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A multi-element ICP-MS survey method as an alternative to the heavy metals limit test for pharmaceutical materials

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Abstract

A multi-element inductively coupled plasma-mass spectrometry (ICP-MS) survey method has been demonstrated as an alternative to the antiquated 'heavy metals limit test' prescribed by United States Pharmacopoeia (USP), European Pharmacopoeia (EP), and British Pharmacopoeia (BP), for drug substances, intermediates, and raw materials. The survey method is simple, fast, sensitive, semi-quantitative to quantitative, and includes all the elements which can be analyzed by atomic spectroscopy.

Keywords: Inductively coupled plasma-mass spectrometry; United States Pharmacopoeia; Heavy metals limit test; Drug substances

1. Introduction

Metal contamination of bulk drug substances and their intermediates may be introduced in many ways, such as from raw materials, reagents, solvents; from electrodes, reaction vessels, plumbing and other equipments used in the synthesis; exposure to the air-borne particles; or from container/closure systems, etc. Most importantly, metals may be introduced through the utilization of catalysts at various steps during the synthesis. Due to the ability of metals to catalyze decomposition and their potential for toxicity, metal content monitoring of process intermediates and final drug substances is widely employed.

The United States Pharmacopoeia (USP) heavy metals test ⟨231⟩, and similar tests provided in the European Pharmacopoeia (EP) and British Pharmacopoeia (BP) [1–3], consist of the precipitation of metal sulfides from an aqueous solution and the visual comparison of the color of that preparation to that of a simultaneously and similarly treated standard lead solution. In order to obtain an aqueous solution for testing, ignition and charring of the samples in a muffle furnace is often required as a preliminary step. In addition, after adjusting the pH, and adding either freshly prepared hydrogen sulfide or thioacetamide-glycerin base TS, the colors of the different metal

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sulfides range from white to yellow, orange, brown and black [4], making the visual comparison with the dark brown colored lead sulfide difficult. Furthermore, apart from the colors of the formed sulfides, there is no information about the identities of the ions which caused the positive result.

Although still widely accepted and used in the pharmaceutical industry, these methods based on the intensity of the color of sulfide precipitation are non-specific, insensitive, time-consuming, labor intensive, and more often than hoped, yield low recoveries or no recoveries at all.

Attempts have been made to modify those Pharmacopeia methods to alleviate some of the limitations and shortcomings [5,6], but no major improvements have been achieved and they are still cumbersome, tedious, and time-consuming. In addition, these methods are suitable only for a few elements and have not been shown to be equally sensitive to all. The USP states that Pb, Hg, Bi, As, Sb, Sn, Cd, Ag, Cu, and Mo will typically respond to this test.

Since 1980, ICP-MS has emerged as a major and powerful technique in the area of elemental analysis [7], an area traditionally dominated by optical atomic spectrometry methods. In approximately 10 years, ICP-MS has progressed from a laboratory experiment to commercial development and widespread analytical applications [8–15]. This growth is primarily due to the fact that ICP-MS offers extremely low detection limits which range from sub part per billion (ppb) to sub part per trillion (ppt) for most elements. In most of the cases, these detection limits are 100 to 1000 times superior to those that can be routinely achieved by inductively coupled plasma-atomic emission spectrometry (ICP-AES). In addition, these detection limits are broadly achieved for almost all the elements across the periodic table. Also, the simple nature of the mass spectra of the elements makes this technique a quick tool for automated qualitative, semi-quantitative, and quantitative elemental analysis.

Table 1
Elan 6000 instrumental conditions and method parameters

RF power (W)	1300
Coolant argon flow (l/min)	15.0
Auxiliary argon flow (l/min)	1
Nebulizer argon flow (l/min)	0.86–1.06
Sample introduction system	Cross flow nebulizer with Scott spray chamber
Operating frequency (MHz)	40
Sample uptake rate (ml/min)	1.5
Detector mode	Dual mode
Sampler/skimmer cones	Platinum
Scanning mode	Peak hopping
Number of points per peak	1
Dwell time (ms)	15
Sweeps per reading	40
Number of replicate	2

In view of the superior and broad detection capability of the ICP-MS and its common availability, and also because of the limitations inherent in the 'heavy metals test' prescribed by USP, EP, and BP, a multi-element survey type ICP-MS method has been developed. This method covers not just a few limited sulfide-forming elements as do the various Pharmacopoeial tests, but almost all elements including even Hg, with the exceptions of H, C, N, O, S, Cl, F and the inert elements. All samples are directly dissolved in either 1 or 80% nitric acid solutions without any further treatment. Unlike semi-quantitative methods provided by some instrument vendors which use a 'response table' obtained by calibrating the instrument with a few limited elements, this method calibrates the instrument with a 69-element working standard. Calibration verification has been performed both in 1 and 80% (v/v) nitric acid solution matrices by analyzing NIST 1643d (trace elements in water). Studies of the precision and accuracy of the method, the limits of detection (LOD) and limits of quantitation (LOQ), as well as the results of some actual sample analysis are presented in this paper.

2. Experimental

2.1. Reagents and materials

Concentrated nitric acid (70%, trace metal

Table 2
Calibration verification with NIST 1643d in 1 and 80% HNO_3 matrices

Element	Isotope	Measured concentration in 1% HNO_3 (ppm)	Measured concentration in 80% HNO_3 (ppm)	Certified or reference (*) value by NIST (ppm)
Li	7	0.0166	0.0168	0.01815 ± 0.00064
Be	9	0.0127	0.0115	0.01253 ± 0.00028
B	11	0.118	0.127	0.1448 ± 0.0052
Na	23	20.6	21.9	22.07 ± 0.64
Mg	24	7.80	8.50	7.989 ± 0.035
Al	27	0.126	0.115	0.1276 ± 0.0035
Si	28	2.89	3.28	2.7*
P	31	<LOQ	<LOQ	No certified or reference value
K	39	2.30	2.37	2.356 ± 0.035
Ca	44	31.4	33.7	31.04 ± 0.64
Sc	45	<LOQ	<LOQ	No certified or reference value
Ti	48	<LOQ	<LOQ	No certified or reference value
Ti	49	<LOQ	<LOQ	No certified or reference value
V	51	0.0343	0.0361	0.0351 ± 0.0014
Cr	52	0.0178	0.0185	0.01853 ± 0.00020
Cr	53	0.0180	0.0194	0.01853 ± 0.00020
Mn	55	0.0378	0.0389	0.03766 ± 0.00083
Fe	54	0.177	0.9383	0.0912 ± 0.0039
Fe	57	0.130	0.1596	0.0912 ± 0.0039
Co	59	0.0241	0.0255	0.02500 ± 0.00059
Ni	58	0.0550	0.0596	0.0581 ± 0.0027
Ni	60	0.0544	0.0612	0.0581 ± 0.0027
Cu	63	0.0201	0.0205	0.0205 ± 0.0038
Cu	65	0.0198	0.0217	0.0205 ± 0.0038
Zn	64	0.0746	0.0850	0.07248 ± 0.00065
Zn	66	0.0760	0.0782	0.07248 ± 0.00065
Ga	69	<LOQ	<LOQ	No certified or reference value
Ge	72	<LOQ	<LOQ	No certified or reference value
As	75	0.0520	0.0530	0.05602 ± 0.00073
Se	77	0.0102	0.0107	0.01143 ± 0.00017
Se	82	0.0118	0.00944	0.01143 ± 0.00017
Rb	85	0.0120	0.0125	0.013*
Sr	88	0.317	0.349	0.2948 ± 0.0034
Y	89	<LOQ	<LOQ	No certified or reference value
Zr	90	<LOQ	<LOQ	No certified or reference value
Nb	93	<LOQ	<LOQ	No certified or reference value
Mo	95	0.110	0.117	0.1129 ± 0.0017
Ru	101	<LOQ	<LOQ	No certified or reference value
Rh	103	<LOQ	<LOQ	No certified or reference value
Pd	105	<LOQ	<LOQ	No certified or reference value
Ag	107	0.00126	0.00135	0.001270 ± 0.000057
Cd	111	0.00616	0.00664	0.00647 ± 0.00037
In	115	<LOQ	<LOQ	No certified or reference value
Sn	118	0.00329	0.00380	No certified or reference value
Sn	120	0.00329	0.00374	No certified or reference value
Sb	121	0.0522	0.0524	0.0541 ± 0.0011
Te	125	0.00098	0.000991	0.001*
Cs	133	0.00470	0.00432	No certified or reference value
Ba	137	0.481	0.507	0.5065 ± 0.0089
La	139	<LOQ	<LOQ	No certified or reference value
Ce	140	<LOQ	<LOQ	No certified or reference value
Pr	141	<LOQ	<LOQ	No certified or reference value

