Measurement of Elemental Impurities in a Higher Daily Dose Drug Product by USP <232>/<233> Using Ultrasonic Nebulization with ICP-AES Detection

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Abstract: On January 1, 2018 the U.S. Pharmacopeia (USP) enacted new criteria for element impurities in finished drug products. These criteria, detailed in USP <232>/<233>, recommend analysis of drug products for element impurities by either ICP-AES or ICP-MS. Laboratories must measure impurities based on a J value for each drug product; drug products may be oral, parenteral (ex. intravenous, injection), or inhalation types. The J value of the drug is calculated based on an established permissible daily exposure (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. An ultrasonic nebulizer (USN) is an accessory for ICP-AES that enables higher sample transport efficiency (versus a standard pneumatic nebulizer) to the ICP-AES plasma. This benefit can be helpful for detection of more difficult elements such as As, Cd, Pb, Sb, and Tl. This work describes the use of the USN for ICP-AES detection of element impurities in aspirin, a drug with a higher daily dose than a low dose drug (ex. 1 tablet per day) such as an allergy or sleep aid medicine.

Instrumentation:

ICP-AES: PerkinElmer Avio 500

Ultrasonic Nebulizer (USN): Teledyne CETAC U5000AT+

Microwave Digestion System: CEM Mars 6

Figure 1. U5000AT+ USN: 1-button operation

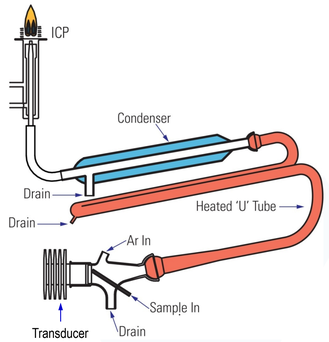

Figure 2. U5000AT+ USN schematic

Table 1. 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%

Sample Preparation - 1

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 below:

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

Sample Preparation – 2

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.

Calibration

The ICP-AES 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. 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 2. 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	0.045
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

Table 3. Operating Conditions: ICP-AES with Standard Nebulizer 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

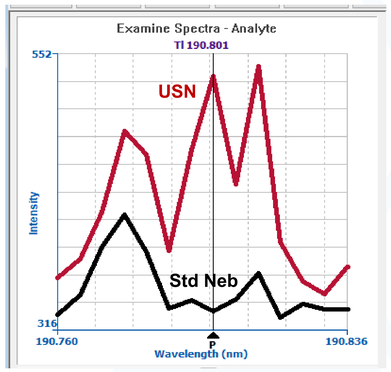

Figure 3. Tl (190.801 nm) spectra at 0.016 mg/L Tl

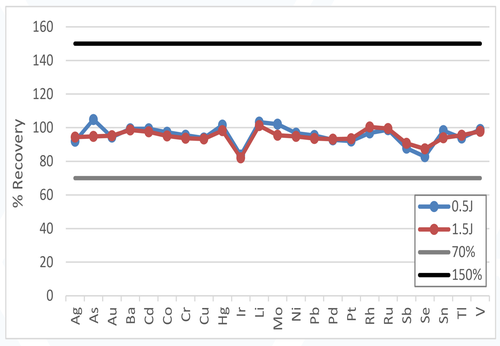

Figure 4. Accuracy: 0.5J and 1.5J spike recoveries in aspirin. Black and gray lines show USP <233> limits.

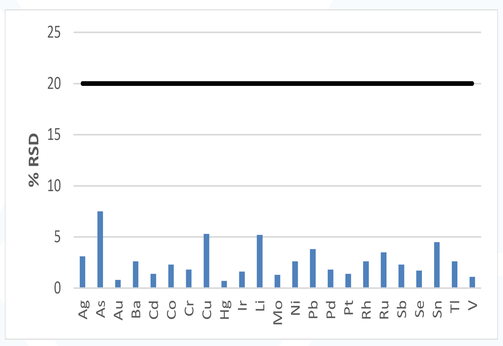

Figure 5. Repeatability: %RSDs of six independent samples spiked at 1J.

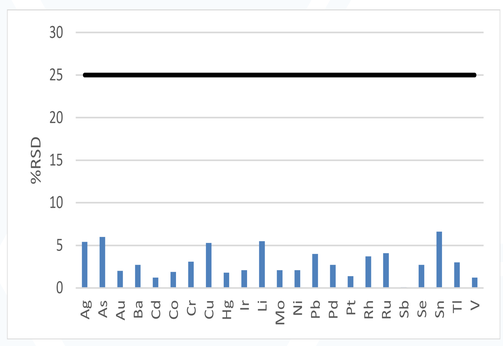

Figure 6. Ruggedness: %RSDs of six independent samples analyzed over two days (12 measurements).

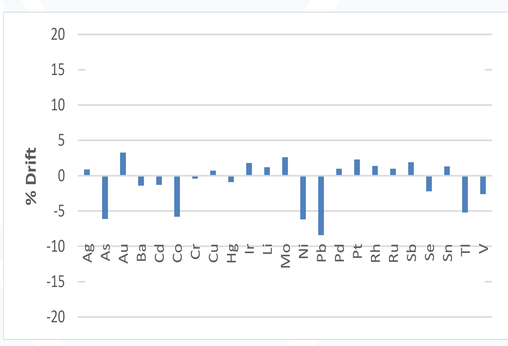

Figure 7. System Suitability: analysis of 1.5J at the beginning and end of analytical run.

Conclusions:

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-AES analysis of a higher daily dose drug product is possible.