Challenge

Determination of trace elemental impurities in pharmaceutical substances and products

Solution

A simple and effective method for routine preparation and analysis of pharmaceutical material according to ICH and USP 232 and 233 using the PlasmaQuant® MS

Elemental impurities in Pharmaceutical Materials according to new ICH Guidelines and USP Chapters <232> and <233>

Introduction

Although the risk factors for heavy metal impurities in pharmaceutical materials have changed dramatically, standard methods for their testing and control have not changed much for more than 100 years. As a result, heavy metal limits have had little basis in toxicology. For that reason, one of the most significant standards introduced by the United States Pharmacopeia (USP) in the past decade has been new methodology for determining elemental impurities and contaminants in drug products and dietary supplements.

These new methods have been going through a review and approval process for a number of years, and a recent announcement by the USP (1) has indicated that these new chapters will be implemented on January 1, 2018, to coincide with the full approval of the International Conference on Harmonization (ICH) Q3D Step 4 guidelines (2), which is expected to be December 16, 2017, for existing pharmaceutical products. The new methods will address the limitations of the current method, extending the list of analytes, reducing the maximum permitted exposure limits and taking into account the route of exposure. The use of closed vessel sample digestion and modern instrumental techniques is also introduced to ensure the accurate recovery and determination of individual analyte concentrations.

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Chapter <232> and ICH Q3D

Chapter <232> and ICH Q3D specify maximum limits for the amount of elemental impurities permitted in drug products, drug substances, active ingredients and excipients. These impurities may be present naturally, derived from the production catalysts or introduced inadvertently through the manufacturing process, or they could be environmental contaminants in the pharmaceutical raw materials. When elemental impurities have the potential to be present, compliance to the specified levels is a requirement.

Table 1 shows a total of 24 elemental impurities together with their toxicity limits, defined as the maximum permitted daily exposure (PDE) level in micrograms per day for oral, parenteral and inhalation drug delivery categories. The PDE levels are based on an arbitrary adult human body weight of 50kg (110lb) and a suggested dosage of 10g of supplement per day. The PDE limits represent the updated levels as proposed in the most recent revision of USP <232>, published for public comment on Mar-Apr 2016 in Pharmacopeial Forum 42(2) (3) and aligned with ICH Q3D Step 4 dated 16 December 2014 (2).

Element Classification

The new Elemental Impurities chapters subdivide the metals desired for testing into several groups. The first group or Class 1 elements consist of the toxic elements Arsenic, Cadmium, Lead and Mercury. These elements will be tested for in all drug products and constitute the minimum requirement for testing. Class 2 elements are to be tested for based on risk of exposure due to components (excipients or drug substances), manufacturing process, or route of exposure. Subclass 2A elements must also be included in all assessments, due to their ubiquity and relative toxicity. Subclass 2B elements only need be evaluated if they are intentionally added to the processes used to generate the product. Class 3 elemental impurities have relatively low toxicity by oral administration, but require assessment if delivered through the parenteral or inhalational routes.

Elemental Speciation

Chapter <232> also addresses elemental speciation, although it does not specify an analytical procedure. Each elemental impurity has the potential to be present in different oxidation states or species. Arsenic and mercury are of particular concern because of the highly variable toxicity of their inorganic and organic forms. The arsenic limits are based on the inorganic form, which is the most toxic. The mercury limits are based on the inorganic form because methyl mercury, the most toxic form, is rarely an issue for pharmaceuticals. However, if there is a known potential for the material to contain methyl mercury, such as those derived from fish or kelp, and appropriate speciation procedure is required.