Table 2 (*Continued*)

Element	Isotope	Measured concentration in 1% HNO_3 (ppm)	Measured concentration in 80% HNO_3 (ppm)	Certified or reference (*) value by NIST (ppm)
Nd	146	<LOQ	<LOQ	No certified or reference value
Sm	147	<LOQ	<LOQ	No certified or reference value
Eu	153	<LOQ	<LOQ	No certified or reference value
Gd	157	<LOQ	<LOQ	No certified or reference value
Tb	159	<LOQ	<LOQ	No certified or reference value
Dy	163	<LOQ	<LOQ	No certified or reference value
Ho	165	<LOQ	<LOQ	No certified or reference value
Er	166	<LOQ	<LOQ	No certified or reference value
Tm	169	<LOQ	<LOQ	No certified or reference value
Yb	172	<LOQ	<LOQ	No certified or reference value
Lu	175	<LOQ	<LOQ	No certified or reference value
Hf	178	<LOQ	<LOQ	No certified or reference value
Ta	181	<LOQ	<LOQ	No certified or reference value
W	182	<LOQ	<LOQ	No certified or reference value
Re	185	<LOQ	<LOQ	No certified or reference value
Os	189	<LOQ	<LOQ	No certified or reference value
Ir	193	<LOQ	<LOQ	No certified or reference value
Pt	195	<LOQ	<LOQ	No certified or reference value
Au	197	<LOQ	<LOQ	No certified or reference value
Hg	202	<LOQ	<LOQ	No certified or reference value
Tl	205	0.00797	0.00791	0.00728 ± 0.00025
Pb	208	0.0193	0.0190	0.01815 ± 0.00064
Bi	209	0.0140	0.0140	0.013*
Th	232	<LOQ	<LOQ	No certified or reference value
U	238	<LOQ	<LOQ	No certified or reference value

grade) was purchased from Seastar (Sidney, B.C., Canada). Four NIST traceable mixed-element stock standard solutions containing 68 elements and the 1000 μg/ml Hg stock standard solution were purchased from High-Purity Standards (Charleston, SC). Deionized water was prepared by passing distilled water through a Milli-Q water system (Millipore, Bedford, MA). All the drug substances and their intermediates used in this study were obtained from Merck Research Laboratories (Merck, Rahway, NJ).

2.2. Preparation of standards

Either 1 or 80% (v/v) nitric acid solution was used as the calibration blank depending on the solvents used in the sample dissolution. A single working calibration standard containing 69 elements was prepared by directly diluting the four multi-element stock standard solutions and the intermediate 10 μg/ml Hg solution (made from the dilution of the 1000 μg/ml Hg stock solution), with either 1 or 80% (v/v) nitric acid solution also to match the solvent used in the sample preparation. The concentration of each of the elements in this standard is 20 μg/l, except Na, Si, P, K, Ca, and Fe which are 1000 μg/l.

2.3. Preparation of samples

Approximately 0.01 g of sample was accurately weighed into a metal-free container and 10 ml of 1 or 80% (v/v) nitric acid was added. With shaking, a majority of process intermediate and drug substance samples are readily soluble (sonication

Table 3
Standard stability with time in 1% nitric acid

Element	Isotope	Recovery after 24 h	Recovery after 1 week	Recovery after 2 weeks	Recovery after 3 weeks	Recovery after 4 weeks
Li	7	96	96	91	98	96
Be	9	105	98	98	95	100
B	11	108	101	97	105	96
Na	23	101	98	99	106	132
Mg	24	102	100	94	103	98
Al	27	101	123	116	101	125
Si	28	97	100	101	103	107
P	31	101	118	117	101	121
K	39	101	102	98	100	100
Ca	44	101	96	100	102	98
Sc	45	99	94	95	99	96
Ti	48	99	95	99	99	95
Ti	49	99	93	95	100	98
V	51	103	98	94	100	99
Cr	52	101	98	97	99	99
Cr	53	100	96	96	99	96
Mn	55	102	95	94	98	98
Fe	54	101	98	96	99	101
Fe	57	101	97	96	104	100
Co	59	102	96	93	98	98
Ni	58	101	97	99	97	100
Ni	60	102	97	97	97	100
Cu	63	97	96	94	99	99
Cu	65	99	93	94	98	95
Zn	64	97	118	123	103	126
Ga	69	98	97	93	99	98
Ge	72	101	97	94	100	98
As	75	98	98	95	98	97
Se	77	94	98	93	97	103
Se	82	101	98	94	92	95
Rb	85	95	97	95	96	97
Sr	88	101	96	93	98	96
Y	89	96	94	84	97	95
Zr	90	101	95	95	96	96
Nb	93	101	95	92	99	102
Mo	95	99	96	93	100	99
Ru	101	96	97	95	98	97
Rh	103	99	95	95	98	97
Pd	105	105	96	93	100	89
Ag	107	111	95	94	100	99
Cd	111	98	97	94	101	97
In	115	101	96	93	101	97
Sn	118	99	97	94	99	99
Sb	121	100	95	95	97	98
Te	125	100	97	94	99	98
Cs	133	99	97	93	104	96
Ba	137	98	97	95	99	96
La	139	98	93	93	101	95
Ce	140	92	92	92	97	93
Pr	141	97	104	92	102	92
Nd	146	96	95	95	99	94
Sm	147	96	94	94	101	97

Table 3 (*Continued*)

Element	Isotope	Recovery after 24 h	Recovery after 1 week	Recovery after 2 weeks	Recovery after 3 weeks	Recovery after 4 weeks
Eu	153	97	94	96	99	95
Gd	157	97	93	95	99	99
Tb	159	99	96	102	98	97
Dy	163	94	94	95	103	97
Ho	165	97	96	89	106	98
Er	166	98	92	95	102	101
Tm	169	99	96	96	104	102
Yb	172	99	93	94	103	97
Lu	175	98	96	96	104	99
Hf	178	101	97	96	103	100
Ta	181	104	96	96	103	95
W	182	102	96	94	103	100
Re	185	98	95	95	104	101
Os	189	112	176	134	108	92
Ir	193	98	96	96	106	96
Pt	195	99	95	95	99	98
Au	197	45	95	90	72	60
Hg	202	98	108	100	144	111
Tl	205	101	97	97	102	99
Pb	208	100	96	95	104	101
Bi	209	100	97	96	104	101
Th	232	98	95	92	108	97
U	238	99	96	88	108	95

is rarely needed), and in most of the cases, the sample is ready for analysis without further dilution or treatment.

