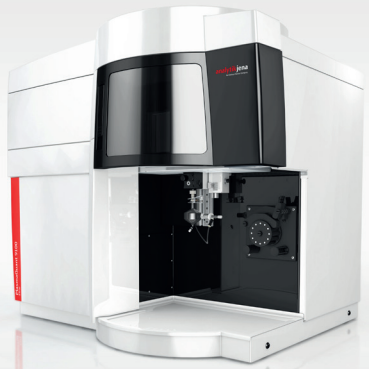

Determination of Elemental Impurities in Pharmaceuticals by HR-ICP-OES according to ICH Q3D and USP 232 and 233

Challenge

Determination of trace elemental impurities in pharmaceutical substances and products.

Solution

High-Resolution ICP-OES with exceptionally high sensitivity, an industry leading high-resolution optical system and a wide working range for the determination of elemental impurities in pharmaceuticals.

Introduction

As of January 2018, pharmaceutical products must comply with specified limits for the allowed exposure to certain trace elemental impurities. The maximum permitted exposure limits and the analytical methods in order to quantify the listed trace elemental impurities are described in the United States Pharmacopeia (USP) chapters <232> Elemental Impurities – Limits[1] and <233> Elemental Impurities - Procedures[2] and are aligned with the International Conference on Harmonization (ICH) Q3D Step 4 guidelines[3].

As discussed below, ICP technology is now a compendial method for the quantification of trace elemental impurities and is becoming the routine method of choice for manufacturers and suppliers of pharmaceutical products, including raw materials, drug substances and excipients. Challenges within this field of application include a large variety of sample types with diverse analyte combinations and target limits. This, in turn, requires ICP instrumentation that can handle a large variety of sample types with varying matrix loading and solvent types (e.g., aqueous or solvent based) and offers the measurement of a wide concentration range. In this regard, the plasma system needs to be able to handle any sample type without compromises in plasma stability and robustness. The accurate and reliable quantification of trace elemental impurities also requires a high sensitivity of the system, as well as the ability to resolve spectral interferences that are common in ICP-OES.

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Within this study, the PlasmaQuant 9100 Elite high-resolution ICP-OES is used in order to determine elemental impurities in pharmaceutical products containing folic acid as the active pharmaceutical ingredient (API). Folic acid is used as the API in tablets as well as in liquid pharmaceutical products, which are administered orally or via injection (parenteral).

As will be shown below, the exceptionally high spectral resolution and sensitivity of the PlasmaQuant 9100 Elite offers new analytical potential. It allows for an interference-free analysis of trace elements in any matrix and any elemental constellation. Furthermore, the high plasma robustness of the High-Frequency Generator and the sample introduction system with its centerpiece, the V-Shuttle torch, allow for the analysis of pharmaceutical products with excellent accuracy and precision. The DualView Plus feature additionally offers the measurement of a wide concentration range within a single measurement. This often avoids the need for measuring several dilution samples in order to collect data for elements in both the low µg/l and the high mg/l range, providing savings in expenditure and time.

Overview of the USP chapters <232>, <233> and ICH Q3D

Chapter <232> Elemental Impurities – Limits and ICH Q3D

Chapter <232> and ICH Q3D specify maximum limits for the amount of elemental impurities permitted in drug products, which we defined to be the final form of the medicine which the patient takes. The elemental impurities may be present in either the drug substances, the active ingredients and/or excipients. These impurities may be present naturally, derived from the production catalysts or introduced inadvertently throughout the manufacturing process. They could also be environmental contaminants in the pharmaceutical raw materials.

Compliance with the specified limits is required for all drug products, with the exceptions as listed in Chapter <232>. If elemental impurities are known to be present, have been added intentionally, or there is a known potential for introduction, it must be shown that compliance with defined limits is assured. Otherwise, a risk-based control strategy may also be considered.

Table 1 shows a total of 24 elemental impurities and the maximum permitted daily exposure (PDE) level in micrograms per day for oral, parenteral and inhalation drug delivery, as listed in Chapter <232>.

Element Classification

The Elemental Impurities chapters classify the elements into three groups. The first group, or Class 1 elements, consist of the toxic elements arsenic, cadmium, lead and mercury. These elements must always be considered in the risk assessment, and should always be measured. Class 2 elements are divided into two subgroups. Subclass 2A elements must also be included in all assessments, due to their ubiquity and relative toxicity. Subclass 2B elements need be considered in the risk assessment only if they are known to be present or are intentionally added during the manufacturing process of the final pharmaceutical product. Class 3 elemental impurities have relatively low toxicity by oral administration, but require assessment if delivered through the parenteral or inhalational routes.

