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SPECTRO ANALYTICAL INSTRUMENTS

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SPECTRO ARCOS

Meeting the new ICH and USP regulation for elemental impurities in pharmaceutical products using the SPECTRO ARCOS with axial plasma observation

Introduction

Elemental impurities include substances such as arsenic, cadmium, lead and mercury, and can appear in a finished pharmaceutical product through various routes. They can occur naturally, resulting from their presence in the ground from which materials are sourced, be added intentionally as part of a product's synthesis (e.g., as a catalyst in chemical reactions), or be introduced inadvertently (e.g., from interactions with processing equipment during manufacturing) [1].

For over 100 years regulators have demanded the testing of heavy metal impurities in pharmaceutical products. Recently, global regulators have issued modern methods and guidelines, e.g. in the form of the United States Pharmacopeia (USP) Chapters USP <232>, <233> and <2232>, or the ICH Q3D, from the International Council on Harmonization (ICH), as observed by the European Medicines Agency.

Meeting the new ICH and USP regulation for elemental impurities in pharmaceutical products using the SPECTRO ARCOS with axial plasma observation

This application report demonstrates that the SPECTRO ARCOS meets the requirements of <232> USP and ICH Q3D for the analysis of pharmaceutical products with low daily doses.

Limits of detection, recoveries and ruggedness fully agree and even exceed the specifications described in the mentioned chapters.

Due to the sensitivity and large dynamic range, major, minor and trace analyte concentrations in pharmaceutical products can be analyzed using a single analytical method, thus requiring minimal dilution of the samples.

USP methods have become official for all drugs products (to be marketed in the USA) on January 1, 2018, ICH Q3D is already in effect since June 01st, 2016 and applicable to all new drug products. From December 1st, 2017 it is also applicable to existing drug products.

The new guidelines describe elemental impurity limits in pharmaceuticals and the analytical procedures to be used for their determination. The ICH Q3D includes 24 elements, including lead, arsenic, mercury and cadmium. These are classified into four groups in terms of their toxicity. Permitted Daily Exposures (PDEs) are established for oral, parenteral and inhalation routes of administration. Additionally, ICH Q3D provides recommendations, which of the 24 elements are to be considered in any pharmaceutical product risk assessment [2]. The USP considers fewer elements and a limit for these metals in pharmaceutical products is based on the "permitted daily exposure" (PDE) as well as the route of administration (oral, parenteral or inhalation).
Table 1 shows the PDE for Elemental Impurities defined in ICH Q3D and USP<232> intended for oral administration [1][2].

Table 1: Permitted Daily Exposure (PDE) for Elemental Impurities defined in USP <232> and ICH Q3D guidelines

			ICH Q3D	USP 232
ICH Class	**Element**		**Oral PDE (µg/day)**	**Oral PDE (µg/day)**
Class 1	Cadmium	Cd	5	5
	Lead	Pb	5	5
	Inorganic Arsenic	As	15	15
	Inorganic Mercury	Hg	30	30
Class 2A	Cobalt	Co	50	
	Vanadium	V	100	100
	Nickel	Ni	200	200
Class 2B	Thallium	Tl	8	
	Gold	Au	100	
	Palladium	Pd	100	100
	Iridium	Ir	100	100
	Osmium	Os	100	100

			ICH Q3D	USP 232
ICH Class	**Element**		**Oral PDE (µg/day)**	**Oral PDE (µg/day)**
Class 2B	Rhodium	Rh	100	100
	Ruthenium	Ru	100	100
	Platinum	Pt	100	100
	Selenium	Se	150	
	Silver	Ag	150	
Class 3	Lithium	Li	550	
	Antimony	Sb	1200	
	Barium	Ba	1400	
	Molybdenum	Mo	3000	3000
	Copper	Cu	3000	3000
	Tin	Sn	6000	
	Chromium	Cr	11000	11000

Chapter <233> USP describes the analytical procedure, including sample preparation, detection method and its validation for measuring elemental impurities. Two instrumental techniques are discussed in chapter <233> USP, namely inductively coupled plasma – optical emission spectroscopy (ICP-OES) and inductively coupled plasma – mass spectrometry (ICP-MS) [3]. Correctly implemented and used, both techniques have the potential to deliver the performance characteristics needed for pharmaceuticals' analysis.