2.4. Instrumentation

A Perkin–Elmer Elan 6000 inductively coupled plasma mass spectrometer (ICP-MS) equipped with an AS-91 autosampler was used throughout this study. The instrumental conditions and general method parameters are listed in Table 1.

3. Results and discussion

3.1. Sample preparation

Sample preparation is frequently the most crucial, challenging and time-consuming step in atomic spectroscopic measurements [16]. The same is true with various Pharmacopoeia methods. USP method I [3] is used for substances that yield clear, colorless aqueous solutions and, other than pH adjustment, sample preparation is straightforward. USP method II [3] is used for substances that do not yield clear, colorless preparations under the test conditions specified for method I, or for substances that interfere with the precipitation of metals by sulfide ion, or for fixed and volatile oils. In this case, samples need to be ignited, charred, digested, and ignited again before they can be turned into liquid form. Method III [3], a wet-digestion method, is used only in those cases where neither method I nor II can be utilized. The EP heavy metals test method A [1] is similar to USP method I with minor differences in the preparation of the solutions. The USP method compares the sample to a Pb standard alone whereas the EP method A compares the sample with a lead standard mixed with the sample solution to be examined. The current EP method B [1] is totally different from the USP method II where in the EP method the substance to be examined is dissolved in an organic solvent containing a mini-

Table 4
Standard stability with time in 80% nitric acid

Element	Isotope	Recovery after 24 h	Recovery after 1 week	Recovery after 2 weeks	Recovery after 3 weeks	Recovery after 4 weeks
Li	7	101	110	102	102	93
Be	9	99	103	104	97	91
B	11	106	168	116	107	84
Na	23	103	114	140	138	93
Mg	24	102	108	102	99	87
Al	27	104	111	93	80	56
Si	28	106	105	100	87	118
P	31	104	134	116	127	97
K	39	104	110	108	107	96
Ca	44	111	108	105	102	90
Sc	45	104	106	104	105	97
Ti	48	101	107	103	104	97
Ti	49	101	106	102	100	96
V	51	103	106	102	104	97
Cr	52	102	107	102	102	98
Cr	53	102	106	104	104	100
Mn	55	101	105	102	105	99
Fe	54	108	126	116	117	101
Fe	57	101	105	105	108	99
Co	59	101	104	102	104	100
Ni	58	104	110	101	101	101
Ni	60	108	110	101	102	98
Cu	63	101	102	103	102	96
Cu	65	101	104	100	103	96
Zn	64	97	107	94	75	90
Zn	66	104	104	102	104	94
Zn	67	105	106	99	103	91
Ga	69	103	103	103	103	101
Ge	72	102	102	101	102	97
As	75	102	101	102	102	98
Se	77	100	102	102	92	96
Se	82	106	99	99	108	100
Rb	85	102	105	104	105	102
Sr	88	104	104	121	104	101
Y	89	104	115	123	104	102
Zr	90	102	103	103	102	100
Nb	93	101	104	102	103	99
Mo	95	102	103	103	103	100
Ru	101	102	104	103	101	100
Rh	103	102	101	100	101	99
Pd	105	98	101	101	98	96
In	115	102	103	102	102	101
Sn	118	102	101	101	100	99
Sb	121	100	99	99	100	101
Te	125	104	100	101	97	100
Cs	133	102	111	100	99	101
Ba	137	100	102	102	101	101
La	139	101	109	102	101	100
Ce	140	101	111	102	100	100
Pr	141	100	103	103	102	102
Nd	146	102	103	98	102	101

Table 4 (*Continued*)

Element	Isotope	Recovery after 24 h	Recovery after 1 week	Recovery after 2 weeks	Recovery after 3 weeks	Recovery after 4 weeks
Sm	147	103	101	101	101	98
Eu	153	102	102	100	103	100
Gd	157	104	104	99	104	99
Tb	159	101	103	103	104	101
Dy	163	99	102	102	103	100
Ho	165	103	104	104	101	101
Er	166	101	101	104	101	101
Tm	169	102	106	103	101	102
Yb	172	98	102	103	100	101
Lu	175	100	102	103	101	101
Hf	178	103	103	100	99	99
Ta	181	109	110	114	113	102
W	182	105	101	102	100	100
Re	185	103	100	99	100	102
Os	189	101	143	171	189	137
Ir	193	101	98	100	101	99
Pt	195	101	98	98	98	100
Au	197	96	98	99	98	100
Hg	202	99	99	99	102	102
Tl	205	100	102	99	101	104
Pb	208	102	103	102	98	99
Bi	209	101	102	102	99	101
Th	232	101	102	102	110	102
U	238	102	106	102	99	102

mum percentage of water. EP method C and D [1] are somewhat similar to USP method II [3], both methods involve charring and ignition in the crucible before the samples are dissolved.

All those sample preparation schemes have something in common — there are too many steps involved and they are too complicated and cumbersome. The end-results also have something in common — they all lack sensitivity and specificity and they are all unreliable in recoveries.

In addition to the extreme sensitivity and specificity of ICP-MS, the sample preparation scheme proposed in this paper is also extremely simple and straightforward. From the handling of hundreds of pharmaceutical samples, it is the finding of the authors that at least 99% of these samples are readily soluble in either 1 or 80% nitric acid solutions. On some occasions, sonication might be needed to solubilize the samples or speed up their solubilization. In rare cases, where samples do not dissolve in either solutions microwave digestion can be used. The USP or EP heavy metals test may take an hour or longer to perform for one sample, particularly when the charring and/or ignition is involved. With the method proposed in this paper, each sample can be prepared and analyzed in less than 15 min after initialization of the instrument. In addition, since only ppm levels of metals of pharmaceutical interest will be noted and reported, data processing and interpretation are also extremely simple.

