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Application News

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Drug Impurity Analysis / ICPMS-2030

Analysis of Elemental Impurities in Pharmaceutical Products Following USP <232>/<233> on ICPMS-2030

❑ Introduction

Elemental impurities contained in pharmaceutical products are getting more and more attention due to their harmful potential on patient health and impact on drug shelf life and efficacy. The United States Pharmacopeia (USP) has been continuously developing new guidelines in recent years to replace the over 100-year-old USP<231>. Heavy Metal Limit Test procedure using colorimetric method in USP<231> is no longer adequate for quantitation of elements at toxicology relevant levels. The new USP chapters for elemental impurities has been implemented since 1st January 2018. After harmonizing to ICH Q3D, the new USP<232> specifies impurities limits for 24 elements based on their toxicities. In USP<233>, two modern measuring techniques, ICP-OES and ICP-MS, are recommended together with the measuring and validation procedures. ICP-MS is indisputably considered as the best technique for determination of the heavy metals in pharmaceutical products at trace levels due to its high sensitivity, superior low detection limit, wide linearity range and multi-element analysis capability. In this application news we describe the ICP-MS analysis method and result of determining 24 elemental impurities in three different pharmaceutical products following USP<232> and USP<233> criteria on Shimadzu ICPMS-2030.

❑ Experimental

Materials and sample preparation

Three standard kits were used to prepare the intermediate mixed stock solution for establishing calibration curves. They are Elemental Impurities, ICH Q3D Standard 1 and 3 obtained from Sigma-Aldrich and USP<232> Precious Metals Elemental Impurities from Inorganic Ventures. Gold (Au) was added separately using single element standard from Sigma-Aldrich. The final mixed stock solution prepared include all the 24 elements that are specified in new USP<232> (see Table 2). The calibration series were then prepared from the mixed stock solution using an aqueous diluent containing 2% of HNO_3 and 0.5% of HCl.

Three pharmaceutical products in different forms, i.e., tablet (drug 1), capsule (drug 2) and liquid (drug 3) were used as testing samples.

Each sample of 0.4 grams was digested with mixed acids of high purity 65% HNO_3, 37% HCl and 30% H_2O_2 in a microwave digester (Milestone Ethos Easy). Digestion condition was optimized to obtain a complete digestion. The applied closed vessel digestion can eliminate potential sample loss of volatile elements such as Hg and Pb, in compliance to the USP <233> requirement. The digested samples were transferred to a graduated polypropylene tube and diluted to 50 mL with 18mΩ deionized water. Drug samples were prepared in the same matrix as the calibration standards. Sc, Y, Ho and Bi were added as internal standards at a concentration of 10 µg/L. The dilution factor (DF) of the above sample pre-treatment was 125.

ICP-MS analytical conditions

Shimadzu ICPMS-2030 coupled with autosampler AS-10 was employed for analysis. Details of instrument configuration and operating conditions are summarized in Table 1. ICPMS-2030 system is equipped with a unique Octaplate type collision cell which can deliver high ion transfer efficiency and ensure measuring accuracy. Helium collision mode is effective to remove polyatomic interferences, e.g. As and ArCl, V and ClO. Thus it enables analysts to use HCl in sample preparation to stabilize certain elements such as Hg. In this work, He mode was applied to all measuring.

Table 1: ICPMS-2030 configuration and operating conditions

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, ICP-MS
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)

❑ Results and Discussion

Calibration curves

Following USP<233>, calibration standard solutions were prepared at blank, 0.5 J, 1.0 J and 2.0 J, where J value of each element was calculated from PDE (Permitted Daily Exposure) defined in USP<232>. The J values are used for convenience in calculating the maximum allowed concentrations of target elements in an analyte solution after digestion and dilution (PDE = J x DF x Max. Daily Dose). In this study, the assumed maximum daily dose (oral administration) is 8 grams. The calculated concentrations of 24 elements corresponding to their calibration standards at 0.5 J, 1.0 J and 2.0 J are shown in Table 2.

Example calibration curves of Class 1 elements (arsenic, cadmium, mercury and lead), Class 2A (cobalt, vanadium and nickel) and Class 3 (chromium) are shown in Figure 1. Class 1 and Class 2A are the compulsory elements for oral administration drug according to USP<233>. The calibration curves for both lowest concentrations of Cd and Pb (2.5~10 µg/L) and highest concentration of Cr (up to 22 mg/L) showed good linearity, indicating the capability of ICPMS-2030 to handle a wide range of concentrations under a universal analytical condition.

