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Application Note

Measurement of Trace Elemental Impurities in Aspirin Using Ultrasonic Nebulization with ICP-OES Detection Following USP <232>/<233> Guidelines

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Introduction

With the implementation of USP <232>/<233> for the measurement of elemental impurities in finished drug products,[1,2] it is important for manufacturers to monitor the trace element content of the final products to be in compliance. These criteria, detailed in USP <232>/<233>, recommend analysis of drug products for trace element impurities by either ICP-OES or ICP-MS.

The maximum permitted daily exposure (PDE) of different target elements is defined in USP <232> and is based on the route of administration which may be oral, parenteral (ex. intravenous, injection), or inhalation. USP <232> lists 24 elements to be measured in drug products, with an element class grouping based on toxicity. Class 1 and 2A elements must be measured; the class 1 elements are most toxic and the Class 2A elements have a high probability of being present. Maximum oral daily exposures for the element impurities listed in USP <232> are given in Table 1.

Laboratories must measure impurities based on the J value for each element. The J values are calculated based on an established PDE, maximum daily dose of the drug (MDD), and the dilution factor used in the sample preparation method. As a result of the J value calculation, drugs with a larger MDD require lower element impurity detection limits. For a higher daily dose drug product such as aspirin, the enhanced analyte transport efficiency of an ultrasonic nebulizer (USN) accessory enables improved trace element detection using ICP-OES. For this aspirin study with the USN and ICP-OES all elements except osmium are measured. The four analytical criteria specified in the validation of the quantitative procedures for USP <233> are accuracy, repeatability, ruggedness, and system suitability, with the requirements of each being summarized in Table 2.

Table 1. Maximum Oral Daily Exposures for Elements Defined in USP <232>

Element	Class	Max. Oral Daily Exposure (µg/day)
Cd	1	5
Pb	1	5
As	1	15
Hg	1	30
Co	2A	50
V	2A	100
Ni	2A	200
Tl	2B	8
Au	2B	100
Pd	2B	100
Ir	2B	100
Rh	2B	100
Ru	2B	100
Se	2B	150
Ag	2B	150
Pt	2B	100
Li	3	550
Sb	3	1200
Ba	3	1400
Mo	3	3000
Cu	3	3000
Sn	3	6000
Cr	3	11000

*PDE = permissible daily exposure based on a 50kg person

Table 2. Analytical Criteria Defined in USP <233> for Quantitative Procedures

Criteria	Description
Accuracy	Spike recoveries at 0.5J, J, and 1.5J must be between 70-150%
Repeatability	The %RSDs of measurements of six independent samples spiked at J must be less than 20%
Ruggedness	Six solutions must be analyzed on different days, with different instruments, or with different analysts. The %RSDs over the 12 measurements must be less than 25%
System Suitability	The difference in the results of the high calibration standard (1.5J) measured at the beginning and end of a batch must be < 20%

This work describes the analysis of aspirin tablets using ICP-OES coupled with a Teledyne CETAC U5000AT+ Ultrasonic Nebulizer (USN). The USN setup requires approximately 5 to 10 minutes after removal of the standard nebulizer kit; no computer control of the USN is needed. Signal enhancement with the USN is especially important for the detection of more difficult elements such as As, Pb, Cd, and Tl. A picture of U5000AT+ USN is given in Figures 1.

Figure 1. Teledyne CETAC Technologies U5000AT+ USN

Experimental

Sample Preparation

Sample preparation was accomplished by adding 0.5 gram of aspirin with multielement spike to each digestion vessel followed by 5 mL of reagent grade HNO_3 and 1 mL of reagent grade HCl. The vessels were left uncapped for 10 minutes in a fume hood to allow any initial gases to vent prior to sealing the vessels. Spiked and un-spiked samples were digested using a closed vessel microwave digestion program as specified by USP <233>; conditions are listed in Table 3.