3.2. Method validation

3.2.1. Calibration verification

Although this method is intended to be semi-quantitative, calibration verification is still needed since only a single mixed-element calibration standard is used. This verification was carried out by calibrating the ICP-MS with a single standard prepared in 1 and 80% nitric acid solutions followed by the analysis of NIST 1643d (trace metals in water) also diluted in both 1 and 80% nitric

Table 5
LODs and LOQs in solid samples

Element	Isotope	1% HNO_3 solution		80% HNO_3 solution	
		LOD (ppm)	LOQ (ppm)	LOD (ppm)	LOQ (ppm)
Li	7	0.09	0.3	0.1	0.5
Be	9	0.09	0.3	0.08	0.3
B	11	5	16	6	22
Na	23	2	8	0.3	1
Mg	24	0.05	0.2	0.2	0.6
Al	27	0.03	0.1	5	16
Si	28	6	21	35	115
P	31	0.7	2	230	766
K	39	2	6	1	4
Ca	44	19	64	4	12
Sc	45	0.09	0.3	1	4
Ti	48	0.06	0.2	0.3	1
Ti	49	0.06	0.2	0.07	0.2
V	51	0.02	0.08	0.02	0.08
Cr	52	0.05	0.2	0.06	0.2
Cr	53	0.09	0.3	0.08	0.3
Mn	55	0.02	0.06	0.03	0.09
Fe	54	3	9	148	493
Fe	57	2	8	1	4
Co	59	0.02	0.06	0.01	0.05
Ni	58	0.06	0.2	3	8
Ni	60	0.02	0.06	2	5
Cu	63	0.03	0.1	0.05	0.2
Cu	65	0.03	0.1	0.09	0.3
Zn	64	0.04	0.1	6	20
Ga	69	0.02	0.06	0.01	0.05
Ge	72	0.03	0.10	0.03	0.10
As	75	0.03	0.1	0.06	0.2
Se	77	0.2	0.5	0.5	2
Se	82	0.1	0.4	0.8	3
Rb	85	0.02	0.05	0.01	0.03
Sr	88	0.01	0.04	0.01	0.03
Y	89	0.01	0.03	0.02	0.05
Zr	90	0.01	0.03	0.01	0.03
Nb	93	0.01	0.03	0.02	0.07
Mo	95	0.02	0.07	0.02	0.08
Ru	101	0.02	0.05	0.01	0.04
Rh	103	0.02	0.07	0.01	0.03
Pd	105	0.03	0.09	0.02	0.08
Ag	107	0.01	0.05	0.02	0.05
Cd	111	0.04	0.1	0.04	0.1
In	115	0.01	0.04	0.01	0.04
Sn	118	0.02	0.06	0.02	0.05
Sb	121	0.02	0.06	0.02	0.08
Te	125	0.06	0.2	0.2	0.6
Cs	133	0.01	0.02	0.01	0.02
Ba	137	0.03	0.10	0.02	0.06
La	139	0.01	0.04	0.01	0.03
Ce	140	0.01	0.03	0.01	0.02
Pr	141	0.01	0.03	0.01	0.03
Nd	146	0.01	0.04	0.01	0.05

Table 5 (*Continued*)

Element	Isotope	1% HNO_3 solution		80% HNO_3 solution	
		LOD (ppm)	LOQ (ppm)	LOD (ppm)	LOQ (ppm)
Sm	147	0.02	0.07	0.02	0.05
Eu	153	0.01	0.04	0.01	0.02
Gd	157	0.01	0.05	0.02	0.06
Tb	159	0.01	0.04	0.01	0.03
Dy	163	0.03	0.09	0.01	0.04
Ho	165	0.01	0.04	0.01	0.03
Er	166	0.01	0.05	0.03	0.09
Tm	169	0.004	0.01	0.01	0.03
Yb	172	0.01	0.04	0.01	0.04
Lu	175	0.01	0.03	0.01	0.04
Hf	178	0.01	0.04	0.01	0.04
Ta	181	0.01	0.03	0.02	0.07
W	182	0.03	0.10	0.07	0.2
Re	185	0.01	0.05	0.01	0.05
Os	189	0.1	0.4	0.2	0.7
Ir	193	0.01	0.04	0.01	0.05
Pt	195	0.02	0.05	0.02	0.07
Au	197	0.05	0.2	0.04	0.1
Hg	202	0.2	0.7	0.05	0.2
Tl	205	0.01	0.04	0.01	0.03
Pb	208	0.01	0.04	0.01	0.04
Bi	209	0.01	0.04	0.01	0.04
Th	232	0.01	0.03	0.01	0.02
U	238	0.01	0.03	0.01	0.02

acid solutions. The results are given in Table 2. Except for Fe in both 1 and 80% nitric acid solutions an excellent agreement was achieved with all elements in both 1 and 80% nitric acid matrices where certified or reference values were given by NIST 1643d. The erroneously high results of Fe using both ^{54}Fe and ^{57}Fe result from spectral interference mainly from $^{14}N^{40}Ar$, $^{16}O^{38}Ar$, and $^{40}Ar^{16}O^{1}H$ which cannot be circumvented with the current instrument capabilities. For ICP-MS, only instruments operated under 'cold' plasma (low power and high nebulizer flow) conditions, instruments with the newest 'chemical resolution' capability, as well the more expensive high resolution instruments can be used to determine the Fe content accurately. If necessary, an alternative instrumental method will be used for accurate analysis of Fe.

3.2.2. Standard stability

Since the 69-element calibration standard used in this method was made by mixing and diluting five separate stock standards, compatibility among all the elements (stability) of the standard needs to be confirmed. Although no precipitation was observed by visual inspection in the standard prepared with either 1 or 80% nitric, and the validity and short-term stability of the standard was demonstrated by the excellent calibration verification in Section 3.2.1, the investigation of the long-term stability of the standard is still warranted. This was performed by the analysis of a standard stored for 24 h, 1 week, 2 weeks, and 4 weeks against a freshly prepared standard. The percent recoveries of the various components are given in Table 3 for 1% nitric acid solution, and in Table 4 for 80% nitric acid solution. These results

Table 6
Spike recoveries in 1% nitric acid solution

Element	Isotope	Spiked level (μg/l)	Recovery (%)			
			9800209	9800288	9800797	98000202
Li	7	10	107	109	101	109
Be	9	10	107	119	108	112
B	10	10	111	86	n/a[a]	91
B	11	10	103	86	n/a[a]	92
Na	23	500	n/a[a]	107	112	108
Mg	24	10	103	103	105	105
Al	27	10	107	108	105	111
Si	28	500	116	107	101	109
P	31	500	114	112	108	117
K	39	500	107	107	105	109
Ca	44	500	107	106	99	107
Sc	45	10	108	110	105	114
Ti	48	10	105	98	93	107
Ti	49	10	106	101	139	103
V	51	10	105	103	101	111
Cr	52	10	123	105	106	109
Cr	53	10	103	100	98	108
Mn	55	10	102	104	100	120
Fe	54	500	99	101	94	107
Fe	57	500	101	102	97	107
Co	59	10	103	102	97	108
Ni	58	10	103	102	94	107
Ni	60	10	102	104	104	109
Cu	63	10	99	101	99	107
Cu	65	10	99	101	99	105
Zn	64	10	103	105	101	107
Zn	66	10	101	101	99	104
Zn	67	10	98	101	99	110
Ga	69	10	101	103	99	108
Ge	72	10	101	100	97	107
As	75	10	113	109	106	118
Se	77	10	119	113	110	121
Se	82	10	114	107	111	114
Rb	85	10	103	99	100	108
Sr	88	10	103	100	101	108
Y	89	10	104	102	102	111
Zr	90	10	104	99	98	106
Nb	93	10	104	98	98	106
Mo	95	10	103	100	89	107
Ru	101	10	101	99	98	105
Rh	103	10	101	100	100	107
Pd	105	10	90	81	58	91
Ag	107	10	91	100	97	107
Cd	111	10	98	97	99	105
In	115	10	101	98	99	106
Sn	118	10	100	97	98	105
Sn	120	10	101	98	100	106
Sb	121	10	102	98	98	105
Te	125	10	106	108	105	112
Cs	133	10	102	98	100	108
Ba	137	10	99	96	97	104