Table 1: Permitted Daily Exposures (PDE) for Elemental Impurities

Element	Class	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalation PDE (µg/day)
Cadmium	1	5	2	2
Lead	1	5	5	5
Arsenic (in-organic)	1	15	15	2
Mercury (inorganic)	1	30	3	1
Cobalt	2A	50	5	3
Vanadium	2A	100	10	1
Nickel	2A	200	20	5
Thallium	2B	8	8	8
Gold	2B	100	100	1
Palladium	2B	100	10	1
Iridium	2B	100	10	1
Osmium	2B	100	10	1
Rhodium	2B	100	10	1
Ruthenium	2B	100	10	1
Selenium	2B	150	80	130
Silver	2B	150	10	7
Platinum	2B	100	10	1
Lithium	3	550	250	25
Antimony	3	1200	90	20
Barium	3	1400	700	300
Molybde-num	3	3000	1500	10
Copper	3	3000	300	30
Tin	3	6000	600	60
Chromium	3	11000	1100	3

Chapter <233>

Chapter <233> (4) deals with the analytical procedure, including the sample preparation procedure, instrumental method, and validation protocols for measuring the elemental impurities using one of two plasma-based spectrochemical techniques — ICP-OES and ICP-MS, or alternatively any other trace-element technique such as Flame Atomic Absorption or Graphite Furnace Atomic Absorption, as long as it meets the data quality objectives of the method defined in the validation protocol section. In addition, before any technique is used, the overall analytical procedure must be confirmed to be appropriate for the instrument being used and the samples being analyzed by meeting the Alternative Procedure Validation protocol. The chapter also recommends reading USP General Chapter <730> on plasma spectrochemistry for further guidance.

Validation Protocol

Meeting the validation protocol described in Chapter <233> is critical for this application as all aspects of the analytical procedures, including the instrumental technique and sample dissolution process, must be validated and shown to be acceptable. This is dependent on the procedure used as to whether it is a limit procedure or a quantitative procedure. Limit procedures must confirm detectability, repeatability and specificity of the measurement, while quantitative procedures must demonstrate accuracy, precision (repeatability and ruggedness) and specificity.
Meeting the performance requirements defined in these tests must be demonstrated experimentally using an appropriate system suitability procedure and reference material. The suitability of the method must be determined by conducting studies with the material under test, supplemented or spiked with known concentrations of each target element of interest at the appropriate acceptance limit concentration. It should also be emphasized that the materials under test must be spiked before any sample preparation steps are performed.

Instrumentation

PlasmaQuant® MS with Analytik Jena ASPQ 3300 autosampler and OneFAST sample introduction system from Elemental Scientific (ESI) were used for the analysis of 24 elements specified in the USP <232> and ICH Q3D. The operating conditions are summarized in table 2 for two different integrated Collision Reaction Cell (iCRC) gas modes (Helium and Hydrogen).

Table 2: PlasmaQuant® MS operating conditions

Parameter	Settings
Plasma Gas Flow	9.0 L/min
Auxiliary Gas Flow	1.25 L/min
Nebulizer Gas Flow	1.05 L/min
iCRC Gas	He and H_2
Plasma RF Power	1.30 kW
Dwell Time	20 ms
Scans per Replicate	20 (peak hopping, 1pt/peak)
No. of replicates	3
Pump Rate	15 rpm - black/black PVC pump tubing (<1mL/min)
Sample uptake time	0s – OneFAST Sample Introduction system used
Ion Optics	Auto-optimized
Spray chamber temperature	3 °C

Reagents Samples

Sample preparation

Since many pharmaceutical products and raw materials require acid digestion; three different types of samples were selected for analysis. The samples were purchased from a local pharmacy.

Sample A – Aspergic (Soluble aspirin product in powder form)
Sample B – Biseptine (Antiseptic topical solution in spray form)
Sample C – Metformin (Oral diabetes medicine in tablet form)

According to the USP <233> recommendation on the use of "strong acids" for digestion of insoluble samples, the preferred approach is closed vessel microwave digestion. The microwave digestion method used for this study is shown in Table 3.

Table 3: Microwave digestion method used for sample dissolution

Parameter	Settings
Microwave oven	
Model	TOPwave® (Analytik Jena)
Rotor Type	12 vessels PL 100
Digestion	
Sample weight	0.2 g
HNO_3	1 mL
HCl	0.25 mL
H_2O_2	0.5 mL
De-ionized water	3.5 mL
Oven program	
Pre-digestion (at room temperature)	15 min
Ramp (to 150°C)	15 min
Hold (at 150°C)	10 min
Cool down	30 min
Final dilution	
De-ionized water	To 50 mL
Total dilution factor	x 250

The samples were measured using an external calibration approach against calibration solutions prepared in the same diluent as the samples (2 % HNO_3 and 0.5 % of HCl). The calibration solutions contained all 24 of the elements listed under the Oral daily dose PDE (in µg/g) in the latest USP <232>, Elemental Impurities - Limits document (Mar-Apr 2016) (4). Internal standardisation was applied using Sc, Y, Tb and Bi at 50 ppb, added on-line via a Y-piece.

