Analysis of Metal Impurities in Pharmaceutical Ingredients in Preparation for the New USP Methods

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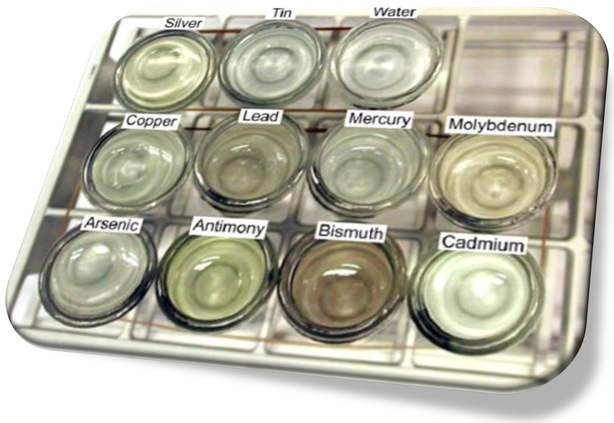
Abstract

A 100 year old method is currently in use by the pharmaceutical industry to determine metal impurities in pharmaceutical products (API and Excipients). With today's available technology it is absolutely absurd that we relay on an archaic method to safeguard us from highly toxic inorganic metals. USP<231> requires the use of a sulfide containing reagent, such as thioacetamide, in a simple precipitation reaction, yielding a colored precipitate. This in turn is colorimetrically compared to 10 PPM Pb standard.



Beside the obvious biases associated with this visually subjective test, the use of thioacetamide and H_2S are not allowed in many parts of the world. Moreover, as the method requires ignition of the sample in a furnace, using temperature of about 800°C, loss of analytes due to volatility is inevitable. This excessive loss of toxic inorganic analytes ultimately necessitated the requirement for a new reliable method.

A total of three **proposed** methods have been suggested, USP <232>/<233> and USP <2232>. While USP <232>/<233> directly deal with inorganic impurities in pharmaceutical ingredient and their analysis via ICP-MS/OES, USP <2232> is solely appropriated for dietary supplements. The new methods set suitable conditions to assure that the analysis is "specific, accurate, and precise." In this study, we tested a variety of pharmaceutical ingredients according to the newly proposed (Oct. 2010) USP <232>/<233>, using the Agilent 7700 and 7500 ICP-MS. The data presented clearly demonstrates that the use of the 7700/7500 ICP-MS with helium mode and KED results in specific, accurate and precise analysis of pharmaceutical samples.

Experimental

The Agilent 7700x ICP-MS was used for analyzing the possible presence of toxic inorganic constituents (16 analytes, catalysts included). The 7700 utilizes Agilent's 3rd generation octopole reaction system (ORS^3)

The ORS^3 is mainly employed in removal of polyatomic interferences via a process known as kinetic energy discrimination (KED).

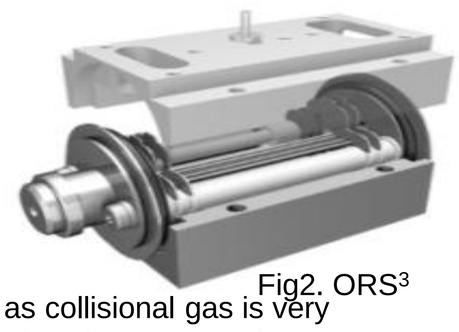


Fig2. ORS^3

KED with the use of He as collisional gas is very much similar to a physical exclusion of the larger polyatomic molecules, a process that is illustrated below.