Table 6 (*Continued*)

Element	Isotope	Spiked level (μg/l)	Recovery (%)			
			9800209	9800288	9800797	98000202
La	139	10	103	99	100	108
Ce	140	10	101	98	99	106
Pr	141	10	99	96	96	104
Nd	146	10	100	97	98	107
Sm	147	10	105	101	101	110
Eu	153	10	106	102	102	110
Gd	157	10	106	104	102	112
Tb	159	10	102	97	96	108
Dy	163	10	105	103	100	110
Ho	165	10	102	101	101	110
Er	166	10	106	105	103	114
Tm	169	10	108	105	103	112
Yb	172	10	104	102	101	109
Lu	175	10	107	105	102	112
Hf	178	10	104	103	99	108
Ta	181	10	103	103	100	110
W	182	10	104	102	99	109
Re	185	10	108	105	100	111
Os	189	10	102	104	100	107
Ir	193	10	104	103	99	109
Pt	195	10	103	100	97	106
Au	197	10	113	38	54	39
Hg	202	10	95	93	98	105
Tl	205	10	101	102	103	110
Pb	208	10	102	103	104	109
Bi	209	10	101	103	104	112
Th	232	10	106	104	105	113
U	238	10	104	101	101	110

[a] Spiked levels too low relative to the metal contents already existed in the samples.

indicate that the 69-element standard is stable for at least 4 weeks and the recovery for all the elements is acceptable for a survey method.

3.2.3. LOD/LOQ

Limits of detection (LOD) and limits of quantitation (LOQ) for all elements in 1 and 80% nitric acid solutions were estimated by analyzing 11 replicate aliquots of the spiked calibration blanks as 11 samples (with rinsing between samples) at concentrations between two to five times of the estimated limit of detection (based on the standard deviation of 11 replicate blanks). The LOD and LOQ are defined as three and ten times of the standard deviation of the 11 measurements, respectively. The results are given in Table 5. The LOD and LOQ for all elements are stated on the basis of a 100-mg sample dissolved in 100 ml of 1 or 80% nitric acid solutions. These are 'best-case-scenarios' and the LODs and LOQs in real samples may be higher, and for some elements they might be worsened dramatically by the presence of interference-causing species, such as sulfur, chlorine, bromine, and titanium, as will be discussed in Section 3.2.7.

It can be seen that the LODs and LOQs of metals of pharmaceutical interest are all below parts per million (ppm) levels which are the current control levels for heavy metals in the pharmaceutical industry. These are also the levels the USP and EP methods are designed to detect and monitor. This ICP-MS method should prove

Table 7
Spike recoveries in 80% nitric acid solution

Element	Isotope	Spiked level (μg/l)	Recovery (%)			
			960972	9701565	980886	98000202
Li	7	10	127	113	117	125
Be	9	10	119	113	112	117
B	10	10	161	144	148	124
B	11	10	116	109	117	87
Na	23	500	116	120	n/a[a]	n/a[a]
Mg	24	10	129	121	123	123
Al	27	10	141	132	136	135
Si	28	500	n/a[a]	n/a[a]	n/a[a]	n/a[a]
P	31	500	n/a[a]	n/a[a]	n/a[a]	n/a[a]
K	39	500	137	118	117	112
Ca	44	500	n/a[a]	n/a[a]	n/a[a]	n/a[a]
Sc	45	10	123	116	117	119
Ti	48	10	118	109	113	117
Ti	49	10	121	108	110	115
V	51	10	121	112	114	117
Cr	52	10	107	109	96	114
Cr	53	10	119	110	110	114
Mn	55	10	124	114	114	125
Fe	57	500	113	96	82	97
Co	59	10	119	108	109	113
Ni	58	10	110	95	97	99
Ni	60	10	112	96	99	100
Cu	63	10	117	106	105	111
Cu	65	10	116	106	105	111
Zn	64	10	110	146	64	77
Zn	66	10	103	102	95	99
Zn	67	10	102	98	96	102
Ga	69	10	122	111	112	115
Ge	72	10	113	105	103	105
As	75	10	118	104	104	109
Se	77	10	116	102	100	102
Rb	85	10	121	113	113	118
Sr	88	10	121	113	114	118
Y	89	10	119	113	112	117
Zr	90	10	118	112	112	115
Nb	93	10	119	111	110	114
Mo	95	10	105	110	141	114
Ru	101	10	118	114	114	113
Rh	103	10	117	113	113	113
Pd	105	10	116	111	112	110
Ag	107	10	122	117	115	114
Cd	111	10	111	104	104	102
In	115	10	117	110	110	111
Sn	118	10	112	103	102	104
Sn	120	10	111	101	100	105
Sb	121	10	107	96	95	98
Te	125	10	115	96	98	101
Cs	133	10	112	98	100	104
Ba	137	10	109	98	96	102
La	139	10	109	99	98	102

Table 7 (*Continued*)

Element	Isotope	Spiked level (μg/l)	Recovery (%)			
			960972	9701565	980886	98000202
Ce	140	10	128	100	99	106
Pr	141	10	104	94	93	99
Nd	146	10	111	100	99	106
Sm	147	10	108	99	97	104
Eu	153	10	111	101	100	106
Gd	157	10	112	99	100	107
Tb	159	10	105	95	96	101
Dy	163	10	113	102	103	110
Ho	165	10	115	99	99	105
Er	166	10	114	103	102	111
Tm	169	10	118	102	101	107
Yb	172	10	112	103	102	111
Lu	175	10	112	101	103	109
Hf	178	10	112	104	103	111
Ta	181	10	104	97	96	109
W	182	10	110	94	100	108
Re	185	10	110	101	102	108
Os	189	10	97	97	99	105
Ir	193	10	108	98	99	102
Pt	195	10	105	94	94	97
Au	197	10	102	94	93	94
Hg	202	10	97	90	89	95
Tl	205	10	115	105	106	112
Pb	208	10	114	102	104	110
Bi	209	10	113	102	102	108
Th	232	10	107	97	98	103
U	238	10	109	98	98	106

[a] Spiked levels too low relative to the metal contents already existed in the samples.

to be increasingly valuable if future heavy metals control limits become more stringent in the pharmaceutical industry, as they have in the semiconductor and environmental industries.