Table 3. Microwave digestion program with CEM Mars 6 system

Stage	Power (W)	Ramp	Hold	Temp (°C)
1	1050	15 min	15 min	200

Once digestions were complete and samples cooled to room temperature, 5 mL of reagent grade HCl was added to each sample and diluted to a final volume of 50 mL with deionized water. For this sample matrix, an acid concentration of 10% HNO_3 / 10% HCl was adequate to digest the aspirin sample and maintain elements in solution. The aspirin tablets did not contain SiO_2 or TiO_2, so the addition of hydrofluoric (HF) acid was not necessary. If a drug tablet contains SiO_2 or TiO_2, then HF would be necessary for digestion. In addition, HF-digested samples would require neutralization of residual HF with boric acid prior to introduction to any nebulizer system (such as the USN) that has glass-wetted components.

The ICP-OES was calibrated using standards that were matrix matched to the acid concentrations of the digested samples. An internal standard solution of 50µg/L was added to all samples and standards using a mixing tee. Samples for the Class 1 elements (includes Hg), 2A elements, and thallium were digested and analyzed separately from the Class 2B and Class 3 elements. For these elements, the reagent L-cysteine, a thiol-containing amino acid, was added to digested samples to assist element transport of Hg through the ultrasonic nebulizer. In this application note, these elements are referred to as the cysteine group (CG) elements. The standards for the CG elements were digested along with the samples. L-cysteine was added to the 50µg/L Y internal standard solution so the final concentration after sample mixing was 3mg/mL. As nitric acid rapidly oxidizes L-cysteine, the internal standard solution was prepared in 0.07M HCl.

The final dilution for each sample after digestion was 100x with deionized water. With that dilution factor and a maximum daily dose of 4.32 g (one aspirin tablet is 0.36g, maximum dose is 12 tablets per day), the calculated J values (rounded down) are listed in Table 4. Following USP <233> protocol, a reagent blank, 0.5 J standard, and 1.5 J standard were used for calibration.

Table 4. Analyte Concentrations at Different J Values

Element	J-value (mg/L)	0.5 J	1.5 J
Cd	0.01	0.005	0.015
Pb	0.01	0.005	0.015
As*	0.03	0.015	0.06
Hg*	0.06	0.03	0.09
Co	0.10	0.05	0.15
V	0.20	0.10	0.30
Ni	0.40	0.20	0.60
Tl	0.016	0.008	0.024
Au	0.20	0.10	0.30
Pd	0.20	0.10	0.30
Ir	0.20	0.10	0.30
Rh	0.20	0.10	0.30
Ru	0.20	0.10	0.30
Se	0.30	0.15	0.45
Ag	0.30	0.15	0.45
Pt	0.20	0.10	0.30
Li	1.1	0.55	1.65
Sb	2.4	1.2	3.6
Ba	2.8	1.4	4.2
Mo	6	3	9
Cu	6	3	9
Sn	12	6	18
Cr	22	11	33

*inorganic

Instrumental Conditions

Analyses were performed with a PerkinElmer Avio® 500 ICP-OES coupled with a Teledyne CETAC U5000AT+ Ultrasonic Nebulizer using the conditions and parameters in Table 5. Operating conditions with the standard glass concentric nebulizer are given for comparison.

Table 5. Operating Conditions: Avio® 500 ICP-OES and U5000AT+ USN

Parameter	Standard Nebulizer	U5000AT+ USN
ICP Power	1500 W	1500 W
Plasma Gas	8.0 L/min	8.0 L/min
Auxiliary Gas	0.2 L/min	0.2 L/min
Nebulizer Gas	0.7 L/min	0.62 L/min
Torch injector diam.	2 mm	2 mm
Uptake Rate	1.5 mL/min	1.0 mL/min
Cassette Position	-3.0	-5.0
Resolution	Normal	Normal
Nebulizer Type	Meinhard K	Piezoelectric
Spray Chamber	Baffled cyclonic	Conical
Heater Temp	N/A	120°C, 140°C
Cooler Temp	N/A	5°C
Integration Time	2 s min, 10 s max	2 s min, 10 s max
Peak area	3 pts/peak	3 pts/peak
Replicates	3	3

