Validating ICP-MS Using USP<232>/<233> for Elemental Impurity Analysis in Pharmaceutical Products

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Introduction

The United States Pharmacopeia (USP) is developing new General Chapters relating to the determination of elemental impurities in pharmaceutical products and ingredients. USP<232> defines the Permitted Daily Exposure (PDE) limits for the regulated inorganic (elemental) impurities: As, Cd, Hg, Pb, V, Cr, Ni, Mo, Mn, Cu, Pt, Pd, Ru, Rh, Os and Ir. USP<233> defines the sample preparation options and validation protocols that must be followed to demonstrate accuracy, repeatability, and the "unequivocal" identification of analytes. USP<233> recommends the use of modern instrumentation, such as multi-element ICP-MS and ICP-OES techniques.

This paper illustrates the successful validation of the Agilent 7700x ICP-MS for the measurement of elemental impurities in pharmaceutical samples following closed vessel microwave digestion, according to USP<232>/<233>.

The regulated elements and PDEs, together with the measurement mode, integration times and 7700x method detection limits (MDLs) are shown in Table 1, below.

Mass	Element	Cell Mode	Internal Standard	Integration Time (sec)	Daily Dose PDE (ug/day)	Component Limits (ug/g)	1J Actual Values (ng/mL)	MDL * (ng/mL)
51	V	He	Sc	0.5	250	25	100	0.162
52	Cr	He	Sc	0.5	250	25	100	0.176
53	Cr	He	Sc	0.1	250	25	100	0.261
55	Mn	He	Sc	0.5	2500	250	1000	1.694
60	Ni	He	Sc	0.5	250	25	100	0.359
62	Ni	He	Sc	0.5	250	25	100	0.339
63	Cu	He	Sc	0.5	2500	250	1000	1.333
65	Cu	He	Sc	0.5	2500	250	1000	1.114
75	As	He	Sc	1	15	1.5	6	0.015
95	Mo	He	Tb	0.5	250	25	100	0.180
97	Mo	He	Tb	0.5	250	25	100	0.183
101	Ru	He	Tb	0.5	100	10	40	0.063
103	Rh	He	Tb	0.5	100	10	40	0.070
105	Pd	He	Tb	0.5	100	10	40	0.063
111	Cd	He	Tb	0.75	5	0.5	2	0.005
114	Cd	He	Tb	0.75	5	0.5	2	0.004
188	Os	He	Bi	0.5	100	10	40	0.274
189	Os	He	Bi	0.5	100	10	40	0.270
191	Ir	He	Bi	0.5	100	10	40	0.065
193	Ir	He	Bi	0.5	100	10	40	0.062
194	Pt	He	Bi	0.5	100	10	40	0.064
195	Pt	He	Bi	0.5	100	10	40	0.066
200	Hg	He	Bi	2	15	1.5	6	0.059
201	Hg	He	Bi	2	15	1.5	6	0.060
202	Hg	He	Bi	2	15	1.5	6	0.061
206	Pb	He	Bi	0.5	10	1	4	0.013
207	Pb	He	Bi	0.5	10	1	4	0.014
208	Pb	He	Bi	0.5	10	1	4	0.011

Experimental

Sample Preparation and Analysis

The sample digestion method and the operating conditions for the 7700x are shown in Table 2, below. It should be noted that simple method development is a key requirement in many pharmaceutical laboratories, where a range of different sample types must be measured routinely. The 7700x was operated in the standard helium (He) mode for all analytes, ensuring the effective removal of all common polyatomic interferences, Confirmation of analyte identification and interference removal was performed using secondary or qualifier isotopes for most elements.

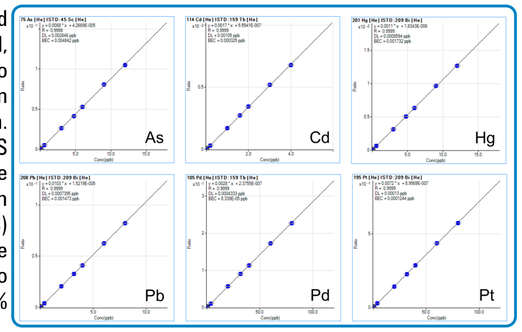
Digestion Conditions	
Microwave Oven Make and Model	Milestone Ethos
Rotor type	High pressure, quartz inserts
Rotor capacity	10 vials of ~20mL sample vol.
Digestion	
Sample weight	0.2g
HNO_3	1mL
HCl	0.25mL
H_2O_2	0.5mL
De-Ionized Water	3.5mL
Oven Program	
Pre-digestion (room temperature)	15 minutes
Ramp (to 1200W, 150ºC)	15 minutes
Hold (at 1200W, 150ºC)	10 minutes
Cool down	15 minutes
Final Dilution	
De-Ionized Water	To 50mL
Total dilution factor	250x

ICP-MS Operating Conditions	
Instrument	Agilent 7700x
Plasma mode	Normal, robust
RF forward power (W)	1550
Sampling depth (mm)	8
Carrier gas flow (L/min)	0.95
Dilution gas flow (L/min)	0.15
Spray chamber temperature (ºC)	2
Extraction lens 1 (V)	0
Kinetic energy discrimination (V)	4
He Cell gas flow (mL/min)	4

Results and Discussion

The list of analytes regulated under the new draft methods includes several elements that are not chemically stable at low concentrations in the HNO_3–based sample preparation that has traditionally been recommended for ICP-MS analysis.