3.2.4. Matrix effects and spectral interference

Matrix effects were minimized by making the calibration blanks and calibration standards in the same matrix as in the samples, and by dissolving a minimum amount of the sample in the solution to be analyzed (0.1% total dissolved solids) taking advantage of the extremely high sensitivity of the ICP-MS. The absence of significant matrix effects was demonstrated by the excellent spike recoveries described in Section 3.2.5. Spectral interferences were monitored by using more than one isotope for the same element whenever possible for some interference-prone low-mass elements. Positive results at moderate levels for some elements in the presence of one or more other high level elements should always be investigated further for spectral interferences, or by confirming the results with an alternative method such as inductively coupled plasma atomic emission spectroscopy (ICP-AES), or graphite furnace atomic absorption spectroscopy (GFAAS). Specific cases of spectral interference will be discussed in Section 3.2.7.

3.2.5. Accuracy of the method

Poor (or no) spike recoveries using the USP and EP heavy metals test for some samples were the major concern in our laboratory, and provided the motive for seeking alternative methods

Table 8
Precision study of 98000202 in 1% nitric acid solution

Element	Isotope	Average	S.D.	R.S.D. (%)
Li	7	11.5	0.178	1.55
Be	9	12.0	0.301	2.52
B	11	14.1	0.485	3.44
Na	23	578	7.75	1.34
Mg	24	12.3	0.181	1.47
Al	27	12.3	0.272	2.20
Si	28	710	8.80	1.24
P	31	613	4.90	0.80
K	39	582	8.42	1.45
Ca	44	641	11.0	1.71
Sc	45	11.9	0.389	3.28
Ti	48	10.5	0.138	1.31
Ti	49	10.8	0.174	1.61
V	51	11.5	0.119	1.04
Cr	52	15.9	0.210	1.32
Cr	53	12.9	0.170	1.32
Mn	55	12.8	0.856	6.67
Fe	54	547	4.60	0.84
Fe	57	537	7.64	1.42
Co	59	10.8	0.110	1.02
Ni	58	10.6	0.203	1.91
Ni	60	10.9	0.149	1.37
Cu	63	10.8	0.148	1.37
Cu	65	10.6	0.164	1.55
Zn	64	12.9	0.148	1.15
Zn	66	12.6	0.198	1.57
Zn	67	13.0	0.219	1.69
Ga	69	10.9	0.065	0.60
Ge	72	10.8	0.172	1.60
As	75	12.0	0.179	1.48
Se	77	13.2	0.233	1.76
Se	82	11.5	0.221	1.93
Rb	85	10.6	0.106	1.00
Sr	88	10.8	0.071	0.65
Y	89	10.9	0.100	0.92
Zr	90	10.5	0.094	0.90
Nb	93	10.5	0.056	0.53
Mo	95	10.6	0.119	1.13
Ru	101	10.4	0.090	0.87
Rh	103	10.6	0.083	0.78
Pd	105	7.48	0.156	2.08
Ag	107	10.6	0.107	1.01
Cd	111	10.4	0.086	0.83
In	115	10.4	0.105	1.01
Sn	118	10.3	0.101	0.97
Sn	120	10.4	0.099	0.95
Sb	121	10.4	0.308	2.98
Te	125	11.2	0.146	1.30
Cs	133	10.5	0.062	0.59
Ba	137	10.4	0.123	1.18
La	139	10.6	0.093	0.88
Ce	140	10.6	0.079	0.74

Table 8 (*Continued*)

Element	Isotope	Average	S.D.	R.S.D. (%)
Pr	141	10.4	0.104	1.01
Nd	146	10.5	0.104	0.99
Sm	147	10.8	0.106	0.99
Eu	153	11.0	0.088	0.80
Gd	157	11.2	0.082	0.74
Tb	159	10.6	0.084	0.79
Dy	163	11.0	0.101	0.92
Ho	165	10.9	0.095	0.87
Er	166	11.4	0.113	0.99
Tm	169	11.2	0.105	0.94
Yb	172	11.0	0.107	0.97
Lu	175	11.3	0.178	1.57
Hf	178	11.0	0.148	1.35
Ta	181	11.1	0.096	0.86
W	182	11.1	0.098	0.88
Re	185	11.2	0.149	1.34
Os	189	11.0	0.070	0.64
Ir	193	11.0	0.118	1.08
Pt	195	10.6	0.108	1.02
Au	197	3.93	0.286	7.28
Hg	202	10.9	0.159	1.46
Tl	205	11.1	0.101	0.90
Pb	208	11.1	0.101	0.92
Bi	209	11.3	0.101	0.90
Th	232	11.3	0.084	0.74
U	238	11.1	0.133	1.20

for these tests. Since no relevant standard reference materials (SRMs) for pharmaceuticals are available at this time, the accuracy of the method was evaluated by spiking studies at levels equivalent to 10 ppm (10 μg/l in solution) with four typical samples dissolved in 1% nitric acid solution, and four typical samples dissolved in 80% nitric acid solution. The recovery results are shown in Tables 6 and 7, and are excellent for most of the elements in both the matrices and consistently acceptable for a survey method. A spike recovery study was performed using sample 98000202 in both 80 and 1% nitric acid solutions. This sample was chosen because 98000202 is a known chelator of metals, and no visible precipitation was observed in the USP heavy metals test with samples spiked with lead at levels >10 ppm. The standard USP heavy metals test could not be validated for this material. The satisfactory spike recovery for all metals of pharmaceutical interest in this material using the ICP-MS method is a clear contrast.

3.2.6. Precision of the method

The study of the precision of the method was carried out by repeated analysis of two spiked samples dissolved in 1% nitric acid solution, and two spiked samples dissolved in 80% nitric acid solution. The spiked levels for most of the elements were the same (except Na, Si, P, K, Ca, and Fe in 80% nitric acid solutions) as used in the spike recoveries (Section 3.2.5). The precision of the method was evaluated by the reproducibility achieved in terms of standard deviation (S.D.) and relative standard deviation (R.S.D.) among the replicate results from the same sample. The results are listed in Tables 8–11, respectively. As shown in the tables, the S.D.s and percent R.S.D.s of 11 measurements for the spiked samples are all well below 1 and 5, respectively, for