Results and Discussion

Interferences and line selection

All elements required by USP <232>, as well as elements potentially in the aspirin sample (ex, Ca, Na, Si, Mg), were run individually to evaluate spectral interferences for each viable emission line. Whenever possible, an emission line free of interferences was selected for analysis. If a suitable interference-free line could not be selected, multicomponent spectral fitting (MSF) or interelement-correction factors (IECs) were used to correct for sample and/or standard interferences. An interference check solution was analyzed during the sample run to verify spectral interference correction techniques were working properly. The analytical wavelengths and view modes used for analysis are listed in Table 6.

Table 6. Elements, Wavelengths, and Plasma View Modes

Element	Wavelength (nm)	View
Cd	228.802	Axial
Pb	220.353	Axial
As	188.979	Axial
hg	253.652	Axial
Co	228.616	Axial
V	292.402	Axial
Ni	231.604	Axial
Tl	190.801	Axial
Au	242.795	Axial
Pd	340.458	Radial
Ir	208.882	Axial
Rh	343.489	Radial
Ru	349.894	Radial
Se	196.026	Axial
Ag	338.289	Axial
Pt	265.945	Axial
Li	670.784	Radial
Sb	231.146	Radial
Ba	493.408	Radial
Mo	202.030	Axial
Cu	324.752	Radial
Sn	189.927	Axial
Cr	267.716	Radial

Sample Analysis

Samples were analyzed using the standard glass concentric nebulizer setup and the U5000AT+ ultrasonic nebulizer. Selected spectra (Figure 2) from an aspirin digestion spiked at the 1J value show the signal enhancement offered by the ultrasonic nebulizer (red line) vs. the standard nebulizer (black line). Note that in this matrix there is no discernible emission peak for Tl 190.801nm at 16 µg/L using the standard nebulizer; measurable signal is enabled by the ultrasonic nebulizer.