Target limit (J Value)

For a better understanding of the suitability of the technique for the analytical task, it's important to know the PDE limit for each target element, and in particular what the USP calls the J-value. This term is defined as the PDE concentration of the element of interest, appropriately diluted to the working range of the instrument after completion of the sample preparation procedure.

As an example, the PDE limit for Cd in an oral medication as defined in Chapter <232> is 5 µg/day. Based on a suggested dosage of 10 g of the drug product per day, that is equivalent to 0.5 µg/g Cd. If 0.2 g of sample is digested or dissolved and made up to 50 mL, (250-fold dilution), the J-value for Cd in this example is equal to 2 µg/L. The method then recommends using a calibration made up of two standards: standard 1 = 0.5 J, standard 2 = 1.5 J. So for Cd, this is equivalent to 1 µg/L for standard 1 and 3 µg/L for standard 2. The calibration range for all elements are shown in Table 4 in accordance to the J value calculated for each.

Table 4: J-Values in accordance to Oral PDE with a Max Daily Dose of ≤ 10 g/day (µg/g) and the method calibration standards

Element	Concentration Limits for Oral Drug with a Maximum Daily Dose of ≤ 10 g/day (µg/g)	J-Value with a Sample Dilution of 0.2g/50 mL (µg/L)	Calibration Std1 (0.5J) (µg/L)	Calibration Std2 (J) (µg/L)	Calibration Std3 (1.5J) (µg/L)
Cadmium	0.5	2	1	2	3
Lead	0.5	2	1	2	3
Arsenic (inorganic)	1.5	6	3	6	9
Mercury (inorganic)	3	12	6	12	18
Cobalt	5	20	10	20	30
Vanadium	10	40	20	40	60
Nickel	20	80	40	80	120
Thallium	0.8	3.2	1.6	3.2	4.8
Gold	10	40	20	40	60
Palladium	10	40	20	40	60
Iridium	10	40	20	40	60
Osmium	10	40	20	40	60
Rhodium	10	40	20	40	60
Ruthenium	10	40	20	40	60
Selenium	15	60	30	60	90
Silver	15	60	30	60	90
Platinum	10	40	20	40	60
Lithium	55	220	110	220	330
Antimony	120	480	240	480	720
Barium	140	560	280	560	840
Molybdenum	300	1200	600	1200	1800
Copper	300	1200	600	1200	1800
Tin	600	2400	1200	2400	3600
Chromium	1100	4400	2200	4400	6600

Results and Discussion

Calibration performance

Low limits of detection are particularly important for some of the potentially toxic trace elements defined in USP <232>, notably As, Cd, Hg and Pb. The method detection limit (MDL) for each isotope is reported in Table 5.

The method detection limits were measured under routine laboratory conditions and are well below the target limits of each element. The MDL is based on the measurement of 12 blank solutions measured on two non-consecutive days and is defined as 3 x the standard deviation of the 12 blank measurements.

Table 5: MDL and J value

Isotope	MDL (µg/L)	J (µg/L)	Isotope	MDL (µg/L)	J (µg/L)
7Li	0.17	220	^{107}Ag	0.03	60
51V	0.28	40	^{111}Cd	0.001	2
52Cr	0.53	4400	^{118}Sn	0.49	2400
59Co	0.01	20	^{121}Sb	0.08	480
60Ni	0.09	80	^{137}Ba	0.16	560
65Cu	0.30	1200	^{189}Os	0.44	40
75As	0.04	6	^{193}Ir	0.11	40
78Se	0.01	60	^{195}Pt	0.01	40
98Mo	0.01	1200	^{197}Au	0.09	40
101Ru	0.02	40	^{202}Hg	0.05	12
103Rh	0.01	40	^{205}Tl	0.001	3.2
105Pd	0.03	40	^{208}Pb	0.03	2