Table 1: Permitted Daily Exposures (PDE) for Elemental Impurities as provided in USP Chapter <232> [1]

Element	Class	Oral PDE [µg/day]	Parenteral PDE [µg/day]	Inhalation PDE [µg/day]
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1

Element	Class	Oral PDE [µg/day]	Parenteral PDE [µg/day]	Inhalation PDE [µg/day]
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

Chapter <233> Elemental Impurities – Procedures

Chapter <233> describes two analytical procedures, including sample preparation procedures, instrumental methods, and validation studies and requirements for measuring elemental impurities. The two compendial procedures are the inductively-coupled plasma-based spectrochemical techniques, ICP-OES and ICP-MS.

The criteria for acceptable alternative procedures (*i.e.* trace-element techniques such as Flame Atomic Absorption or Graphite Furnace Atomic Absorption) are also included. Alternative procedures must meet the described validation requirements in order to be used.

It must be emphasized that in addition to the system suitability requirements for the compendial ICP-OES and ICP-MS methods, before any procedure (including compendial) is initially used, the overall analytical procedure including sample preparation (if not otherwise indicated in the monograph) should be confirmed to be appropriate, for both the instrument being used and the samples being analyzed. This is done by meeting the requirements for alternate procedure validation, as described in Chapter <233>.

Method Validation

Meeting the requirements for the alternate procedure validation, as described in Chapter <233>, is critical as all aspects of the analytical procedures including the instrumental technique and sample preparation process must be validated and shown to be acceptable. As defined in Chapter <233>, the validation parameters for acceptability of the alternative procedure depend on whether the procedure is a "Limit Procedure" or a "Quantitative Procedure".

Since the ICP-OES procedure is a "Quantitative Procedure" the requirements for the following validation parameters must be met: accuracy, precision (repeatability and ruggedness), specificity and limit of quantitation, range and linearity (demonstrated by meeting the accuracy requirement). 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 is 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.

Materials and Methods

Samples and reagents

The API tested in this study is folic acid. It can be administered orally in the form of tablets or via injection (parenteral) in liquid form. Due to the different possible routes of administration and different formulation processes, multiple classes (as described above) of elemental impurities should be analyzed in folic acid products. For this reason, this study includes all 24 elements specified within the USP and ICH guidelines as well as a full validation of the applied methodology. For single products, only a subsection of these elements may be of interest, e.g., Class 1 and 2A elements for oral drugs.

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. For the microwave digestion 0.5 g of the folic acid drug product was accurately weighed and transferred into a digestion vessel (CX 100). The sample was spiked with 7 mL of conc. nitric acid. The mixture was then shaken carefully and left standing for 10 minutes before the vessel was closed. Subsequent digestion was performed in the TOPwave microwave by Analytik Jena with the following program:

Table 2: Digestion program for folic acid pharmaceutical product

Step	T [°C]	p_{max} [bar]	Ramp time [min]	Hold time [min]
1	160	80	5	10
2	190	80	5	10
3	210	80	5	20
4	50	80	-	20

After complete digestion and cooling to room temperature, the clear solution was filled up to 100 mL with deionized water. For the measurement of gold, iridium, osmium, palladium, platinum, rhodium and ruthenium 5% (v/v) conc. hydrochloric acid was added to the diluted sample, for stabilization of these elements in solution. Spiked samples were prepared by adding element concentrations according to USP <232> and <233> (Table 3) using concentration-balanced multi-element standards (Sigma Aldrich, Elemental Impurities according to ICH Q3D oral Standard 1–3).
Matrix-matched (7% (v/v) conc. nitric acid, optional 5% (v/v) conc. hydrochloric acid) calibration standards were prepared from concentration-balanced multi-element standards (Sigma Aldrich, Elemental Impurities according to ICH Q3D oral Standard 1–3). The resulting concentrations are shown in Table 3.

Target limit (J-Value)

In order to assess the suitability of the technique for the analytical task, it is important to know the PDE limit for each target element, and in particular what the USP calls the J-value. The J-value 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 cadmium in an oral medication as defined in Chapter <232> is 5 µg/day (see Table 1). If the maximum dosage of the final drug product is 1 g per day this is equivalent to 5 µg of cadmium / 1 g of drug product. If 0.5 g of the drug product is digested or dissolved (sample preparation above) and made up to 100 mL, (200-fold dilution), the J-value for cadmium in this example is equal to 25 µg/L (see Table 3).
The method then recommends using a calibration made up of two standards: standard 1 = 0.5 J, standard 2 = 1.5 J. For cadmium, this is equivalent to 12.5 µg/L for standard 1 and to 37.5 µg/L for standard 2. The calibration ranges for all elements are displayed in Table 3 in accordance to the J-value calculated for each element.
In the Results and Discussion section (see page 12) the calculated J-values (in Table 3) are compared with the Limits of Quantification (LOQ). The LOQ values should be well below the target limits of each target element. Should this not be the case, it may be necessary to use an alternative sample preparation procedure (*i.e.* different starting mass of sample for dilution, different dilution factor, etc.) or a different analysis technique, such as ICP-MS.