Table 9
Precision study of 98000209 in 1% nitric acid solution

Element	Isotope	Average	S.D.	R.S.D. (%)
Li	7	11.9	0.607	5.11
Be	9	11.0	0.437	3.97
B	10	15.7	0.608	3.89
B	11	16.2	0.550	3.39
Mg	24	17.0	0.257	1.51
Al	27	12.1	0.358	2.97
Si	28	677	12.5	1.85
P	31	580	14.0	2.42
K	39	575	9.03	1.57
Ca	44	619	12.3	1.99
Sc	45	11.5	0.208	1.80
Ti	48	16.4	0.859	5.24
Ti	49	11.7	0.142	1.22
V	51	10.3	0.085	0.83
Cr	52	15.3	0.211	1.38
Cr	53	10.4	0.142	1.36
Mn	55	10.0	0.091	0.92
Fe	54	498	4.77	0.96
Fe	57	490	5.35	1.09
Co	59	9.84	0.111	1.13
Ni	58	9.65	0.123	1.28
Ni	60	9.9	0.107	1.08
Cu	63	10.4	0.130	1.25
Cu	65	9.90	0.088	0.89
Zn	64	12.1	0.188	1.55
Zn	66	9.79	0.133	1.36
Zn	67	10.1	0.269	2.67
Ga	69	10.0	0.136	1.36
Ge	72	10.0	0.105	1.06
As	75	11.0	0.153	1.39
Se	77	11.4	0.341	2.99
Se	82	11.0	0.226	2.05
Rb	85	9.80	0.086	0.88
Sr	88	10.2	0.088	0.86
Y	89	10.0	0.078	0.78
Zr	90	9.88	0.093	0.94
Nb	93	10.0	0.095	0.95
Mo	95	10.0	0.107	1.07
Ru	101	9.73	0.070	0.72
Rh	103	9.86	0.112	1.14
Pd	105	9.09	0.152	1.67
Ag	107	8.77	0.065	0.74
Cd	111	9.47	0.112	1.19
In	115	9.59	0.049	0.51
Sn	118	9.37	0.066	0.70
Sn	120	9.45	0.057	0.61
Sb	121	9.52	0.061	0.64
Te	125	10.3	0.191	1.85
Cs	133	9.77	0.072	0.73
Ba	137	9.66	0.106	1.09
La	139	9.72	0.071	0.73
Ce	140	9.69	0.073	0.75
Pr	141	9.50	0.070	0.74
Nd	146	9.67	0.047	0.49
Sm	147	9.93	0.084	0.85
Eu	153	10.1	0.106	1.04
Gd	157	10.3	0.131	1.28
Tb	159	9.77	0.079	0.81
Dy	163	10.1	0.108	1.07
Ho	165	10.1	0.074	0.73
Er	166	10.5	0.065	0.62
Tm	169	10.4	0.113	1.09
Yb	172	10.1	0.104	1.03
Lu	175	10.5	0.096	0.92
Hf	178	10.2	0.111	1.09
Ta	181	10.2	0.101	0.99
W	182	10.3	0.156	1.52
Re	185	10.6	0.130	1.22
Os	189	10.6	0.089	0.84
Ir	193	10.1	0.087	0.86
Pt	195	10.0	0.085	0.85
Au	197	11.8	1.083	9.17
Hg	202	9.9	0.122	1.24
Tl	205	10.0	0.111	1.12
Pb	208	10.0	0.105	1.05
Bi	209	10.1	0.086	0.86
Th	232	10.5	0.106	1.01
U	238	10.2	0.139	1.37

elements normally present in these pharmaceutical samples at trace or ultra-trace levels.

3.2.7. Application of the method

This ICP-MS survey method has been successfully used in the screening of heavy metals in drug substances and their intermediates as an alternative to the USP and EP heavy metals limit test. Analyses of typical drug substances and intermediate samples in 1% nitric acid solution are given in Table 12, and the results obtained in 80% nitric acid solution are given in Table 13, respectively. Results above the LOQ of each element in the corresponding solutions are listed, although at this stage only ppm levels of heavy metals are pharmaceutically relevant.

The detrimental effect on the LOQ of some of the metals as well as the severity of the polyatomic interferences from elements such as Cl, C, Br, and Ti at high levels, are clearly demonstrated

Table 10
Precision study of 960972 in 80% nitric acid solution

Element	Isotope	Average	S.D.	R.S.D. (%)
Li	7	13.6	0.668	4.92
Be	9	12.1	0.271	2.23
B	10	101	3.56	3.53
B	11	84.5	4.068	4.82
Na	23	16.6	0.184	1.11
Mg	24	17.9	0.739	4.14
Al	27	18.4	0.255	1.39
Si	28	175	16.9	9.67
P	31	1080	75.2	6.97
K	39	10.5	0.393	3.75
Ca	44	44.7	12.9	29.0
Sc	45	12.4	0.345	2.77
Ti	48	15.7	0.217	1.38
Ti	49	12.4	0.216	1.74
V	51	11.6	0.106	0.91
Cr	52	15.3	0.820	5.34
Cr	53	12.3	0.151	1.23
Mn	55	11.7	0.162	1.38
Fe	54	638	18.0	2.82
Fe	57	7.97	0.583	7.31
Co	59	10.7	0.200	1.87
Ni	58	9.24	0.286	3.09
Ni	60	9.45	0.323	3.42
Cu	63	10.6	0.202	1.91
Cu	65	10.8	0.142	1.31
Zn	64	12.8	2.349	18.35
Zn	66	8.96	0.281	3.13
Zn	67	9.16	0.375	4.09
Ga	69	11.5	0.166	1.44
Ge	72	10.3	0.187	1.82
As	75	10.2	0.209	2.04
Se	77	10.2	0.312	3.07
Se	82	13.4	1.238	9.25
Rb	85	11.6	0.137	1.18
Sr	88	11.7	0.201	1.72
Y	89	11.6	0.200	1.73
Zr	90	11.2	0.165	1.48
Nb	93	11.2	0.174	1.56
Mo	95	11.7	0.170	1.45
Ru	101	11.0	0.098	0.89
Rh	103	10.7	0.155	1.45
Pd	105	10.5	0.162	1.55
Ag	107	10.7	0.162	1.52
Cd	111	9.47	0.208	2.19
In	115	10.6	0.202	1.90
Sn	118	9.80	0.161	1.65
Sn	120	9.79	0.185	1.89
Sb	121	8.75	0.179	2.04
Te	125	9.02	0.264	2.93
Cs	133	9.48	0.137	1.44
Ba	137	9.27	0.181	1.95
La	139	9.10	0.170	1.87
Ce	140	9.38	0.431	4.59
Pr	141	8.90	0.123	1.39
Nd	146	9.58	0.178	1.86
Sm	147	9.47	0.185	1.95
Eu	153	9.80	0.146	1.49
Gd	157	9.81	0.195	1.99
Tb	159	9.40	0.152	1.62
Dy	163	10.2	0.123	1.20
Ho	165	10.1	0.435	4.33
Er	166	10.4	0.147	1.41
Tm	169	10.6	0.494	4.65
Yb	172	10.5	0.137	1.30
Lu	175	10.6	0.260	2.45
Hf	178	10.5	0.144	1.37
Ta	181	10.3	0.329	3.20
W	182	10.1	0.134	1.33
Re	185	10.1	0.128	1.27
Os	189	10.3	0.144	1.40
Ir	193	9.10	0.179	1.97
Pt	195	8.29	0.197	2.37
Au	197	8.23	0.184	2.23
Hg	202	8.45	0.192	2.27
Tl	205	10.6	0.138	1.29
Pb	208	10.3	0.173	1.68
Bi	209	10.1	0.147	1.45
Th	232	9.71	0.096	0.99
U	238	10.2	0.125	1.23

in Tables 12 and 13. Sample # 7 in Table 12 and Sample # 15 in Table 13 are Br-containing raw materials, and due to the formation of $^{79}Br^{16}O$ in the ICP-MS, the LOQ of ^{95}Mo was increased by two to three orders of magnitude. Sample # 16 in Table 13 is another raw material that contains about 20% Ti, the LOQs of ^{63}Cu, ^{65}Cu, ^{64}Zn, ^{93}Nb are degraded to different extents due to the formation of $^{47}Ti^{16}O$, $^{49}Ti^{16}O$, $^{48}Ti^{16}O$, and $^{46}Ti^{47}Ti$ in ICP-MS. That is why higher LOQs are shown in Tables 12 and 13 for these elements and others due to serious polyatomic interferences in the presence of some concomitant elements, as explained in the footnotes. These results emphasize the necessity of using more than one isotope whenever possible to monitor spectral interferences and reconfirming 'positive hits' with an alternative technique.