Alternative acids (HCl and H_2SO_4) have been avoided, due to their contribution to background interferences in the ICP-MS spectrum. However, modern ICP-MS instruments such as the 7700x are equipped with collision/reaction cell (CRC) technology that can reduce such interferences to negligible levels, so 0.5% HCl is now used routinely.



The calibrations in Figure 1 (above) show As, Cd, Hg, Pb, Pd and Pt in He mode, demonstrating limits of detection of 1ng/L or below, and good sensitivity and linearity for elements (Hg, Pd and Pt) that require stabilization in HCl.

USP<233> defines a "system suitability check" that requires the selected analytical method to demonstrate drift of not more than 20% for a 2J standard measured before and after the batch of samples. Table 3, right, illustrates that the 7700x stability was significantly better than the required performance, at around 2 or 3% drift for most analytes.

Mass	Element	2J Actual Values	Measured Mean (n=6)	% RSD	Drift (%)	Limit
51	V	200	202.3	0.6	-0.3	20%
52	Cr	200	202.0	0.6	-0.5	20%
53	Cr	200	202.9	0.9	-0.5	20%
55	Mn	2000	2025.8	1.2	2.6	20%
60	Ni	200	202.3	0.7	-0.9	20%
62	Ni	200	201.9	0.8	-1.5	20%
63	Cu	2000	2105.4	2.8	7.0	20%
65	Cu	2000	2112.4	3.1	7.5	20%
75	As	12	12.2	0.8	-1.7	20%
95	Mo	200	202.2	0.5	-0.5	20%
97	Mo	200	202.2	0.6	-0.5	20%
101	Ru	80	80.6	0.9	2.1	20%
103	Rh	80	80.3	0.9	2.1	20%
105	Pd	80	80.3	0.8	1.5	20%
111	Cd	4	3.9	0.8	-0.1	20%
114	Cd	4	4.0	0.6	0.0	20%
188	Os	80	78.3	1.3	-2.9	20%
189	Os	80	78.4	1.2	-2.6	20%
191	Ir	80	81.6	1.5	3.6	20%
193	Ir	80	81.7	1.4	3.2	20%
194	Pt	80	82.0	1.6	3.7	20%
195	Pt	80	82.1	1.6	4.0	20%
200	Hg	12	12.2	1.3	3.1	20%
201	Hg	12	12.2	1.6	3.6	20%
202	Hg	12	12.2	1.5	3.2	20%
206	Pb	8	8.0	0.6	0.9	20%
207	Pb	8	8.0	0.6	1.1	20%
208	Pb	8	8.0	0.6	1.2	20%

Accurate spike recovery must be demonstrated at several spike levels and Table 4 (below) illustrates both the accurate spike recovery (easily within the 70% to 150% limit) and good precision (well within 20%RSD) obtained on the 7700x.

		Samples at 0.5J (n=6)		Recovery		Samples at 1.5J (n=6)		Recovery	
Mass	Element	Actual (ppb)	Mean (ppb)	(%)	%RSD	Actual (ppb)	Mean (ppb)	(%)	%RSD
51	V	50	52.84	106	1.6	150	157.4	105	1.6
52	Cr	50	52.63	105	2.3	150	155.9	104	1.4
53	Cr	50	52.74	106	2.2	150	157.2	105	1.6
55	Mn	500	524.0	105	1.7	1500	1696	113	1.1
60	Ni	50	52.96	106	1.9	150	155.9	104	1.5
62	Ni	50	52.72	105	1.9	150	156.1	104	1.5
63	Cu	500	523.9	105	1.7	1500	1733	116	1.4
65	Cu	500	524.0	105	1.2	1500	1727	115	1.4
75	As	3	3.21	107	3.9	9	9.53	106	3.2
95	Mo	50	52.61	105	1.8	150	157.5	105	1.5
97	Mo	50	52.65	105	1.6	150	157.1	105	1.4
101	Ru	20	20.75	104	2.0	60	62.64	104	1.2
103	Rh	20	20.91	105	2.0	60	62.57	104	1.2
105	Pd	20	20.77	104	2.2	60	62.19	104	1.2
111	Cd	1	1.03	103	2.7	3	3.04	101	1.2
114	Cd	1	1.04	104	2.5	3	3.08	103	1.3
188	Os	20	17.15	86	1.8	60	52.51	88	1.3
189	Os	20	17.17	86	1.6	60	52.63	88	1.2
191	Ir	20	20.56	103	1.6	60	63.33	106	1.2
193	Ir	20	20.63	103	1.9	60	63.42	106	1.1
194	Pt	20	20.63	103	1.8	60	63.77	106	1.2
195	Pt	20	20.64	103	1.6	60	63.87	107	1.1
200	Hg	3	3.09	103	2.0	9	9.51	106	1.3
201	Hg	3	3.09	103	2.3	9	9.47	105	1.0
202	Hg	3	3.08	103	1.9	9	9.47	105	1.3
206	Pb	2	2.08	104	1.9	6	6.21	104	1.5
207	Pb	2	2.08	104	1.9	6	6.22	104	1.4
208	Pb	2	2.08	103	2.1	6	6.20	103	1.1