Table 3: J-Values in accordance to oral PDE with a maximum daily dose of ≤ 1 g/day and the method calibration standards

Element	Concentration Limits for Oral Drug with a Max. Daily Dose of ≤ 1 g/day [µg/g]	0.5 J [µg/L]	0.8 J [µg/L]	1.0 J [µg/L]	1.5 J [µg/L]
As	15	37.5	60	75	112.5
Cd	5	12.5	20	25	37.5
Hg	30	75	120	150	225
Pb	5	12.5	20	25	37.5
Co	50	125	200	250	375
Ni	200	500	800	1000	1500
V	100	250	400	500	750
Ag	150	375	600	750	1125
Au	100	250	400	500	750
Ir	100	250	400	500	750
Os	100	250	400	500	750
Pd	100	250	400	500	750
Pt	100	250	400	500	750
Rh	100	250	400	500	750
Ru	100	250	400	500	750
Se	150	375	600	750	1125
Tl	8	20	32	40	60
Ba	1400	3500	5600	7000	10500
Cr	11000	27500	44000	55000	82500
Cu	3000	7500	12000	15000	22500
Li	550	1375	2200	2750	4125
Mo	3000	7500	12000	15000	22500
Sb	1200	3000	4800	6000	9000
Sn	6000	15000	24000	30000	45000

Instrumentation

Instrument settings

For the analysis a PlasmaQuant 9100 Elite ICP-OES equipped with a standard sample introduction kit was used in combination with a Teledyne Cetac ASX 560 autosampler incl. ENC-560DC enclosure. The detailed system configuration is shown in Table 4.

Table 4: Configuration of the PlasmaQuant 9100 Elite equipped with standard kit

Parameter	Specification
Plasma power	1200 W
Plasma gas flow	12.0 L/min
Auxiliary gas flow	0.5 L/min
Nebulizer gas flow	0.6 L/min
Nebulizer	Concentric, 1.0 mL/min, Borosilicate
Spray chamber	Cyclonic spray chamber,50 mL, Borosilicate
Outer tube/Inner tube	Quartz/quartz
Injector	Quartz, ID: 2mm
Pump tubing	PVC (black, black)
Sample pump rate	1.0 mL/min
Sample uptake time	55 s

Method parameters

Table 5: Overview of method-specific evaluation parameters

Element	Line [nm]	Plasma view	Integration mode	Read time [s]	Evaluation			
					No. of pixel	Baseline fit, No. of pixel	Polyn. degree	Correction
As	188.979	axial	peak	10	3	ABC[1]	auto	-
Cd	214.441	axial	peak	3	3	ABC	auto	-
Hg	184.886	axial	peak	3	3	ABC	auto	-
Pb	220.353	axial	peak	10	3	ABC	auto	-
Co	237.863	axial	peak	3	3	ABC	auto	-
Ni	231.604	axial	peak	3	3	ABC	auto	-
V	292.464	axial	peak	3	3	ABC	auto	-
Ag	328.068	axial	peak	3	3	ABC	auto	-
Au	242.795	axial	peak	3	3	ABC	auto	-
Ir	212.681	axial	peak	3	3	ABC	auto	-
Os	442.047	axial	peak	3	3	ABC	auto	-
Pd	340.458	axial	peak	3	3	ABC	auto	-
Pt	214.424	axial	peak	3	3	ABC	auto	-
Rh	369.236	axial	peak	3	3	ABC	auto	-

Element	Line [nm]	Plasma view	Integration mode	Read ime [s]	Evaluation			
					No. of pixel	Baseline Fit, No. of pixel	Polyn. degree	Correction
Ru	240.272	axial	peak	3	3	ABC	auto	-
Se	196.028	axial	peak	3	3	ABC	auto	-
Tl	190.796	axial	peak	3	3	ABC	auto	-
Ba	455.403	radial plus	peak	3	3	ABC	auto	-
Cr	205.552	radial plus	peak	3	3	ABC	auto	-
Cu	324.754	radial	peak	3	3	ABC	auto	-
Li	670.791	radial plus	peak	3	3	ABC	auto	-
Mo	202.030	radial	peak	3	3	ABC	auto	-
Sb	217.581	axial	peak	3	3	ABC	auto	-
Sn	189.927	radial	peak	3	3	ABC	auto	-

[1] automatic baseline fit

Results and Discussion

In order to demonstrate that the ICP-OES procedure, including sample preparation, as described above is appropriate for the samples being analyzed, the following measurements, tests and validations must be performed, as per USP <233>:

- Calibration and system suitability
- Method validation
  - Accuracy
  - Precision (repeatability and ruggedness)
  - Specificity
  - Limits of quantitation and sensitivity
  - Range and linearity (demonstrated by meeting the accuracy requirement)

Calibration and system suitability

USP <233> recommends using a calibration made up of two standards: standard 1 = 0.5 J, standard 2 = 1.5 J. The calibration ranges for all elements are shown in Table 3 in accordance to the J-value calculated for each element. Representative calibration functions of all Class 1 elements are displayed in Figure 1.