SPECTRO ICP-OES instruments can handle high matrix loads allowing for an efficient sample analysis without additional dilution and are therefore the instruments of choice for the analysis of raw materials and finished oral drugs products.

This application report demonstrates that the SPECTRO ARCOS meets the requirements of <232> USP and ICH Q3D for the analysis of pharmaceutical products with low daily doses.

Experimental

Instrumentation

All measurements were performed with the SPECTRO ARCOS inductively coupled plasma-optical emission spectrometer (SPECTRO Analytical Instruments, Kleve, Germany) with axial plasma observation. The SPECTRO ARCOS features a Paschen-Runge spectrometer mount, employing the Optimized Rowland Circle Alignment (ORCA polychromator) technique. Consisting of two hollow section cast shells, optimized small volume and 32 linear CCD detectors, the wavelength range between 130 and 770 nm can be simultaneously analyzed, allowing complete spectrum capture within 2s. Due to the unique reprocessing capabilities of the system, a new measurement is not required even if additional elements or lines are to be determined at a later date. The optic is hermetically sealed and filled with argon, continuously circulated through a filter, which absorbs oxygen, water vapor and other species. High optical transmission in the VUV is achieved, allowing the determination of non-metals as well as the use of prominent and interference free lines in this region. Utilizing SPECTRO's "Intelligent Calibration Logic (iCAL)", which normalizes the wavelength scale, the state of the optical system is automatically monitored.

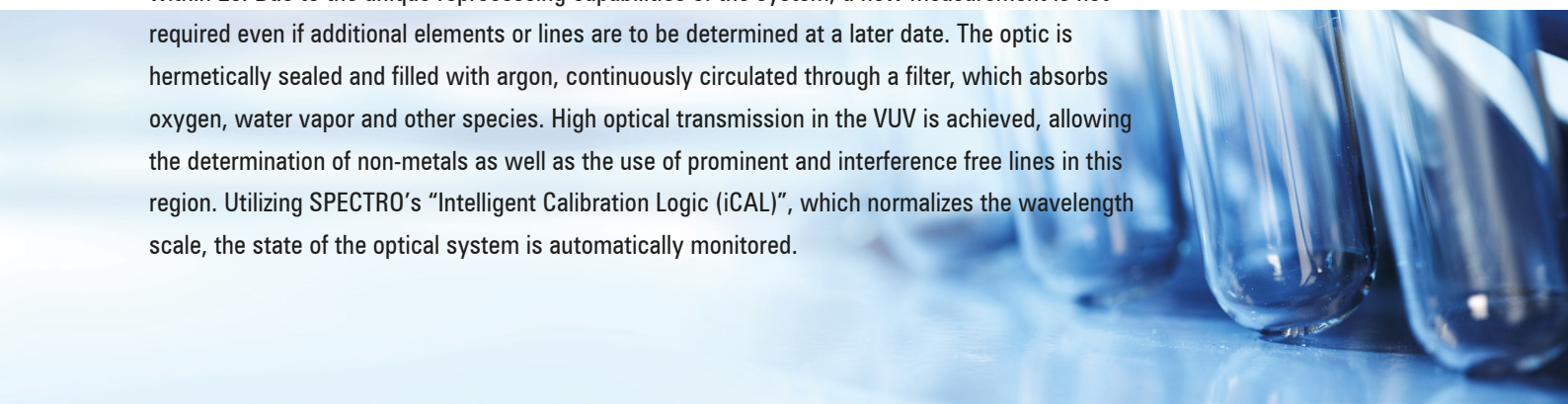

Table 2: ICP Operating Conditions employed for the measurements

Plasma Power	1300 W
Coolant flow	13 L/min
Auxiliary flow	0.8 L/min
Nebulizer flow	0.8 L/min
Plasma torch	Quartz, demountable, 2.0 mm Injector tube
Spray chamber	Cyclonic
Nebulizer	SeaSpray
Sample aspiration rate	2 mL/min
Replicate read time	28 s

An air-cooled, 27.12 MHz, free running type LDMOS (laterally diffused metal oxide semiconductor) ICP-generator is installed, which ensures excellent stability of the forward power even in the case of rapidly changing sample loads. All relevant ICP operating parameters are software controlled, allowing for an easy selection of the optimum operating conditions. For sample introduction, a cyclonic spray chamber and a SeaSpray (Glass Expansion, Port Melbourne Vic, Australia) nebulizer were used. The ICP operating parameters are given in Table 2.

