 in this analysis.*

Table 3. PDEs of classified elemental impurities, calibration standards and correlation coefficients

3. Results and Discussion

3.1 Calibration linearity

Linear calibrations were achieved for all 24 target elements with r shown in Table 3. Calibration curves of Class 1 elements (As, Cd, Hg and Pb) and Class 2 (Co, Ni and V) which is mandatory for oral drug products were shown in Figure 2. Cr has the highest concentration range among the impurity elements. Good linearity of Cr calibration was also shown in Figure 2.

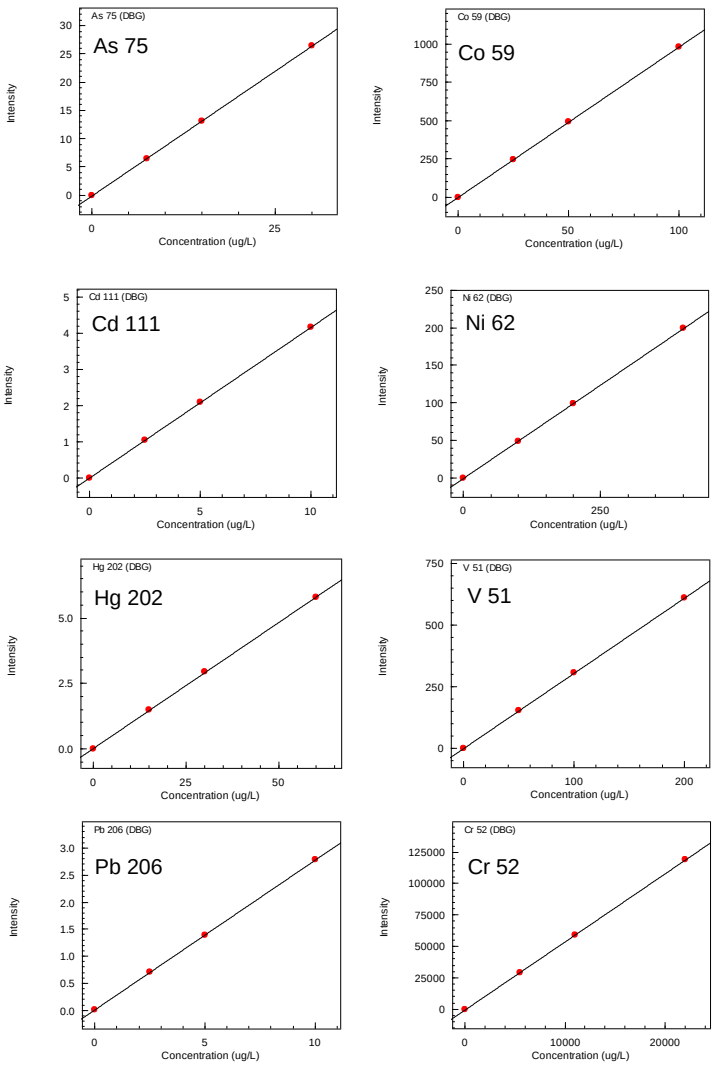

Figure 2. Calibration curves of Class 1 elements (As, Cd, Hg and Pb), Class 2A elements (Co, Ni, V) and Cr.

3.2 Quantitative sample results

The results of impurity elements in three drugs determined are summarized in Table 4. The targeted elements were either not detected or well below the calculated limits (J values) in accordance to oral PDEs. It is worth to note that the LODs and LOQs of the method are far below the J values indicating the capability of ICPMS in trace contamination detection.

Element	Drug 1 (µg/L)	Drug 2 (µg/L)	Drug 3 (µg/L)	LOD (µg/L)	LOQ (µg/L)	J value (µg/L)
Cd	N.D.	N.D.	N.D.	0.003	0.010	5
Pb	N.D.	N.D.	N.D.	0.002	0.007	5
As	N.D.	N.D.	N.D.	0.009	0.030	15
Hg	N.D.	N.D.	N.D.	0.010	0.032	30
Co	<LOQ	N.D.	<LOQ	0.002	0.008	50
V	0.28	0.16	0.29	0.015	0.050	100
Ni	0.21	0.54	N.D.	0.058	0.193	200
Tl	N.D.	N.D.	N.D.	0.002	0.008	8
Au	N.D.	N.D.	N.D.	0.133	0.439	100
Pd	N.D.	N.D.	0.31	0.098	0.327	100
Ir	N.D.	N.D.	N.D.	0.002	0.006	100
Os	N.D.	N.D.	0.09	0.024	0.079	100
Rh	N.D.	N.D.	N.D.	0.000	0.001	100
Ru	N.D.	N.D.	N.D.	0.001	0.003	100
Pt	N.D.	N.D.	N.D.	0.001	0.003	100
Se	N.D.	N.D.	0.14	0.075	0.250	150
Ag	N.D.	N.D.	N.D.	0.025	0.070	150
Li	N.D.	N.D.	N.D.	7.620	25.40	550
Sb	0.91	N.D.	N.D.	0.278	0.928	1200
Ba	N.D.	N.D.	N.D.	0.021	0.069	1400
Mo	N.D.	N.D.	N.D.	0.039	0.131	3000
Cu	N.D.	N.D.	N.D.	0.187	0.624	3000
Sn	N.D.	N.D.	N.D.	0.216	0.721	6000
Cr	N.D.	N.D.	N.D.	0.043	0.145	11000

N.D. means not detected

Table 4. Concentrations of 24 elemental impurity in three digested drug sample solutions.

3.3 Method Validation

The established method was validated following the procedures described in USP<233> for ICP-MS using drug sample 2. The results were summarized in Table 5.