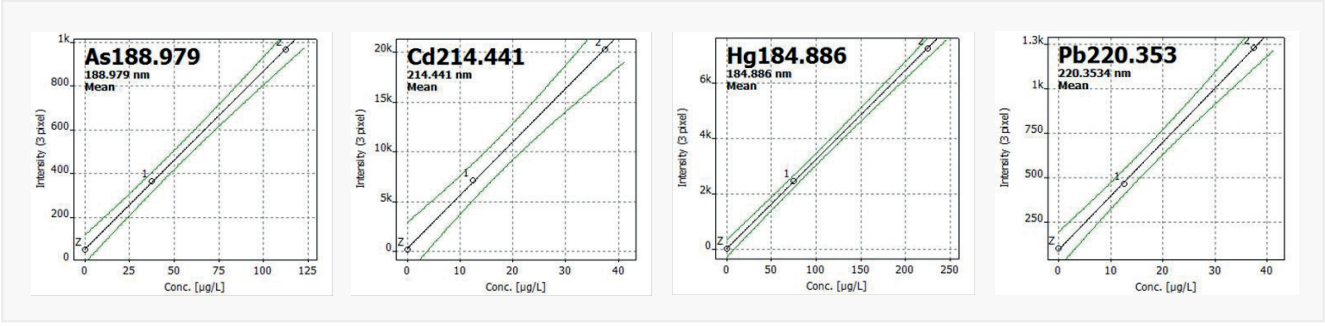

Figure 1: Exemplary calibration curves (black) and confidence levels (green) for Class 1 Elemental Impurities

The system suitability test described in USP <233> requires a QC check standard with the concentration of 1.0 J to be measured before and after a batch of samples. The acceptance criteria defined in USP <232> for this test is a deviation of less than 20% for each target element.

Table 6: Results of System Suitability Test

Element	Standard 1 at start of sequence [µg/L]	Standard 1 at end of sequence [µg/L]	RSD [%]
As	112.8	110.1	2.5
Cd	38.21	36.29	5.3
Hg	224.2	217.6	3.0
Pb	37.62	35.88	4.8
Co	377	359.4	4.9
Ni	1530	1439	6.3
V	764.4	723.2	5.7
Ag	1129	1039	8.7
Au	764.9	719	6.4
Ir	762.2	714.6	6.7
Os	736.9	754.8	2.4
Pd	758.8	711.7	6.6
Pt	762.6	710.3	7.4
Rh	754.4	735.1	2.6
Ru	759.6	711.4	6.8
Se	1151	1067	7.9
Tl	60.84	57.26	6.3
Ba	10660	10640	0.2
Cr	81930	81130	1.0
Cu	22730	22810	0.4
Li	4165	4142	0.6
Mo	22770	22840	0.3
Sb	9087	8926	1.8
Sn	44610	44410	0.5

The obtained RSD values are well within the required 20% (Table 6). Within this study a batch of samples covering a full working day of 8 hours was measured in-between the QC check standards.

Method validation

Spike recoveries – Accuracy

In accordance to USP <233> guidelines, the accuracy of the method can be assessed by spike recoveries. Figure 2 shows averaged spike recoveries for all samples prepared in triplicate at the levels 0.5 J, 1.0 J and 1.5 J.

The acceptance criteria defined in USP <232> for this kind of test are recoveries between 70 and 150%. Figure 2 clearly shows that these criteria are easily met using the PlasmaQuant 9100 Elite, with average recoveries ranging from 87% to 105%.