Sample Preparation

The pharmaceutical product chosen as example for this study was acetylsalicylic acid, purchased from a local pharmacy. Closed vessel microwave digestion was chosen as the sample preparation method. 0.5g of the sample was digested with 9 mL HNO_3 and 0.5 mL H_2O_2 using a Discover SP-D microwave digestion system (CEM Corp. NC, USA). All reagents were suprapure grade and supplied from Merck (Darmstadt, Germany). Table 3 shows the microwave program used for the digestion method.

Table 3: Microwave digestion program

Temp [°C]	Ramp Time [min]	Hold Time [min]	Cool Time [min]	Pressure max. [bar]	Power [W]	Stirring
210	5:00	5:00	15:00	28	300	medium

The digested samples were diluted with deionized water to a final volume of 25 mL and acidified with 2% (v/v) suprapure HCl. Yttrium at a concentration of 1mg/L was added to the samples as internal standard.

Calibration Standards

For external calibration, commercially available single-element standards (Inorganic Ventures, Christiansburg, USA) with concentrations of 1000 and 10000 mg/L were used. As specified in USP Chapter <233>, three standards at a concentration level of 0, 0.5J and 2J, where J indicates the Target Limit, were used. All standard solutions were acidified with 36% (v/v) suprapure HNO3 and 2% (v/v) suprapure HCl. It was found that the addition of HCl is necessary to stabilize the Os concentration in the solution. To account for the carbon components remaining in the samples even after digestion, affecting the spectral background in the 165-200 nm spectral region, ascorbic acid at a concentration of 10g/L was added to all calibration standards.

Results and Discussion

In order to check the suitability of the technique, whether its detection capability is appropriate for the analytical task, it is important to investigate the target limits of the elements, defined in chapter <232> USP as the J value. The J value is determined according to the following formula:

$$J = \frac{\mathbf{PDE}}{\mathbf{Maximum\ Daily\ Dose} * \mathbf{dilution\ factor}}$$

Where:

PDE	=	Permitted Daily Exposure [μg/day]
Maximum Daily Dose	=	Maximum Daily Dose= the maximum allowed dose of the pharmaceutical product per day [g]
Dilution factor	=	the dilution factor used for the sample preparation procedure

As it can be easily seen from this equation, the J value will vary with the pharmaceutical product. A larger daily dose will result in a lower J value, and, vice versa, a smaller daily dose in a higher J value. As an example, the PDE limit for Pb in an oral medication is 5 μg/day.

Table 4: Limits of detection achieved, compared to the target limits (in µg/L), for the respective elements

Element	Wavelength [nm]	LOD [µg/L]	Target Limit 1J [µg/L]
Ag	328.068	0.44	1000
As	189.042	1.0	100
Au	242.795	0.50	667
Ba	233.527	0.09	9333
Cd	228.802	0.07	33
Co	228.616	0.18	333
Cr	267.716	0.18	73333
Cu	324.754	0.25	20000
Hg	184.950	0.60	200
Ir	212.681	0.80	667
Li	670.780	0.03	3667
Mo	202.095	0.32	20000
Ni	221.648	0.26	1333
Os	228.226	080	667
Pb	220.353	0.90	33
Pd	324.270	6.68	667
Pt	177.708	2.20	667
Rh	343.489	1.77	667
Ru	240.272	0.70	667
Sb	206.833	1.20	8000
Se	196.090	3.35	1000
Sn	189.991	0.97	40000
Tl	190.864	0.80	53
V	292.464	0.42	667

Using the maximum allowed dosage for acetylsalicylic acid of 3 g/day, this equals a maximum allowed concentration of 1.7 µg/g in the product, which needs to be controlled. For this study, 0.5 g of the sample were digested and diluted to 25 mL (50- fold dilution) This means the J- value e.g. for Pb, is 33 µg/L. The J-values calculated for each element, as well as the obtained limits of detection, are reported in Table 4.