Spike recoveries - Accuracy

In accordance to USP <232> guidelines, the accuracy of the ICP-MS can be assessed by spike recoveries. Figures 2 and 3 show spike recoveries for all samples prepared in triplicate at the two levels, 0.5J and 1.5J.v

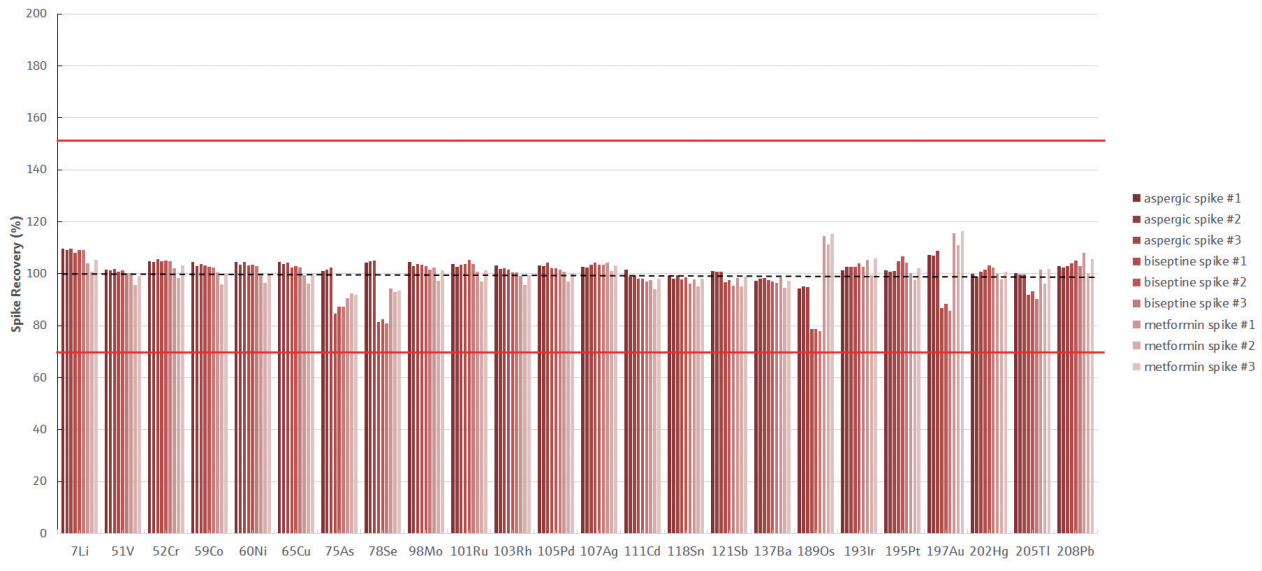

Figure 1: Recoveries (in %) for 0.5J spike level for all samples in triplicate.