•System suitability: Drift was measured by comparing standard solution at 2.0J before and after sample analysis. The drift results of all target elements were less than 5% which was well below suitability criteria (≤20% for each element).

•Accuracy: Accuracy test was performed by spiking samples at 0.5J and 1.5J. Spike recoveries were 88-114% and 81-115%, respectively. The acceptance range is 70%-150%.

•Precision: Repeatability was evaluated by analyzing 6 replicates of sample 2 spiked at 1.0J. Ruggedness was evaluated by analyzing samples in a different day. The RSD% of both days for all 24 elements were below 2.5% which was far less than the required 20% criteria.

•Detectability: Detectability was confirmed by comparing sample spiked at 0.8J and 1.0J. The calculated ratios were from 0.61 to 0.87 which was in agreement with USP <233> requirement of less than 1

Elements	Drift % Std. at 2.0J	Repeatability 1.0J, n=6, RSD%, Day 1	Repeatability 1.0J, n=6, RSD% Day2	0.5J spike recovery	1.5J spike recovery	Detectability 0.8J/1.0J
Cd	-2.8%	1.48	1.34	105%	97%	79%
Pb	-1.0%	0.21	1.36	111%	96%	79%
As	-2.6%	1.47	0.49	97%	99%	79%
Hg	-2.3%	0.48	1.18	98%	95%	79%
Co	-3.7%	1.03	0.44	100%	97%	80%
V	-2.5%	1.03	0.71	99%	97%	79%
Ni	-3.0%	0.92	0.59	98%	97%	80%
Tl	-1.0%	0.63	1.17	95%	94%	79%
Au	-1.9%	0.47	1.99	114%	111%	61%
Pd	-3.8%	1.73	0.78	98%	79%	84%
Ir	-2.5%	0.37	1.77	99%	96%	79%
Os	-2.6%	0.32	1.57	88%	81%	80%
Rh	-2.9%	1.46	0.95	98%	111%	78%
Ru	-3.6%	1.58	1.14	99%	97%	80%
Pt	-2.0%	0.55	1.78	96%	83%	79%
Se	-2.0%	1.04	1.49	103%	102%	80%
Ag	0.6%	1.49	0.22	105%	100%	87%
Li	-3.8%	2.37	1.50	105%	91%	78%
Sb	-0.8%	0.78	0.78	101%	101%	79%
Ba	-2.8%	1.18	0.82	97%	115%	79%
Mo	-4.0%	1.15	0.72	99%	99%	79%
Cu	-4.2%	1.28	0.26	98%	103%	83%
Sn	-2.5%	0.77	0.92	101%	101%	79%
Cr	-3.6%	0.98	0.45	100%	99%	79%

Table 5. Method validation results according to USP<233>.

- Specificity: Mass peak profiles were examined to ensure that each target element is free of interference from other elements and matrix components. Peak profile of As, Cd and Hg of the blank matrix used for sample preparation and calibration standards are shown in Figure 3.

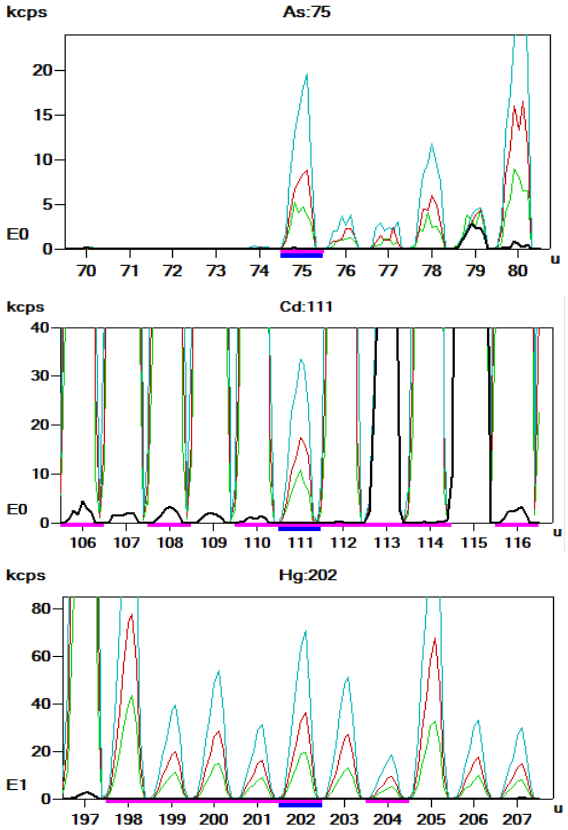

Figure 3. Mass peaks profiles of As75, Cd111 and Hg202 of calibration standards and blank matrix.

4. Conclusions

Targeted elemental impurities in three drug products were analysed following new USP <232>/<233> using ICPMS-2030. The method was validated following the procedures defined by USP<233> and combined with microwave digestion for sample preparation. Excellent calibration linearity, repeatability and low drift were achieved for all 24 elements. Low LODs and LOQs were achieved as compared to the J values for all 24 elements. The simple method that using only He collision mode can reduce the time to shift between different mode and thus improve the throughput for routine trace elemental impurity analysis in pharmaceutical product.

References:

[1] USP General Chapter <232> Elemental Impurities – Limits, USP 40- NF 35, **2017**

[2] USP General Chapter <233> Elemental Impurities – Procedures, USP 38- NF 33, **2015**

[3] Wang T.; Wu J.; Hartman R.; Jia X.; Egan RS, A multi-element ICP-MS survey method as an alternative to the heavy metals limit test for pharmaceutical materials. *J. Pharm. Biomed. Anal.* **2000**, 23(5), 867-890.

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