As it can be seen in Table 4, the limits of detection obtained for all the elements are at least an order of magnitude lower than the required Target Limit.
The target elements were determined in triplicate in the studied, unspiked drug sample and were found to be below the instrument detection limit.

The USP <233> guidelines include a procedure for the validation of the analyses. This involves the measurement of defined standards and test samples under specified conditions to test the accuracy and repeatability of the method.
To test the accuracy of the procedure, samples were prepared in triplicate containing the target elements at concentrations of 0.5 and 1.5 times their respective target limit values (J value). The resulting recoveries are shown in Figure 1 and Figure 2 for the 0.5J and 1.5J test level, respectively.

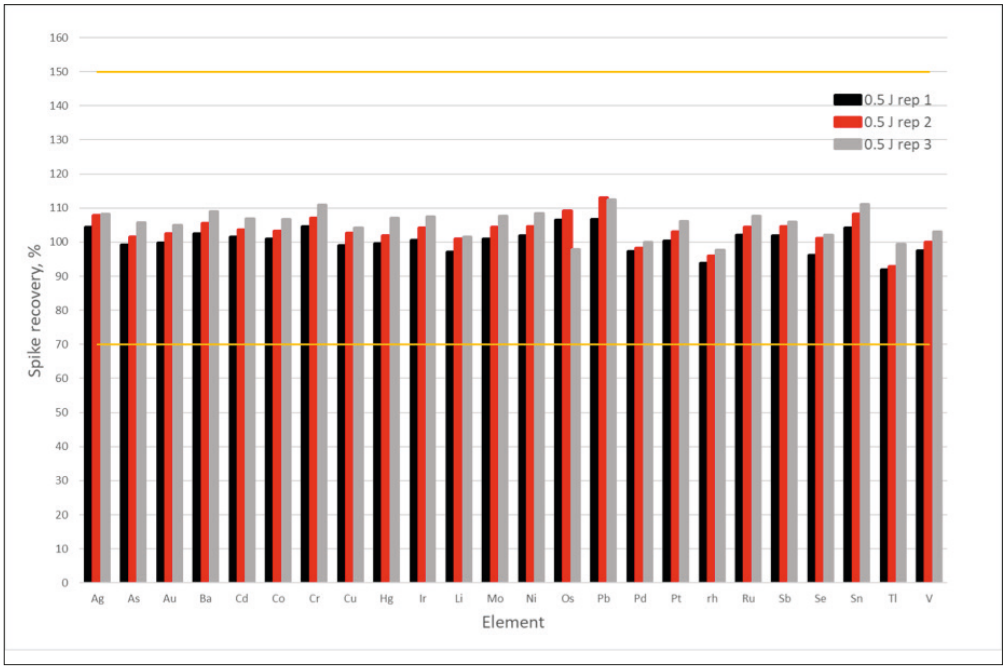

Figure 1: Recoveries for the 0.5J spike level for the sample investigated in triplicate.