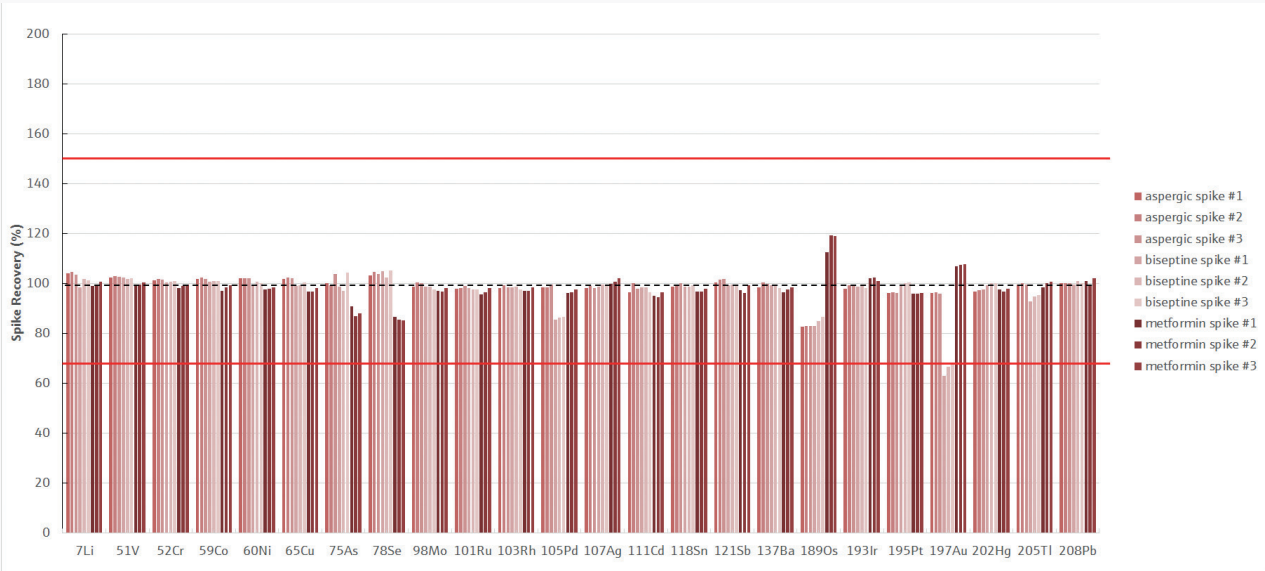

Figure 2: Recoveries (in %) for 1.5J spike level for all samples in triplicate.

The acceptance criteria defined in USP <232> for this kind of test are recoveries of between 70 and 150 %. Figures 1 and 2 clearly shows that these criteria are easily met using the PlasmaQuant® MS, with average recoveries ranging from 80 to 110 %, for all three sample types.

Repeatability

In terms of repeatability, six independent aliquots of each sample were spiked with concentration J. Table 6 shows the repeatability for sample C – Metformin.

Table 6: Repeatability test results of six independent aliquots of the Metformin sample

Isotope	Target value	Metformin Sample spiked with concentration J						Mean (µg/L)	Std. Dev.	%RSD
	1J (µg/L)	Spike 1	Spike 2	Spike 3	Spike 4	Spike 5	Spike 6			
^{7}Li	220	218	226	223	221	219	221	221	3.04	1.37
^{51}V	40.0	39.7	40.9	40.3	40.3	39.9	40.2	40.2	0.41	1.02
^{52}Cr	4400	4316	4489	4364	4384	4357	4378	4381	57.8	1.32
^{59}Co	20.0	19.4	20.4	19.7	19.7	19.7	19.9	19.8	0.32	1.59
^{60}Ni	80.0	78.0	80.2	78.2	78.5	78.3	78.7	78.7	0.80	1.01
^{65}Cu	1200	1162	1196	1169	1174	1163	1177	1173	12.4	1.06
^{75}As	6.00	5.45	5.25	5.38	5.49	5.21	5.28	5.34	0.11	2.13
^{78}Se	60.0	52.0	51.5	52.0	52.2	51.2	51.1	51.7	0.46	0.88
^{98}Mo	1200	1163	1198	1158	1169	1159	1179	1171	15.5	1.32
^{101}Ru	40.0	38.3	39.2	38.9	38.6	38.6	39.3	38.8	0.39	1.01
^{103}Rh	40.0	38.8	39.8	38.9	39.1	38.9	39.4	39.1	0.38	0.97
^{105}Pd	40.0	38.5	39.4	38.7	39.0	38.6	39.0	38.8	0.35	0.89
^{107}Ag	60.0	59.9	61.1	59.8	60.2	60.4	61.2	60.4	0.61	1.01
^{111}Cd	2.00	1.90	1.96	1.85	1.89	1.89	1.93	1.90	0.04	1.98
^{118}Sn	2400	2319	2386	2338	2344	2320	2349	2342	24.5	1.04
^{121}Sb	480	467	479	469	469	462	477	471	6.28	1.33
^{137}Ba	560	540	548	550	554	547	551	548	4.94	0.90
^{189}Os	40.0	45.0	47.6	47.1	45.8	47.7	47.6	46.8	1.13	2.42
^{193}Ir	40.0	40.8	41.4	40.5	40.9	40.9	40.4	40.8	0.36	0.88
^{195}Pt	40.0	38.4	39.3	38.7	39.0	38.4	38.5	38.7	0.37	0.95
^{197}Au	40.0	42.8	43.3	41.9	43.9	43.0	43.1	43.0	0.66	1.53
^{202}Hg	12.0	11.7	12.0	11.9	11.8	11.6	11.8	11.8	0.14	1.16
^{205}Tl	3.20	3.15	3.19	3.11	3.19	3.20	3.22	3.18	0.04	1.25
^{208}Pb	2.00	2.02	2.11	2.00	2.02	1.99	2.04	2.03	0.04	2.11