Table 2: PDE values for oral administration and 3-level mixed calibrants (0.5 J ~ 2.0 J) of 24 elements

Element	USP/ICH Class	*PDE (µg/day)	0.5J (µg/L)	1.0J (µg/L)	2.0J (µg/L)
Cd	1	5	2.5	5	10
Pb	1	5	2.5	5	10
As(Inorg.)	1	15	7.5	15	30
Hg(Inorg.)	1	30	15	30	60
Co	2A	50	25	50	100
V	2A	100	50	100	200
Ni	2A	200	100	200	400
Tl	2B	8	4	8	16
Au	2B	100	50	100	200
Pd	2B	100	50	100	200
Ir	2B	100	50	100	200
Os	2B	100	50	100	200
Rh	2B	100	50	100	200
Ru	2B	100	50	100	200
Pt	2B	100	50	100	200
Se	2B	150	75	150	300
Ag	2B	150	75	150	300
Li	2C	550	275	550	1100
Sb	2C	1200	600	1200	2400
Ba	2C	1400	700	1400	2800
Mo	2C	3000	1500	3000	6000
Cu	2C	3000	1500	3000	6000
Sn	2C	6000	3000	6000	12000
Cr	2C	11000	5500	11000	22000

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

*^ **J value** is calculated from J = PDE/(Dilution Factor x Max. Daily Dose) assuming maximum daily dose is 8 g per day and DF is 125 in this analysis.*

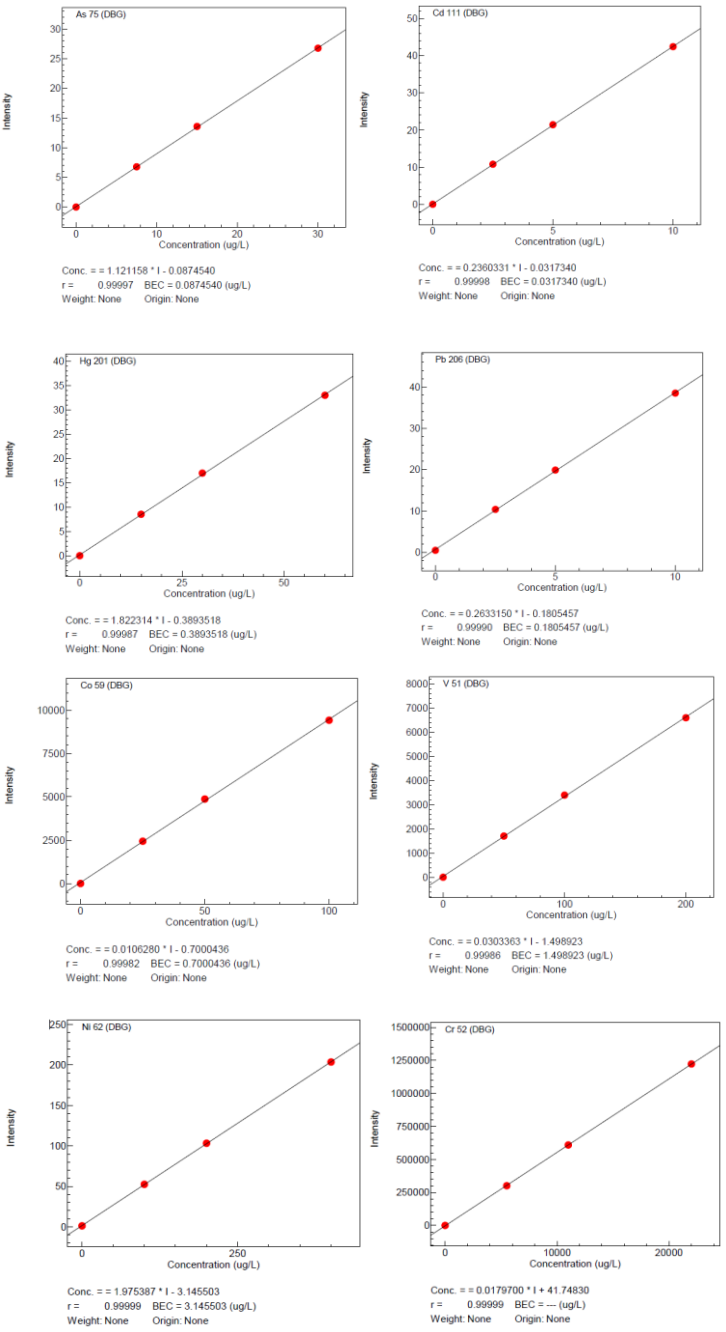

Figure 1: Example calibration curves of Class 1 (As, Cd, Hg and Pb), Class 2A (Co, V, Ni) and Class 3 (Cr) elements.

Method evaluation

Method performance was evaluated by spike recovery test using sample Drug 2. As shown in Table 3, spiked recoveries for the impurity elements at 1.0 J were between 88% and 110%. All recovery rates obtained are well within USP chapter <233> specification of 70% - 150%. Excellent measurement precisions were achieved with RSD below 2.0% (n=3) for spiked sample at the concentration level of 1.0 J, except for Li with RSD slightly higher of 2.16%. One major benefit to use ICP-MS for elemental impurity determination is its high sensitivity and superior low detection limit. The limit of detection (LOD) and limit of

quantification (LOQ) were calculated from 3 and 10 times the standard deviation of 10 measurements of calibration blank solutions. As shown in Table 3, the LODs and LOQs obtained are much below the J values required by new USP <232>/<233> for all 24 elements. Good linearities were seen for target elements with correlation coefficients r > 0.9995. In addition, the low detection limits compared to J values allow analysts to apply a larger dilution factor in sample preparation and thus reduce the sample consumption in routine analysis.