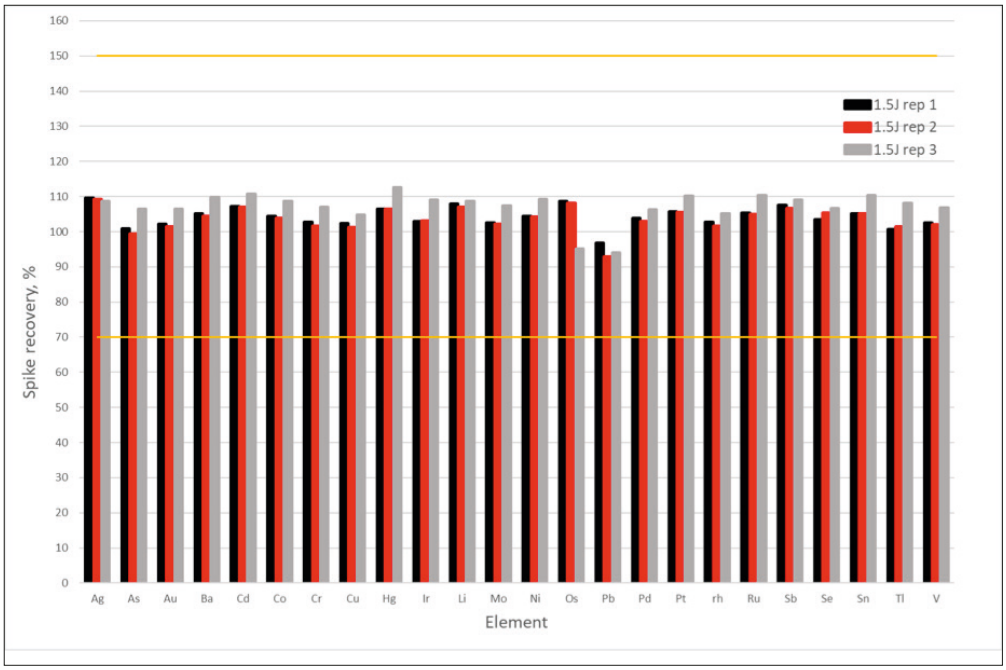

Figure 2: Recoveries for the 1.5J spike level for the sample investigated in triplicate.

The acceptance criteria defined in USP <233> requires a spike recovery between 70% and 150% for the mean of three replicate preparations, at each concentration. Figure 1 and Figure 2 show the recoveries found for all the elements and the two spike concentrations well within the specified limit of 70-150%.

To meet the repeatability requirements of the guideline, six independent samples, spiked with the elements of interest at the 1J level, were measured. Table 5 shows the repeatability results for the drug sample investigated.

Table 5: Repeatability test results of six independent samples spiked at a level of 1J

Element Line nm	Acetylsalicylic acid sample spiked at 1J level						Mean [mg/L]	SD	RSD [%]
	Spike 1	Spike 2	Spike 3	Spike 4	Spike 5	Spike 6			
Ag 328.068	1091	1048	1051	1056	1039	1099	1064	24.8	2.3
As 189.042	104	103	104	101	102	102	103	1.1	1.1
Au 242.795	700	696	702	692	694	696	697	3.7	0.5
Ba 233.527	10180	9967	10009	9926	9935	10010	10004	93.1	0.9
Cd 228.802	36	35	35	35	35	35	35	0.4	1.0
Co 228.616	355	350	350	347	349	350	350	2.9	0.8
Cr 267.716	79506	78750	79306	77718	78502	78247	78671	666.7	0.8
Cu 324.754	20953	20805	20840	20604	20747	20642	20765	129.7	0.6
Hg 184.950	216	212	215	212	211	214	213	1.9	0.9
Ir 212.681	718	709	712	708	708	715	712	4.2	0.6
Li 670.780	3994	3856	3835	3880	3877	3914	3893	56.2	1.4
Mo 202.095	21208	21158	21251	20907	21009	21024	21093	133.5	0.6
Ni 221.648	1424	1402	1409	1387	1397	1405	1404	12.3	0.9
Os 228.226	681	684	684	684	695	686	686	4.7	0.7
Pb 220.353	36	36	36	36	36	35	36	0.4	1.2
Pd 324.270	686	677	681	675	678	677	679	4.0	0.6
Pt 177.708	708	700	701	696	698	699	700	4.0	0.6
Rh 343.489	669	668	667	658	664	661	664	4.2	0.6
Ru 240.272	713	708	715	704	706	709	709	4.1	0.6
Sb 206.833	8539	8435	8383	8384	8448	8516	8451	65.3	0.8
Se 196.090	1114	1066	1067	1074	1071	1094	1081	19.0	1.8
Sn 189.991	43061	42824	42993	42440	42656	42702	42779	229.5	0.5
Tl 190.864	55	55	56	55	55	55	55	0.5	1.0
V 292.464	698	687	688	679	683	686	687	6.5	0.9

Excellent repeatability, with RSDs below 2.5% for all 24 elements, were found, well below the stipulated acceptance criterium of 20% max. RSD.