The excellent repeatability achieved with RSD < 2.5 % for all 24 elements in the Metformin sample from 6 independent preparations, illustrates the robustness and reliability of the method being well below the acceptance criteria of 20 %. For the other two samples (Aspergic and Biseptine), a repeatability of <3.5 % RSD was achieved for all elements under the same measurement conditions.

Intermediate Precision (Ruggedness)

The results of 12 repeat analyses for each sample from 6 independent aliquots spiked with target value J, were analyzed over two non-consecutive days with a different operator, new calibration and re-optimization of the instrument.
The results for the Aspergic samples over the two working days are shown in table 7.

Table 7: Repeatability test results of six independent aliquots of the Aspergic sample.

Isotope	Aspergic Sample - Day 1						Aspergic Sample - Day 2						Mean (µg/L)	Std. Dev.	%RSD
	Spike 1a	Spike 2a	Spike 3a	Spike 4a	Spike 5a	Spike 6a	Spike 1b	Spike 2b	Spike 3b	Spike 4b	Spike 5b	Spike 6b			
^{7}Li	239	241	240	241	238	243	229	226	230	231	230	227	235	6.27	2.67
^{51}V	40.4	40.7	40.5	40.7	40.3	41.1	41.0	41.1	41.2	41.0	41.1	41.1	40.8	0.32	0.78
^{52}Cr	4585	4613	4602	4645	4593	4683	4450	4457	4474	4456	4475	4463	4541	86.4	1.90
^{59}Co	20.6	20.9	20.6	20.8	20.6	20.9	20.4	20.3	20.5	20.4	20.5	20.4	20.6	0.20	0.97
^{60}Ni	82.8	83.6	82.8	83.7	82.7	84.1	81.6	81.3	81.8	81.5	81.8	81.7	82.5	0.97	1.17
^{65}Cu	1235	1254	1245	1250	1244	1263	1221	1215	1228	1218	1227	1226	1236	15.4	1.24
^{75}As	6.64	6.72	6.32	6.45	6.70	6.44	6.00	6.58	5.95	6.36	6.26	6.22	6.39	0.25	3.97
^{78}Se	68.6	69.6	69.0	70.3	69.7	69.4	62.0	62.8	62.8	63.2	64.2	62.3	66.1	3.48	5.26
^{98}Mo	1223	1255	1235	1244	1233	1257	1185	1193	1203	1194	1209	1203	1220	25.0	2.05
^{101}Ru	40.7	41.5	41.1	41.4	41.1	41.8	39.1	39.1	39.2	39.6	39.8	39.6	40.3	1.03	2.56
^{103}Rh	40.4	41.3	40.8	40.9	40.8	41.0	39.3	39.6	39.7	39.4	40.1	39.3	40.2	0.72	1.80
^{105}Pd	40.8	41.2	41.2	41.7	40.9	41.8	39.3	39.5	39.4	39.3	39.8	39.8	40.4	0.97	2.40
^{107}Ag	61.1	61.6	61.5	62.1	61.6	62.4	59.0	59.2	59.4	59.4	59.6	58.9	60	1.34	2.22
^{111}Cd	1.98	1.97	1.97	2.02	1.96	2.00	1.93	1.98	2.00	1.95	1.97	1.96	1.97	0.02	1.23
^{118}Sn	2344	2380	2352	2384	2360	2376	2366	2401	2388	2397	2404	2403	2380	20.4	0.86
^{121}Sb	476	485	483	484	482	484	482	493	488	485	490	489	485	4.52	0.93
^{137}Ba	541	545	549	550	545	545	551	564	563	558	557	559	552	7.69	1.39
^{189}Os	36.1	37.8	38.0	38.0	36.6	37.4	33.1	33.0	33.2	34.3	33.2	33.1	35.3	2.18	6.17
^{193}Ir	39.9	40.5	41.0	41.0	40.4	41.7	39.2	39.8	39.7	40.0	39.9	39.6	40.2	0.73	1.81
^{195}Pt	39.1	40.5	40.3	40.4	40.2	41.0	38.5	38.8	38.6	38.9	39.0	38.5	39.5	0.91	2.31
^{197}Au	42.0	42.9	42.7	43.5	42.6	44.0	38.5	36.1	38.6	37.5	38.2	38.4	40.4	2.78	6.88
^{202}Hg	11.7	12.0	11.9	12.1	11.9	12.2	11.6	11.7	11.7	11.7	11.7	11.7	11.8	0.18	1.55
^{205}Tl	3.12	3.21	3.19	3.19	3.15	3.23	3.19	3.20	3.20	3.17	3.21	3.19	3.19	0.03	0.92
^{208}Pb	2.05	2.06	2.05	2.06	2.04	2.07	2.00	1.99	2.00	2.00	2.00	2.00	2.03	0.03	1.51