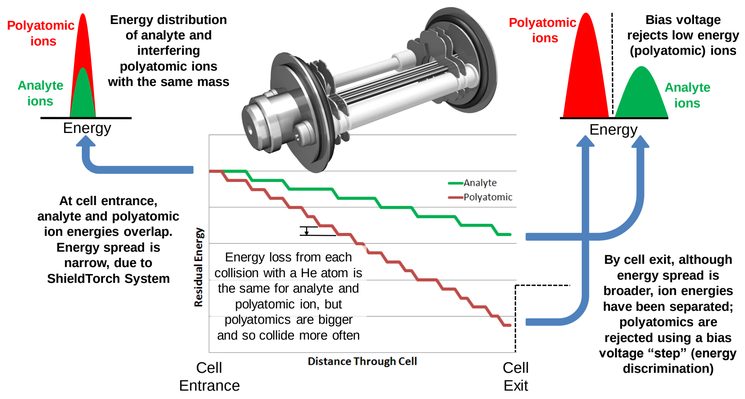


Fig. 3 Illustration of KED

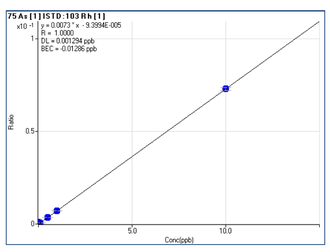
Although KED is the standard mode of operation, the use of a reactive gas such as H_2 is also possible, allowing detection limits for a handful of analytes, such as Se and Fe, to reach down to the ppq levels.

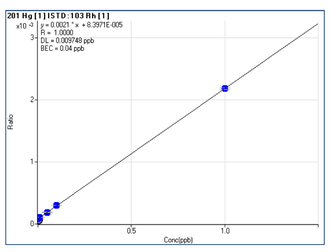
The Agilent 7700 ICP-MS is also equipped with the High Matrix Interface, HMI, which enables analysis of samples with high total dissolved solids (TDS), as is the case in analyzing pharmaceutical ingredients (Fig. 4). The ability to run high TDS samples requires the use of a robust plasma. The plasma robustness is measured as a function of oxide formation. The hotter the plasma the lower the oxides (CeO/Ce), more energy is available to a) break down the matrix and b) efficiently ionize the analytes. Through the use of aerosol dilution (HMI) in this analysis the oxide levels were about 0.5%, enabling the analysis of these pharmaceutical ingredients. For high %TDS samples, the HMI may be operated in the ultra-robust mode yielding oxide levels between 0.1-0.2%

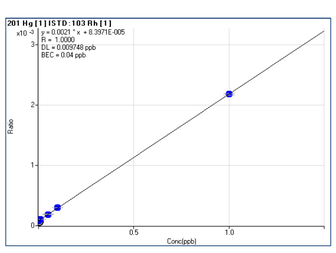
Fig. 4 HMI

Results and Discussion

Calibration curves were prepared in 1% HNO_3 and 0.5% HCl. The analysis utilized both no gas and helium modes. Helium mode was used for those analytes which require the removal of polyatomic interferences. Although no gas mode is used for those analytes that harbor no polyatomic interferences, the helium mode may be used uniformly for all the 16 analytes in USP <232> an example of which is shown for the "Big 4" analytes.







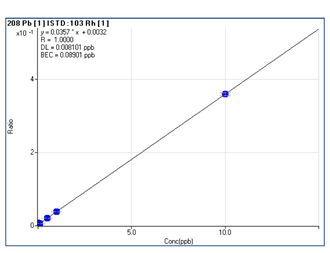


Table 2. Elemental Impurities for Drug Products

Element	Daily Dose PDE[a] (µg/day)	LVP Component Limit (µg/g)
Inorganic Arsenic[b]	15	0.15
Cadmium	5	0.05
Lead	10	0.1
Inorganic Mercury	15	0.15
Chromium	250	2.5
Copper	2500	25
Manganese	2500	25
Molybdenum	250	2.5
Nickel	250	2.5
Palladium	100	1.0
Platinum	100	1.0
Vanadium	250	2.5
Osmium	100 (Combination not to exceed)	1.0 (Combination not to exceed)
Rhodium		
Ruthenium		
Iridium		

[a] PDE = permitted daily exposure based on a 50 Kg person
[b] See *Speciation section*

	Exposure Factor
Oral (solids and liquids)	1
Parenteral (Injectables and implants)	0.1
Topicals and Dermal	1
Mucosal (ophthalmics, nasal, otic, rectal, vaginal, urethral, others)	1
Inhalational (aerosols, inhalers, and gases)	0.1