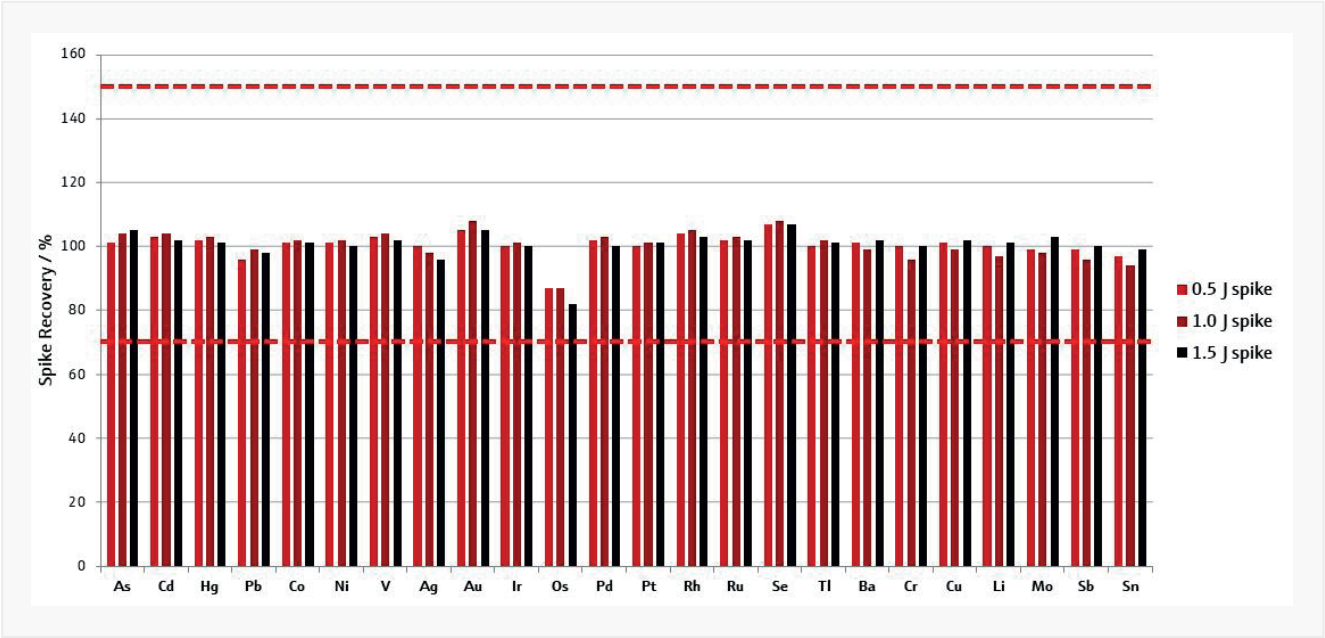

Figure 2: Spike recovery results for 0.5 J, 1.0 J and 1.5 J

Precision (Repeatability)

In terms of repeatability, six independent aliquots of each sample were spiked with concentration 1.0 J. Table 7 shows the repeatability for folic acid. The excellent repeatability achieved with RSD well below 2% from six independent preparations, illustrates the robustness and reliability of the method being well below the acceptance criteria of 20%.

Table 7: Results of repeatability test

Element	Spike 1	Spike 2	Spike 3	Spike 4	Spike 5	Spike 6	RSD / %
As	82.3	82.7	82.3	82.4	84.2	82.0	1.0
Cd	27.7	27.6	27.2	27.3	27.7	27.5	0.7
Hg	162.1	160.6	161.6	161.4	161.2	159.9	0.5
Pb	26.0	26.1	26.2	26.0	26.1	26.1	0.3
Co	264.0	263.6	263.4	265.2	264.8	267.4	0.6
Ni	1093	1072	1065	1067	1061	1077	1.1
V	535.2	533.4	534.6	535.3	536.0	537.3	0.2
Ag	654.1	747.4	699.4	735.0	790.3	733.9	6.3
Au	557.3	553.9	554.9	545.8	563.6	557.9	1.1
Ir	523.3	522.9	533.4	526.4	539.6	530.2	1.2
Os	428.0	419.7	422.2	425.5	431.5	423.9	1.0
Pd	535.4	525.2	529.0	518.5	528.4	528.0	1.0
Pt	529.2	532.1	528.0	528.8	536.6	530.5	0.6
Rh	536.3	533.6	536.2	528.5	539.3	541.9	0.9
Ru	535.5	542.1	528.1	529.7	544.8	535.0	1.2
Se	844.2	854.0	850.1	839.4	847.9	851.3	0.6
Tl	42.0	42.0	41.6	41.1	42.7	42.5	1.3

Element	Spike 1	Spike 2	Spike 3	Spike 4	Spike 5	Spike 6	RSD / %
Ba	7393	7513	7354	7310	7347	7366	1.0
Cr	57530	58330	56770	56180	55890	55940	1.7
Cu	15680	15960	15550	15400	15530	15450	1.3
Li	2869	2897	2834	2788	2794	2821	1.5
Mo	15950	16120	15820	15620	15640	15350	1.7
Sb	6206	6351	6132	6202	6157	6185	1.2
Sn	31170	31350	30410	30160	30150	30100	1.8

Intermediate precision (Ruggedness)

The results of 12 repeat analyses for each sample from six independent aliquots spiked with target value 1.0 J, were analyzed over two non-consecutive days with a different operator, new calibration and re-optimization of the instrument. The results for the folic acid samples over the two working days are shown in Table 8.