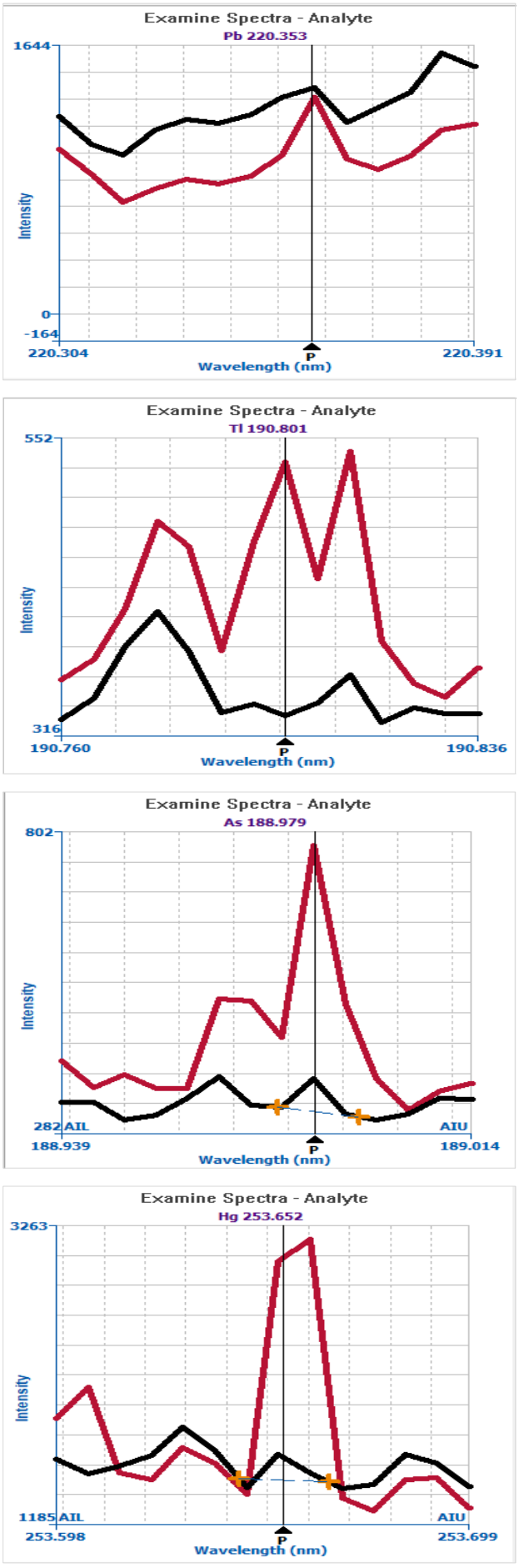

Figure 2. Overlay of selected emission spectra, elements spiked at 1J

Meeting the USP <233> Criteria

Accuracy

To test the accuracy of the method, three replicate preparations of the sample spiked at 0.5J and 1.5J respectively were analyzed using the U5000AT+ USN and the host ICP-OES. Adding the spikes and carrying these through the complete sample preparation and analysis procedure proves that analyte is not lost. Figure 3 shows that all recoveries are between 82.0% and 104.9%, easily meeting the method criteria of 70% to 150% spike recovery.

Repeatability and Ruggedness

To determine repeatability, six independent samples were spiked at 1J and analyzed; the relative standard deviations of the results must be less than 20%. To assess ruggedness, the same sample solutions were analyzed on a different day. The relative standard deviations for all 12 analyses must be less than 25%. All elements have less than 8% RSDs for replicate measurements as shown in Figure 4 and Figure 5.

System Suitability

The final requirement concerns the analysis of the 1.5J calibration standard at the beginning and end of the analytical run. The drift in the measured concentration must be less than 20%. The % drift range for all elements was from 0.4% to 8.4%, easily achieving the acceptance limit of 20% as shown in Figure 6.

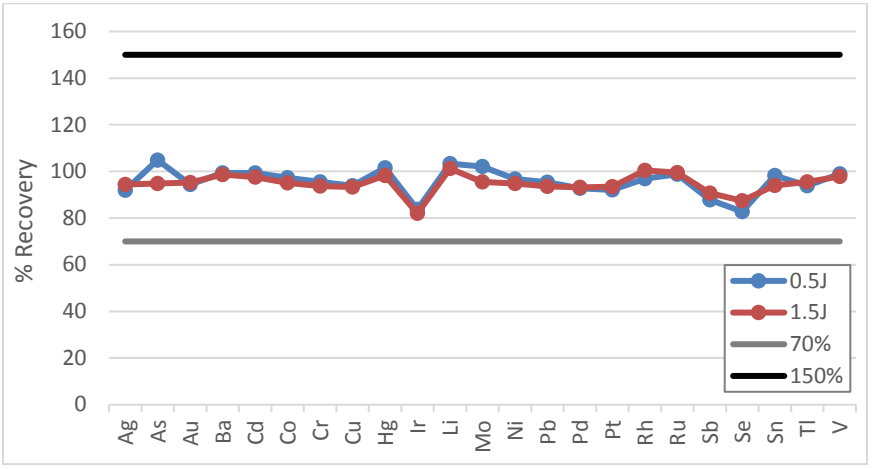

Figure 3. Accuracy: 0.5J and 1.5J spike recoveries in aspirin. Black and gray lines show USP <233> limits.