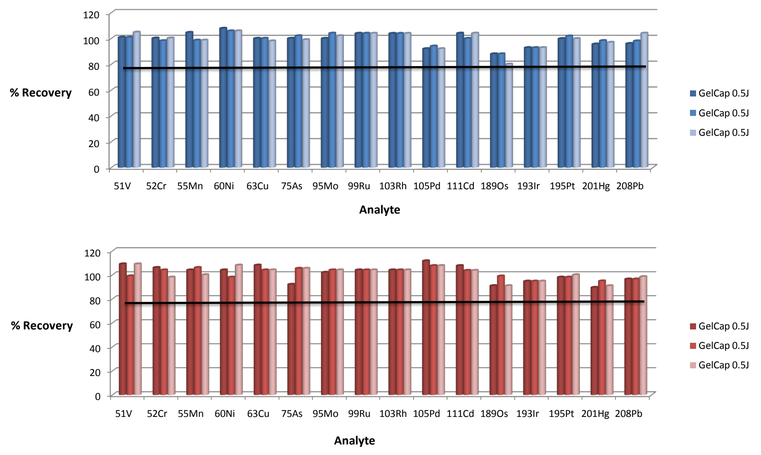
USP <232> dictates the permitted daily exposure for each analyte in the suite of elements which varies depending on the mode of exposure.

Spiked Levels in Gelatin Capsules

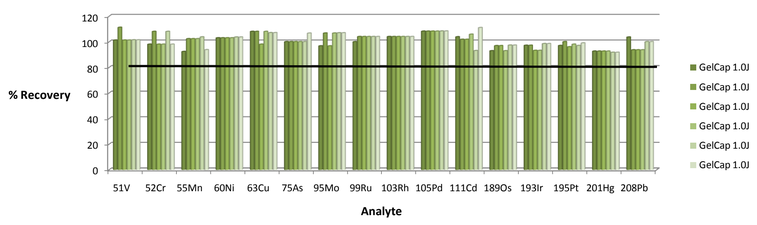
In-sample spike levels				
	levels	0.5J	J	1.5J
PPM	As, Hg	0.75	1.5	2.25
	Cd	0.25	0.5	0.75
	Pb	0.5	1	1.5
	Cr-V	5	10	15
	Os-Ir	1.25	2.5	3.75
250X Dilution				
	levels	0.5J	J	1.5J
	As, Hg	3	6	9
PPB	Cd	1	2	3
	Pb	2	4	6
	Cr-V	20	40	60
	Os-Ir	5	10	15

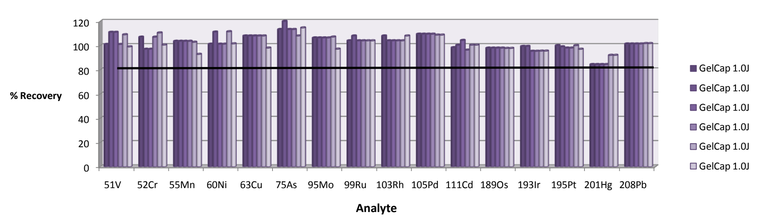
	Units	Component Limit	Gel Caps
75 As [He]	µg/g	1.5	0.91
111 Cd [NG]	µg/g	0.5	0.011
208 Pb [NG]	µg/g	1	0.088
201 Hg [NG]	µg/g	1.5	0.039
52 Cr [He]	µg/g	25	0.13
63 Cu [He]	µg/g	250	0.43
55 Mn [He]	µg/g	250	0.08
95 Mo [NG]	µg/g	25	0.03
60 Ni [He]	µg/g	25	0.16
105 Pd [NG]	µg/g	10	0.012
195 Pt [He]	µg/g	10	0.000061
51 V [He]	µg/g	25	0.095
189 Os [NG]	µg/g	10	0.064
103 Rh [He]	µg/g		0.000067
99 Ru [NG]	µg/g		0
193 Ir [NG]	µg/g		0.017

Gelatin Capsules 0.5 J Spike Recovery

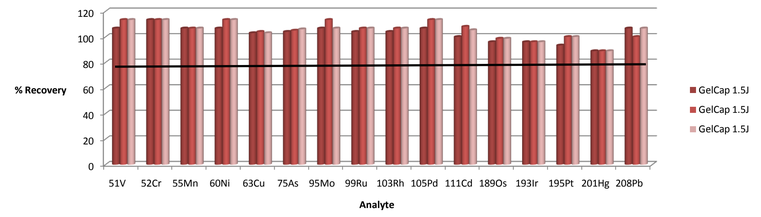


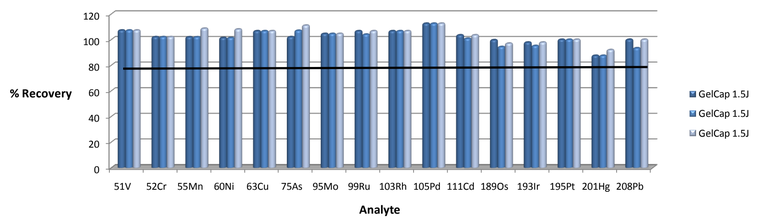
Gelatin Capsules 1.0 J Spike Recovery





Gelatin capsules 1.5 J Spike Recovery





Amoxicillin (API)