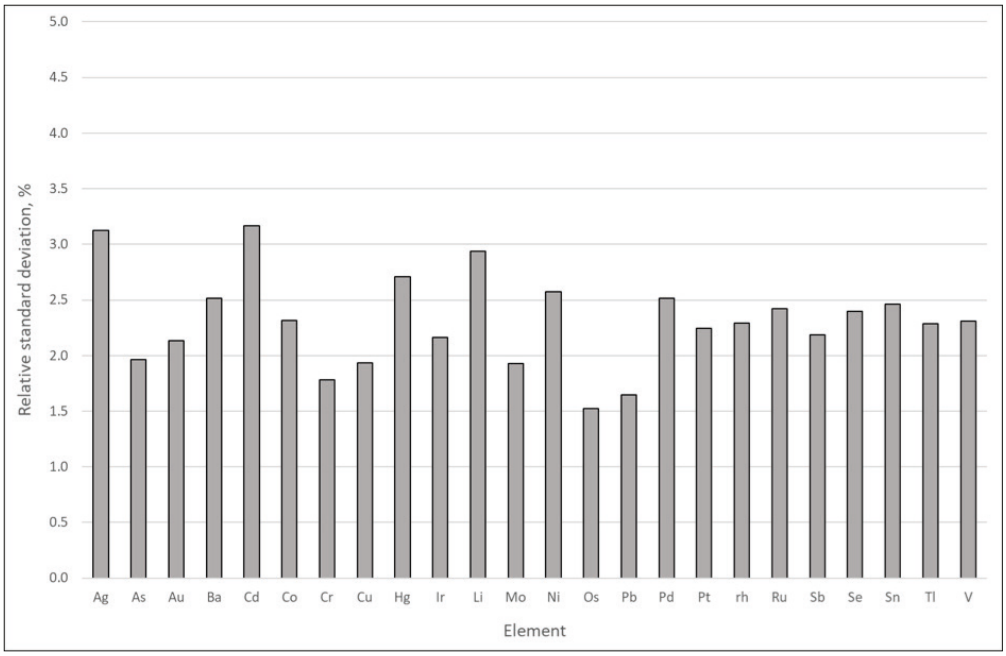

Figure 3: Ruggedness: The relative standard deviation obtained for the analyses of the Acetylsalicylic acid sample on three different days.

The "Ruggedness" of the procedure is assessed by performing repeatability measurements on different days, or using different instruments, or with different operators. In this study, Ruggedness was determined by analyzing samples on three different days, on the same instrument by the same operator. The results obtained are presented in the Figure 3.

As it can be seen in Figure 3, a very good result for the Ruggedness criterium was achieved, with RSDs <3.5%, well below the stipulated acceptance criteria of 25% max. The repeatability and ruggedness results demonstrated the robustness and reliability of the developed and applied method.

Conclusions

This study demonstrates that the SPECTRO ARCOS with axial plasma observation can meet and exceed the requirements of USP chapter <232/233> and the ICH Q3D regulation for pharmaceutical products with low daily doses.

The SPECTRO ARCOS with axial plasma observation offers high sensitivity with excellent LODs and can still handle high levels of dissolved solids. Due to the sensitivity and large dynamic range, major, minor and trace analyte concentrations in pharmaceutical products can be analyzed using a single analytical method, thus requiring minimal dilution of the samples.

In combination with an autosampler, all SPECTRO ICPs can be fully automated. Independent from the number of lines and elements, an analysis (including three replicates, pre-flush and method rinse) can be performed in less than three minutes.

References

[1] Elemental Impurities – Limits, Chapter USP <232>, (Pharm. Forum 2016), 42 (2),

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

[3] Elemental Impurities – Procedure, Chapter USP <233>, Second Supplement to USP 38-NF 33, 2015

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