Table 8: Results of ruggedness test

Element	Spike 1a	Spike 2a	Spike 3a	Spike 4a	Spike 5a	Spike 6a	Spike 1b	Spike 2b	Spike 3b	Spike 4b	Spike 5b	Spike 6b	RSD / %
As	82.3	82.7	82.3	82.4	84.2	82.0	84.3	83.5	83.6	84.2	82.5	83.1	1.0
Cd	27.7	27.6	27.2	27.3	27.7	27.5	27.6	27.6	27.6	26.7	26.5	26.6	1.6
Hg	162.1	160.6	161.6	161.4	161.2	159.9	157.3	156.3	159.1	151.4	157.0	154.5	2.1
Pb	26.0	26.1	26.2	26.0	26.1	26.1	25.2	25.1	25.5	25.1	24.5	24.3	2.6
Co	264.0	263.6	263.4	265.2	264.8	267.4	265.7	264.7	267.5	270.3	261.1	258.4	1.2
Ni	1093	1072	1065	1067	1061	1077	1084	1060	1081	1072	1051	1021	1.7
V	535.2	533.4	534.6	535.3	536.0	537.3	521.8	527.5	526.9	523.4	517.7	508.8	1.7
Ag	654.1	747.4	699.4	735.0	790.3	733.9	906.1	975.4	923.7	963.7	858.4	912.2	13
Au	557.3	553.9	554.9	545.8	563.6	557.9	538.0	540.4	534.2	535.0	530.6	526.3	2.3
Ir	523.3	522.9	533.4	526.4	539.6	530.2	514.3	515.4	512.4	518.1	506.3	503.0	2.1
Os	428.0	419.7	422.2	425.5	431.5	423.9	481.9	479.2	494.4	477.8	474.7	497.4	7.0
Pd	535.4	525.2	529.0	518.5	528.4	528.0	517.0	520.3	521.0	517.3	513.7	504.1	1.6
Pt	529.2	532.1	528.0	528.8	536.6	530.5	529.4	524.4	523.9	528.3	516.5	514.2	1.2
Rh	536.3	533.6	536.2	528.5	539.3	541.9	516.4	514.5	511.8	509.3	508.4	493.6	3.0
Ru	535.5	542.1	528.1	529.7	544.8	535.0	530.8	542.1	539.0	544.9	525.4	517.9	1.6
Se	844.2	854.0	850.1	839.4	847.9	851.3	826.4	842.2	840.0	834.7	827.1	821.9	1.3
Tl	42.0	42.0	41.6	41.1	42.7	42.5	41.6	41.9	42.2	42.0	39.4	40.2	2.3
Ba	7393	7513	7354	7310	7347	7366	7175	7171	7105	7212	7139	7123	1.8
Cr	57530	58330	56770	56180	55890	55940	58390	57730	56890	57970	57190	57060	1.5
Cu	15680	15960	15550	15400	15530	15450	15690	15600	15400	15700	15350	15330	1.2
Li	2869	2897	2834	2788	2794	2821	2851	2824	2802	2874	2811	2828	1.2

Element	Spike 1a	Spike 2a	Spike 3a	Spike 4a	Spike 5a	Spike 6a	Spike 1b	Spike 2b	Spike 3b	Spike 4b	Spike 5b	Spike 6b	RSD / %
Mo	15950	16120	15820	15620	15640	15350	15250	15540	15370	15940	15690	15560	1.7
Sb	6206	6351	6132	6202	6157	6185	6386	6289	6201	6435	6308	6204	1.5
Sn	31170	31350	30410	30160	30150	30100	31360	30950	30740	31250	30620	30740	1.5

The criterion of 25% RSD in terms of ruggedness is easily achieved with the PlasmaQuant 9100 Elite, as precision values of less than 3% were achieved for the spiked folic acid samples. These results over two non-consecutive days illustrate the robustness and reliability of the method. A considerable deviation from the excellent RSD values is observed for the elements silver and osmium. Comparatively high RSD values of 13% and 7% are due to insufficient stabilization of these elements throughout the sample preparation process. Osmium requires hydrochloric acid in order to be stable throughout the digestion, the dilution and the storage of the obtained solutions. On the other hand silver may form precipitates of silver chloride in the presence of hydrochloric acid, which is then not fully available within the measurement solution. Additionally the respective standards are made up in different acidic mixtures. A mixture of the different stock standard solutions may also cause instability of elements like osmium and silver in the measurement solution. It has to be stated that the RSD values are still well within the required limits of 25%, even with the approach of running all 24 elements from one combined multi-element stock solution. Improved results can be obtained with separate, acid specific sample preparations.