	Average (n=3) µg/g	µg/day	Limit µg/day	Pass/Fail
Arsenic	0.075	0.075	15	Pass
Mercury	0.009	0.009	15	Pass
Lead	0.031	0.031	10	Pass
Cadmium	0.002	0.002	5	Pass
In-sample	Avg (n=3) µg/g	µg/day	Limit (µg/day)	Pass/Fail
Chromium	0.194	0.194	250	Pass
Copper	0.032	0.032	2500	Pass
Manganese	0.014	0.014	2500	Pass
Molybdenum	0.013	0.013	250	Pass
Nickel	0.059	0.059	250	Pass
Palladium	0.002	0.002	100	Pass
Platinum	0.009	0.009	100	Pass
Vanadium	0.019	0.019	250	Pass
Rhodium	0.019	0.019	Total NMT 100	Pass
Ruthenium	0.001	0.001		Pass
Iridium	0.005	0.005		Pass
Osmium	0.007	0.007		Pass

Serving size/day-1g

Amoxicillin Spike Recoveries

	Arsenic	Mercury	Lead	Cadmium	Chromium	Copper	Manganese	Molybdenum
Specification (J) (µg/g)	1.5	1.5	1	0.5	25 "J" = 10	250 "J" = 10	250 "J" = 10	25 "J" = 10
Avg. %Rec 0.5J (n=3)	81 RSD = 0.86	102 RSD = 2.8	105 RSD = 0.57	98 RSD = 0.82	97 RSD = 0.52	100 RSD = 0.20	103 RSD = 0.29	96 RSD = 0.21
Avg. %Rec 1J (n=6)	86 RSD = 2.4	102 RSD = 0.83	105 RSD = 0.27	99 RSD = 1.7	98 RSD = 0.31	102 RSD = 0.40	103 RSD = 0.31	96 RSD = 0.30
Avg. %Rec 1.5J (n=3)	87 RSD = 0.82	103 RSD = 0.90	106 RSD = 0.33	101 RSD = 0.27	100 RSD = 0.58	111 RSD = 0.64	104 RSD = 0.68	96 RSD = 0.90
	Nickel	**Palladium**	**Platinum**	**Vanadium**	**Rhodium**	**Ruthenium**	**Iridium**	**Osmium**
Specification (J) (µg/g)	25 "J" = 10	10	10	25 "J" = 10	"J" = 2.5	"J" = 2.5	"J" = 2.5	"J" = 2.5
Avg. %Rec 0.5J (n=3)	99 RSD = 0.40	99 RSD = 0.20	100 RSD = 1.4	93 RSD = 0.43	96 RSD = 0.63	98 RSD = 0.41	98 RSD = 0.31	94 RSD = 0.64
Avg. %Rec 1J (n=6)	100 RSD = 0.42	99 RSD = 0.15	101 RSD = 0.30	95 RSD = 0.56	96 RSD = 0.62	98 RSD = 0.49	105 RSD = 0.20	94 RSD = 0.46
Avg. %Rec 1.5J (n=3)	102 RSD = 0.51	105 RSD = 0.19	102 RSD = 0.32	95 RSD = 0.54	102 RSD = 0.22	98 RSD = 0.38	106 RSD = 0.47	95 RSD = 0.30

Conclusion

There are many changes to the newly revised USP method. Most importantly is the definition of "J", the spike limit, which is defined as the in-sample limit. Furthermore, speciation of As and Hg is now required should the level exceed the PDE. We clearly demonstrated that using the Agilent 7700 ICP-MS easily enables the analysis of inorganic impurities in pharmaceutical ingredients. Moreover, as the leader in speciation analysis, we can easily "hyphenate" any chromatographic instrument to achieve the required speciation.