Use of Ultrasonic Nebulization with ICP-AES for Enhanced Detection of Regulated Elements in Pharmaceuticals per USP <232>/<233>

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Abstract: On January 1, 2018 the U.S. Pharmacopeial Convention (USP) is enacting new regulations (USP <232>/<233>) for the measurement of inorganic Impurities in pharmaceutical products. One product type is low daily dose oral medications; examples include allergy, blood pressure, sleep-aid, and acid-reducer tablets.

The analytical parameter of interest is the "J" value, based on the pre-set PDE (permissible daily exposure in micrograms/gram), the daily dose, and the sample dilution factor after digestion. This poster will examine the use of ultrasonic nebulization with ICP-AES for the detection of 13 elements (except osmium), with emphasis on the lower PDE elements As, Cd, Hg, and Pb. Figures of merit will include calibration, USP <232> repeatability requirements, and spike recoveries.

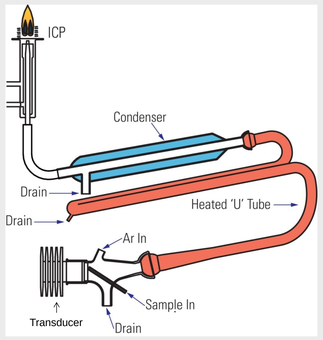
Instrumentation:

ICP-AES: PerkinElmer Optima 5300DV

Ultrasonic Nebulizer (USN): Teledyne CETAC U5000AT+

Digestion System: SCP Science DigiPREP Jr. Hot Block Digestion System

Teledyne CETAC U5000AT+ USN



USN Schematic

PerkinElmer 5300DV ICP-AES & USN

USN Close-Up View

Elemental Impurities - Limits

Element	Oral Daily Dose PDE (µg/day)*
Cd	5
Pb	5
Inorganic As	15
Inorganic Hg	30
Ir	100
Os	100
Pd	100
Pt	100
Rh	100
Ru	100
Cr	11,000
Mo	3000
Ni	200
V	100
Cu	3000

*Published in USP38-NF33, 2nd Supplement, official Dec. 1, 2015

Target or "J" Value

J = (PDE) / (Max. Daily Dose x Dilution Factor)

PDE = max. permissible daily exposure in µg/g

Max. Daily Dose = max. dose of the drug in grams

Dilution Factor = final volume of the prepared sample

Analyte recovery must be measurable at 0.5J. For this study the maximum daily dose is 0.10 gram and the dilution factor is 1000. Calibration standards made at 0.5J, and 2.0J; yttrium added as an internal standard.

Note that Hg calibration standards were prepared in glass volumetric flasks using 3% HCl; all other standards prepared in 125-mL LDPE bottles using 2% HNO_3 / 0.5% HCl.

Sample and Reagents

Sample Type:

Oral allergy relief tablet (antihistamine) with dose of 1 tablet daily (not more than 1 tablet in 24 hours). Mass of 1 allergy relief tablet is 0.10 grams.

Reagents:

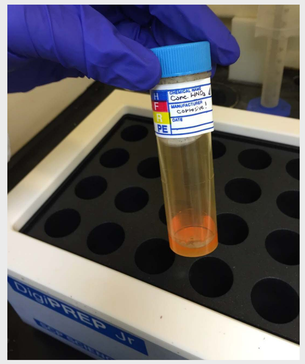
1. **Nitric acid, 68%, double distilled, GFS Chemicals, Columbus, OH USA**
2. **Hydrochloric acid, 30-35%, double distilled, GFS Chemicals, Columbus, OH USA**
3. **Various single element standards, Inorganic Ventures, Christiansburg, VA USA**
4. **L-Cysteine, ≥ 97%, SAFC, St. Louis, MO, USA**

Sample Preparation

Digestion Method:

1. **One 0.10 gram allergy relief tablet sample was added to individual pre-cleaned 50-mL polypropylene digestion tubes.**
2. **Four mL of conc. double-distilled HNO_3 and 1.0 mL of conc double-distilled HCl were added to each digestion tube. The tablet with added reagents was allowed to stand at room temperature for 10 minutes.**
3. **Analyte element spikes at 1.0J were then added to each digestion tube and the tubes placed in open slots of the hot block. A temperature program with heating at 80°C for 45 minutes was entered into the system controller and initiated.**
4. **Digested samples were allowed to cool to room temperature and diluted to 100 mL with deionized water in 125-mL LDPE bottles. 50 µg/L Y was added as an internal standard and 0.01% L-Cysteine added to improve Hg transport through the USN.**

Example Digest



Calculated "J" Values

Element	1J (µg/L)	0.5J (µg/L)
Cd	50	25
Pb	50	25
Inorganic As	150	75
Inorganic Hg	300	150
Ir	1000	500
Os	1000	500
Pd	1000	500
Pt	1000	500
Rh	1000	500
Ru	1000	500
Cr	110,000	55,000
Mo	30,000	15,000
Ni	2,000	1,000
V	1,000	500
Cu	30,000	15,000

ICP-AES & USN Operating Parameters

ICP-AES:

ICP Power:	1350 W
Plasma Gas:	15 L/min
Auxiliary Gas:	0.2 L/min
Nebulizer Gas:	0.55 L/min
Resolution:	Normal
Viewing:	Axial
Injector:	2 mm alumina
Torch Position:	-4
Points/peak:	3
Integration Time:	20 sec
Replicates:	3

USN:

Sample uptake rate:	2.0 mL/min
Heater temperature:	140°C
Condenser temperature:	3°C

Instrument Det. Limits & Limits of Quantitation

Element	Wavelength (nm)	IDL (µg/L)	LOQ (µg/L)
Cd	226.502	0.03	0.10
Pb	220.353	0.05	0.18
As	188.979	0.23	0.77
Hg	253.652	0.22	0.75
Ir	208.882	0.07	0.23
Pd	340.458	0.07	0.23
Pt	265.945	0.20	0.68
Rh	343.489	0.10	0.34
Ru	240.272	0.08	0.27
Mo	203.845	0.20	0.67
Ni	221.648	0.04	0.14
V	290.880	0.02	0.08
Cu	222.778	0.19	0.64

Repeatability Measurements

Element	Mean of 6 tablets spiked at 1.0J (µg/L)	% RSD
Cd	58.8	1.2
Pb	52.9	1.3
As	179.7	1.3
Hg (see notes)	279.8	1.4
Ir	1209	0.9
Pd	941.5	0.9
Pt	1072	0.9
Rh	900.7	0.9
Ru	1302	0.9
Mo	39210	0.8
Ni	2324	1.2
V	1182	0.9
Cu	31290	1.0

Summary & Notes

- **LOQs for Cd, Pb, As, and Hg are all less than 1 µg/L with the USN and ICP-AES.**
- **One tablet sample digested as above but diluted to 100-mL in a glass volumetric flask (with added L-Cysteine) and measured 6 times for Hg at 1.0J – this experimental change to a glass container improved Hg recovery.**
- **Repeatability measurements of the other 12 elements using 6 separate tablet samples exhibit %RSDs in a range from 0.8% to 1.3%, well below the 20% USP criteria.**