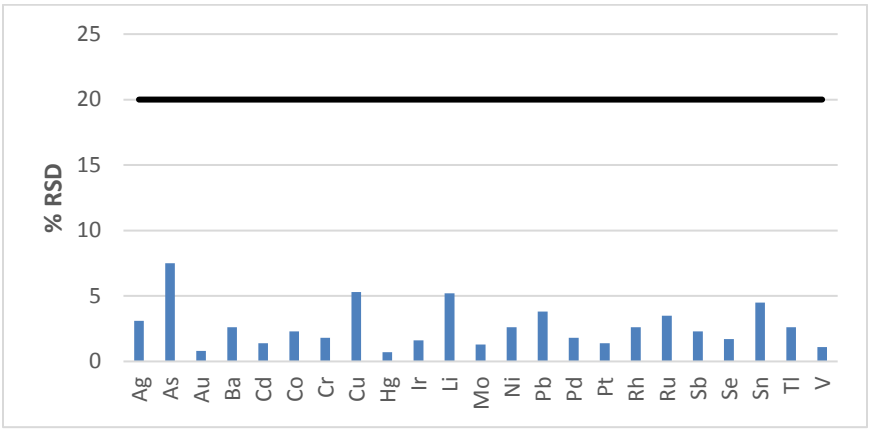

Figure 4. Repeatability: %RSDs of six independent samples spiked at 1J.

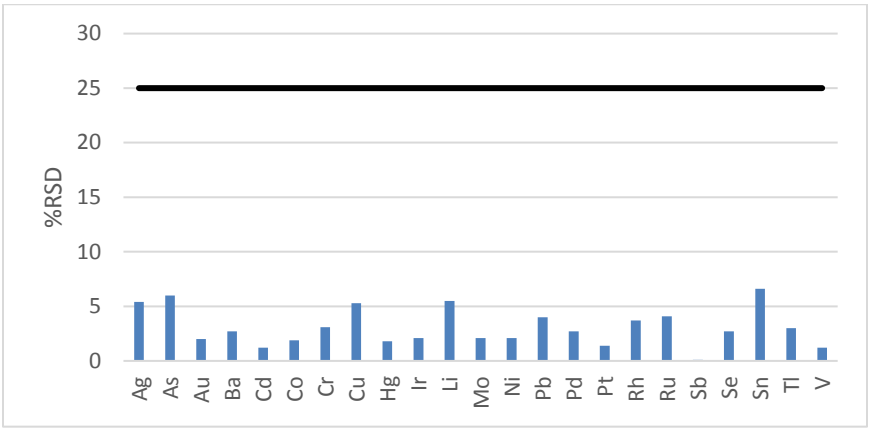

Figure 5. Ruggedness: %RSDs of six independent samples analyzed over two days (12 measurements).

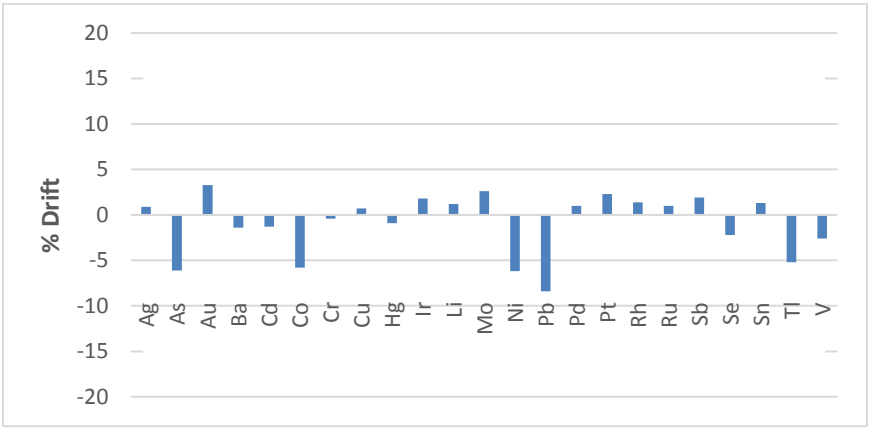

Figure 6. System Suitability: analysis of 1.5J at the beginning and end of analytical run.

Conclusion

All criteria required by the USP <233> were met using the U5000AT+ USN with ICP-OES detection of trace elements in the drug product aspirin. The USN enabled enhanced analyte sensitivity and lower background emission such that improved ICP-OES analysis of a higher daily dose drug product is possible.

References

1. General Chapter <232> Elemental Impurities – Limits: 2nd Supplement of USP 35-NF 30.
2. General Chapter <233> Elemental Impurities – Procedures: 2nd Supplement of USP 35-NF 30.

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