Specificity

The definition of specificity within USP <233> is that the established method must be able to unequivocally assess each target element in the presence of components that may be expected to be present, including other target elements and matrix components. Further definition and means to determine specificity is given in USP chapter 1225[4]. Here, specificity is defined to serve the purpose of: "ensuring that all of the analytical procedures performed allow an accurate statement of the content of impurities of an analyte."[4] Hence it has to be validated, that the obtained results are interference-free and no false-positive or false-negative results are obtained. The proposed determination of specificity for impurity procedures is: "by spiking the drug substance or product with appropriate levels of impurities and demonstrating that these impurities are determined with appropriate accuracy and precision."[4]

Within this study the validation for specificity was undertaken by measuring the unspiked sample and two spiked samples with different levels of spiked target elements at 0.8 J and 1.0 J. Figure 3 depicts the obtained results normalized to the respective J-value of each impurity. For each analyte, the spikes show a distinctive increase in signal in comparison to the unspiked sample. Also, the 1 J spike shows a significantly greater signal in comparison to the 0.8 J spike. Both spike recoveries fulfill the requirements of the above described Accuracy and Repeatability tests and therefore prove that each target element is assessed unequivocally.

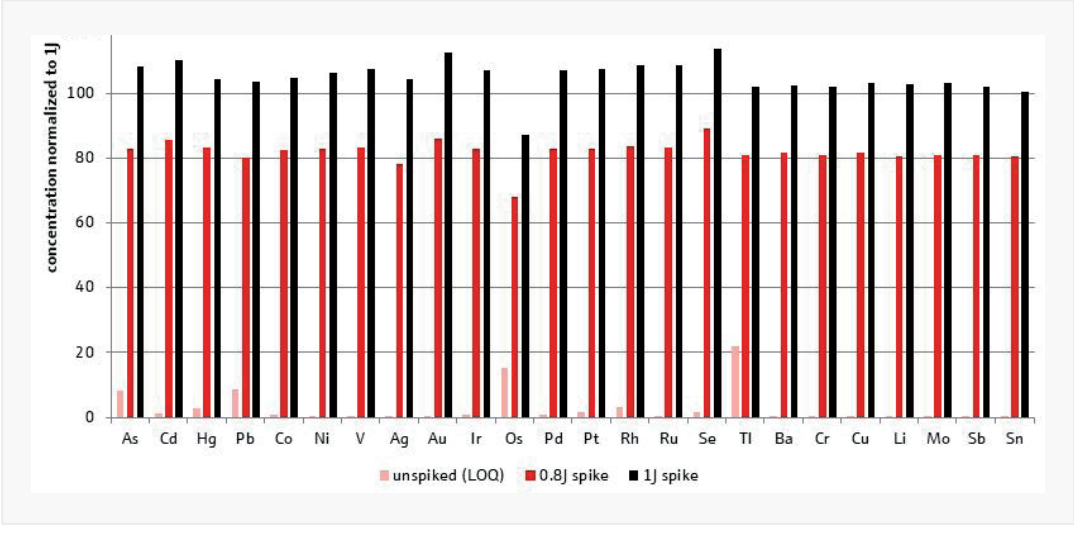

Figure 3: Results of specificity test 0.8 J and 1.0 J spike recoveries normalized to respective J-value; for unspiked samples the LOQ is displayed since none of the target elements was found in the test specimen

Further confidence in the accuracy of the results is obtained by the high-resolution spectra of the PlasmaQuant 9100 Elite. Figure 4 displays a spectral overlay of the unspiked sample and the two respective spikes at 0.8 J and 1.0 J for three target elements (cadmium, mercury and platinum). It can be seen that these peaks clearly gain in signal intensity with increasing target element concentration and that the peaks are clearly separated from any adjacent peak that might interfere and cause a false-positive result.