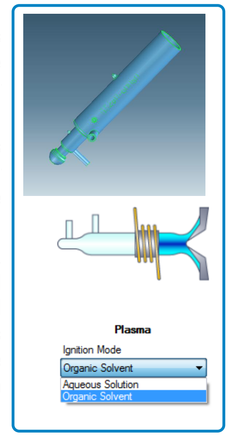
Analysis of Organic Solvents

New Torch Design, Firmware and Software

Many APIs are soluble only in organic solvents such as DMSO, DGME, or 2-butoxyethanol in water,. Routine analysis of organic solvents is therefore a requirement for many pharmaceutical laboratories.

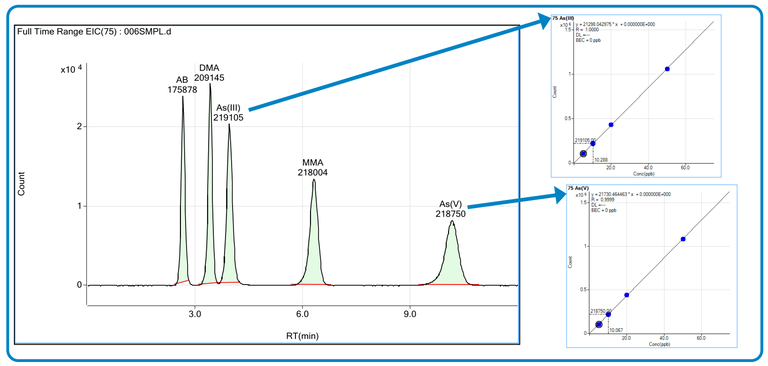
A new organics torch with a 1.5mm internal diameter has recently been developed for the 7700, providing higher sensitivity than the 1mm torch previously used, while maintaining plasma tolerance to volatile solvents.

In addition to the new torch design illustrated in Figure 2, right, a new revision of MassHunter software and modified firmware in the 7700 provides optimized flow rates and timings for the carrier, make-up and option gas parameters during the ignition sequence. This greatly increases the tolerance of the plasma to solvents and allows the plasma to be ignited reliably with very volatile organic solvents.



LC-ICP-MS for Pharmaceutical Analysis

USP<232> contains a section relating to the elemental form (species) of elements, and notes that As and Hg are of particular concern as some forms are much more toxic than others. The PDE for As is based on inorganic As and, if the total As concentration exceeds the limit, the sample must be reanalyzed using a procedure that allows the different As species to be separated and quantified. This is required because inorganic As is much more toxic than the common organic forms, such as arsenobetaine, so speciation is necessary to separate the different chemical forms and confirm that the level of inorganic As – the sum of arsenite (As(III)) and arsenate (As(V)) – is below the limit. The 7700 is easily coupled with HPLC allowing routine separation of the species required in USP<232>, as illustrated in Figure 3 below.



The chromatogram and calibration plots for As(III) and As(V) by LC-ICP-MS with the Agilent 1260 LC and Agilent 7700x ICP-MS illustrate the fast (less than 12 minutes) and complete separation of both As(III) and As(V) from the organic As species.

Conclusions

The 7700x has been demonstrated to be suitable for routine analysis according to the proposed new USP General Chapters <232> and <233> for Elemental Impurities in Pharmaceutical samples. The 7700x provides accurate, stable, and precise measurement of all the elements regulated in the proposed new methods, including those that require HCl for chemical stability. Simple method development and He mode operation is combined with unequivocal identification of analytes through the use of secondary isotopes, and the 7700x is also suitable for organic solvent analysis, full-mass screening, and speciation using LC- (or GC-) coupled to the ICP-MS.