The criterion of 25 % RSD in terms of ruggedness is easily achieved with the PlasmaQuant® MS, as shown in table 7 with precision of <7 % for all 24 elements measured in the spiked Metformin samples. For the other two matrices, the results revealed similar performance behavior. These results from three different matrices and independent digestion procedures over two non-consecutive days illustrate the robustness and reliability of the method.

Sample Results

The target elements in the three pharmaceutical materials, each prepared in triplicate, were measured and the concentrations in the analyzed solutions are reported in Table 8. All elements were found to be either below the instrument detection limit or well below the calculated target value.

Table 8: Concentration results (in ug/L) of USP target elements in three digested pharmaceutical sample solutions (n.d = not detected).

Isotope	Aspergic			Biseptine			Metformin		
	#1	#2	#3	#1	#2	#3	#1	#2	#3
^{7}Li	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{51}V	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{52}Cr	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{59}Co	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{60}Ni	n.d	n.d	n.d	n.d	n.d	n.d	0.38	0.38	0.39
^{65}Cu	n.d	n.d	n.d	n.d	n.d	n.d	n.d	1.2	0.98
^{75}As	n.d	n.d	n.d	n.d	0.04	n.d	n.d	0.11	n.d
^{78}Se	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{98}Mo	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{101}Ru	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{103}Rh	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{105}Pd	n.d	n.d	n.d	n.d	n.d	n.d	0.11	0.04	n.d
^{107}Ag	n.d	n.d	n.d	n.d	n.d	n.d	0.07	n.d	n.d
^{111}Cd	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{118}Sn	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{121}Sb	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{137}Ba	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{189}Os	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{193}Ir	n.d	n.d	n.d	n.d	n.d	n.d	0.92	0.55	0.55
^{195}Pt	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{197}Au	n.d	n.d	n.d	n.d	n.d	n.d	3.12	1.61	0.22
^{202}Hg	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{205}Tl	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d
^{208}Pb	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d

Conclusion

The PlasmaQuant® MS was shown to be well suited to the determination of trace elemental impurities in pharmaceutical materials by its ability to easily meet the target values and performance criteria as defined in the ICH Guideline and USP Chapter <232>.

The PlasmaQuant® MS includes unique and patented technologies that significantly lower running costs and provide greater ease-of-use without compromising performance. These include the Eco Plasma, the only plasma system that runs on <10L/min of argon gas without compromising plasma robustness or analyte sensitivity. The integrated Collision Reaction Cell is a powerful, yet simple to use interference management system that removes spectroscopic interferences on important pharmaceutical elements including Cr, As, Se, V and Cu.

This application note presents a simple and effective method for routine preparation and analysis of pharmaceutical material by ICP-MS in combination with closed vessel microwave digestion.

References

[1] United States Pharmacopeia Update Communication, January 14, 2015: *http://www.usp.org/usp-nf/key-issues/elemental-impurities*
[2] International Conference on Harmonization, ICH Q3D Step 4 - *Guideline for Elemental Impurities (ICH, Geneva, Switzerland, 2014)*
[3] General Chapter <232> Elemental Impurities—Limits, USP39. *Publishing in Pharmacopeial Forum 42(2) [Mar.–Apr. 2016]*
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