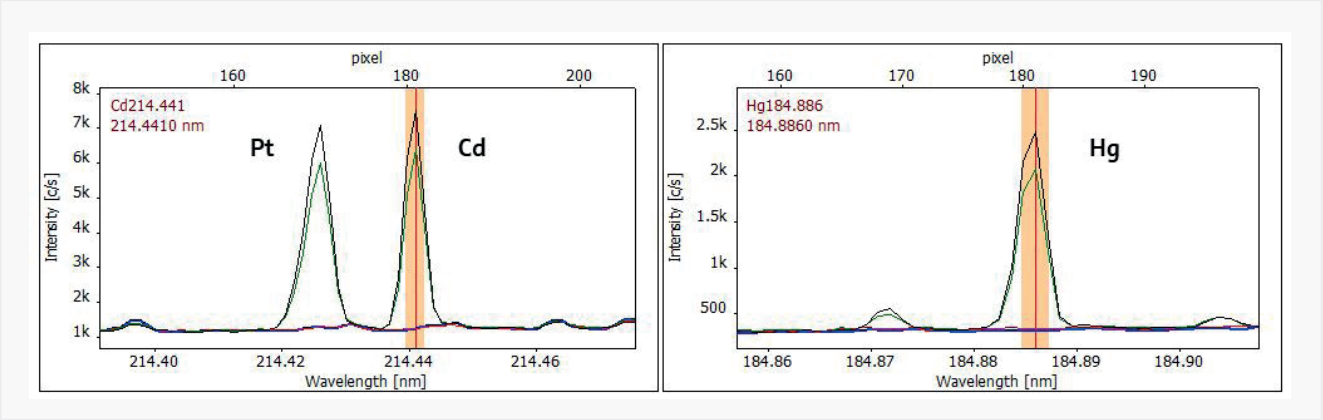

Figure 4: High resolution spectral overlay of Cd, Pt and Hg; blue – blank, red - sample, green – 0.8J spike, black – 1.0 J spike

Limits of quantification and sensitivity

Low limits of quantification (LOQ) are particularly important for some of the potentially toxic trace elements defined in USP <232>, notably arsenic, cadmium, mercury and lead. The LOQ for each target element is reported in Table 9. The LOQs were measured under routine laboratory conditions and are well below the target limits of each target element. The LOQ is based on the measurement of 11 blank solutions measured on two non-consecutive days and is defined as 10 times the standard deviation of the 11 blank measurements.

Table 9: Comparison of Limits of Quantification (LOQ) and J-values

Element	Line [nm]	LOQ [µg/L]	J-value [µg/L]
As	188.979	6.2	75
Cd	214.441	0.3	25
Hg	184.886	3.8	150
Pb	220.353	2.1	25
Co	237.863	1.6	250
Ni	231.604	1.1	1000
V	292.464	0.9	500
Ag	328.068	1.6	750
Au	242.795	1.2	500
Ir	212.681	3.2	500
Os	442.047	76.0	500
Pd	340.458	2.7	500
Pt	214.424	7.8	500
Rh	369.236	15.0	500
Ru	240.272	2.3	500

Element	Line [nm]	LOQ [µg/L]	J-value [µg/L]
Se	196.028	11.4	750
Tl	190.796	8.8	40
Ba	455.403	0.3	7000
Cr	205.552	5.4	55000
Cu	324.754	2.9	15000
Li	670.791	2.5	2750
Mo	202.030	8.2	15000
Sb	217.581	10.0	6000
Sn	189.927	7.1	30000

Conclusion

This application note shows a simple and effective method for routine preparation and analysis of pharmaceutical materials by ICP-OES in combination with closed vessel microwave digestion. The analysis of elemental impurities in pharmaceutical products by ICP spectrochemical techniques represents a routine task in QC labs of drug manufacturers and suppliers of materials involved in the manufacturing and handling process of these products. Each developed method to investigate such elemental impurities needs to be validated according to the guidelines and regulations of the International Conference on Harmonization (ICH) and the United States Pharmacopeia (USP).

The major challenges for this application include: varying sample types in terms of matrix composition, varying matrix loading, drug specific target limits and analyte combinations, the possibility of spectral interferences, as well as the requirement of analyzing elements over a large concentration range (low µg/L to high mg/L) in a single run. The PlasmaQuant 9100 Elite successfully meets all of these challenges and is well suited for the determination of 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 High-Frequency Generator in combination with the unique V-Shuttle torch allows for the measurement of almost any sample type including undiluted solvents and high matrix samples, which gives the operating laboratory great flexibility for the analysis for pharmaceutical applications. At the same time, spectral interferences are resolved easily by the high-resolution optical system (2 pm @ 200 nm) ensuring high accuracy of the obtained results as well as high confidence in the developed methodology.

The challenge of large differences in target values, for example, if Class 1 elements are to be analyzed together with Class 3 elements (mandatory for parenteral or inhalation products), is successfully addressed by the DualView Plus feature of the PlasmaQuant 9100 Elite. Besides the common radial and axial plasma observation modes it offers axial plus and radial plus, which attenuates the signal in the respective observation mode. The here described method uses radial plus plasma observation to measure the high levels of barium, lithium and chromium alongside the trace levels of all Class 1 elements in a single measurement run. Running several dilutions to cover the entire concentration range is therefore avoided. The high spectral resolution and sensitivity of the PlasmaQuant 9100 Elite by Analytik Jena offers new analytical potential.

References

[1] General Chapter <232> Elemental Impurities—Limits, USP39. Publishing in Pharmacopeial Forum 42(2) [Mar.–Apr. 2016]

[2] General Chapter <233> Elemental Impurities—Procedures, Second Supplement to USP 38–NF 33, 2015

[3] International Conference on Harmonization, ICH Q3D Step 4 - Guideline for Elemental Impurities (ICH, Geneva, Switzerland, 2014)

[4] General Chapter <1225> Validation of compendial procedures, First Supplement to USP 40–NF 35

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