Table 3: Summary of method performance evaluation with spiked sample of 1.0 J standard solution for Drug 2

Element & Mass	Spiked Conc.	Recovery (%)	RSD % (n=3)	LOD* (µg/L)	LOQ* (µg/L)	r
Cd ^{111}	5	103%	0.42	0.002	0.008	0.99998
Pb ^{206}	5	106%	0.15	0.004	0.014	0.99990
As ^{75}	15	100%	0.92	0.004	0.012	0.99997
Hg ^{201}	30	100%	0.14	0.005	0.018	0.99987
Co ^{59}	50	107%	1.64	0.003	0.010	0.99982
V ^{51}	100	106%	1.1	0.038	0.126	0.99986
Ni ^{62}	200	97%	0.85	0.069	0.229	0.99999
Tl ^{203}	8	104%	0.34	0.0004	0.001	0.99988
Au ^{197}	100	96%	0.32	0.073	0.242	0.99999
Pd ^{105}	100	91%	0.85	0.154	0.513	0.99987
Ir ^{193}	100	101%	0.54	0.005	0.017	1.00000
Os ^{188}	100	98%	0.31	0.265	0.882	0.99975
Rh ^{103}	100	100%	0.34	0.001	0.002	1.00000
Ru ^{99}	100	108%	0.37	0.006	0.019	0.99967
Pt ^{194}	100	98%	1.06	0.001	0.003	0.99997
Se ^{78}	150	105%	0.33	0.049	0.163	0.99993
Ag ^{107}	150	88%	0.48	0.006	0.021	0.99975
Li ^{7}	550	110%	2.16	0.747	2.489	0.99987
Sb ^{121}	1200	100%	0.87	0.011	0.035	1.00000
Ba ^{135}	1400	94%	0.85	0.014	0.047	0.99996
Mo ^{95}	3000	99%	0.4	0.020	0.067	0.99998
Cu ^{65}	3000	100%	1.31	0.109	0.364	0.99996
Sn ^{118}	6000	103%	0.53	0.208	0.693	1.00000
Cr ^{52}	11000	100%	1.34	0.047	0.157	0.99999

** LOD and LOQ are to be compared to J values based on 125x dilution (e.g 0.4 g of drug sample digested to a final 50mL solution) calculated from PDE in USP <232>.*

Analysis results of actual samples

Elemental contents in three drug samples were determined and converted results are listed in Table 4. The average concentrations of 24 elements were either below instrument detection limit (marked as N.D.) or well below the allowed values calculated from PDEs defined by new USP <232> based on a maximum daily dose of 8 g/day.

Table 4: Average concentration results (n=3) of three digested drug samples and PDE requirements from USP <232>. (N.D.= not detected)

Element	Drug 1 (µg/g)	Drug 2 (µg/g)	Drug 3 (µg/g)	PDE (µg/day)	PDE (µg/g)
Cd	N.D.	0.032	0.002	**5**	0.625
Pb	0.017	0.127	0.106	**5**	0.625
As	0.007	0.015	N.D.	**15**	1.875
Hg	N.D.	N.D.	N.D.	**30**	3.75
Co	N.D.	0.002	N.D.	**50**	6.25
V	0.014	0.056	N.D.	**100**	12.5
Ni	0.068	0.262	0.020	**200**	25
Tl	0.001	0.003	N.D.	**8**	1
Au	N.D.	N.D.	N.D.	**100**	12.5
Pd	N.D.	N.D.	N.D.	**100**	12.5
Ir	N.D.	N.D.	N.D.	**100**	12.5
Os	N.D.	N.D.	N.D.	**100**	12.5
Rh	N.D.	N.D.	N.D.	**100**	12.5
Ru	N.D.	N.D.	N.D.	**100**	12.5
Pt	N.D.	N.D.	N.D.	**100**	12.5
Se	N.D.	0.004	N.D.	**150**	18.75
Ag	N.D.	N.D.	N.D.	**150**	18.75
Li	N.D.	N.D.	N.D.	**550**	68.75
Sb	N.D.	0.054	N.D.	**1200**	150
Ba	N.D.	0.120	N.D.	**1400**	175
Mo	N.D.	N.D.	N.D.	**3000**	375
Cu	N.D.	0.225	N.D.	**3000**	375
Sn	N.D.	N.D.	N.D.	**6000**	750
Cr	N.D.	N.D.	N.D.	**11000**	1375

❑ Conclusions

24 elemental impurities contained in three drug products are determined using microwave digestion methods following new USP guidelines on Shimadzu ICPMS-2030. The detected impurities levels were found to be far below daily permits defined in USP <232>, based on maximum exposure of 8 g/day. Good calibration linearities were achieved for all target elements over a wide range of concentration using a single set of calibration standards. With good accuracy, excellent repeatability, low detection limits, single He mode method and low Ar consumption, ICPMS-2030 is proven to be a high performance and cost effective instrument for analysis of elemental impurities in pharmaceutical products following new USP<232>/<233>.

❑ References

1. United States Pharmacopeia General Chapter <232> Elemental Impurities – Limits.
2. United States Pharmacopeia General Chapter <233> Elemental Impurities – Procedures.

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