The results show that, in addition to commonly occurring elements such as Si, Na, K, Ca, etc., the

Table 11
Precision study of 980886 in 80% nitric acid solution

Element	Isotope	Average	S.D.	R.S.D. (%)
Li	7	13.5	1.05	7.81
Be	9	11.8	0.16	1.37
B	10	96.1	4.39	4.57
B	11	84.9	10.5	12.31
Na	23	9.2	0.833	9.01
Mg	24	16.9	0.835	4.95
Al	27	17.2	0.557	3.23
Si	28	101	27.0	26.64
P	31	884	104	11.77
K	39	10.7	0.428	4.00
Ca	44	35.9	12.7	35.3
Sc	45	12.2	0.432	3.53
Ti	48	16.4	0.261	1.59
Ti	49	12.4	0.174	1.41
V	51	11.5	0.161	1.41
Cr	52	14.2	1.03	7.22
Cr	53	11.9	0.113	0.95
Mn	55	11.6	0.176	1.52
Fe	57	8.4	0.607	7.20
Co	59	10.7	0.189	1.76
Ni	58	9.89	0.359	3.63
Ni	60	10.0	0.412	4.10
Cu	63	10.4	0.158	1.51
Cu	65	10.6	0.183	1.72
Zn	66	8.72	0.270	3.10
Zn	67	8.88	0.355	4.00
Ga	69	11.3	0.187	1.65
Ge	72	10.3	0.176	1.70
As	75	10.1	0.174	1.73
Se	77	9.50	0.327	3.44
Rb	85	11.4	0.136	1.19
Sr	88	11.6	0.160	1.38
Y	89	11.4	0.124	1.09
Zr	90	11.3	0.457	4.04
Nb	93	11.1	0.160	1.44
Mo	95	13.2	0.240	1.81
Ru	101	11.4	0.166	1.45
Rh	103	11.2	0.167	1.48
Pd	105	11.1	0.197	1.78
Ag	107	11.3	0.184	1.62
Cd	111	10.1	0.184	1.82
In	115	11.1	0.198	1.79
Sn	118	10.2	0.154	1.51
Sn	120	10.0	0.169	1.69
Sb	121	9.13	0.182	2.00
Te	125	9.19	0.250	2.71
Cs	133	9.60	0.158	1.65
Ba	137	9.43	0.149	1.58
La	139	9.28	0.157	1.70
Ce	140	9.46	0.168	1.77
Pr	141	9.03	0.166	1.84
Nd	146	9.69	0.158	1.63
Sm	147	9.62	0.179	1.86
Eu	153	10.0	0.216	2.17
Gd	157	10.0	0.194	1.94
Tb	159	9.51	0.192	2.02
Dy	163	10.3	0.240	2.33
Ho	165	10.0	0.213	2.13
Er	166	10.5	0.209	2.00
Tm	169	10.7	0.561	5.22
Yb	172	10.4	0.219	2.09
Lu	175	10.4	0.179	1.71
Hf	178	10.5	0.201	1.91
Ta	181	9.68	0.156	1.61
W	182	10.8	0.273	2.54
Re	185	10.1	0.139	1.39
Os	189	10.3	0.094	0.91
Ir	193	9.36	0.159	1.69
Pt	195	8.70	0.194	2.23
Au	197	8.55	0.202	2.37
Hg	202	8.79	0.099	1.13
Tl	205	10.6	0.187	1.76
Pb	208	10.4	0.153	1.47
Bi	209	10.1	0.157	1.55
Th	232	9.64	0.112	1.16
U	238	10.0	0.209	2.09

only pharmaceutically important elements detected above ppm levels in these samples are Rh, Pd, Os, and Sn. These are expected results since those metals were once used as catalysts in the synthetic pathways of these compounds.

3.2.8. Utilization of the method

A survey method that permits simultaneous qualitative to quantitative (depending on the elements and the concentration levels) detection of up to 69 elements (including all those of pharmaceutical interest) in less than 15 min would be viewed by some as a giant leap compared with the antiquated USP and EP methods. The use of such a method, which employs a very sophisticated and expensive instrument, as an alternative to a seemingly economical wet chemical test that has been in use for decades would be viewed by others as technological overkill.

We take a less extreme view, and believe that since the technology is here, and present in the laboratory to address, often very challenging ana

Table 12
Results (μg/g) for eight samples in 1% HNO_3 solution

Element	Isotope	Sample #1	Sample #2	Sample #3	Sample #4	Sample #5	Sample #6	Sample #7	Sample #8
Li	7	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5
Be	9	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
B	11	<20	<20	<20	<20	<20	<20	<20	S[a1]
Na	23	59	<10	66	278	<10	<10	<10	S[a1]
Mg	24	7	<0.2	6	13	1	2	1	690
Al	27	21	0.4	0.4	1.5	0.6	<0.2	<0.2	0.6
Si	28	100	<20	2060	2430	28	27	<20	<20
P	31	12	<2	9	35	3	3	<2	<2
K	39	9	<6	11	48	<6	<6	<6	19
Ca	44	293	<65	358	306	400	500	<65	475
Sc	45	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
Ti	48	4.9	<0.2	3.2	3.9	<0.2	<0.2	<0.2	<0.2
Ti	49	1.2	<0.2	1.1	1.2	<0.2	<0.2	<0.2	<0.2
V	51	0.14	<0.08	0.19	0.22	<0.08	<0.08	<1[b1]	<1[b1]
Cr	52	3.3	<0.2	<4[c1]	<4[c1]	<2[c1]	<2[c1]	<0.2	<0.2
Cr	53	3.3	<0.3	<1[d1]	<1[d1]	<0.3	<0.3	<0.3	<0.3
Mn	55	0.22	<0.06	<0.06	<0.06	0.06	0.06	0.06	0.06
Fe	54	<10	<10	<10	<10	<10	<10	<10	<10
Fe	57	<10	<10	<10	<10	<10	<10	<10	<10
Co	59	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06
Ni	58	<0.2	<0.2	<0.2	0.5	<0.2	<0.2	<0.2	<0.2
Ni	60	<0.06	0.08	0.18	0.87	<0.06	<0.06	<0.06	<0.06
Cu	63	4.9	<0.1	0.7	<2[e1]	<0.1	<0.1	0.1	<5[e1]
Cu	65	5.1	<0.1	0.6	1.3	<0.1	<0.1	0.1	<0.1
Zn	64	<7[f1]	<0.1	<3[f1]	<4[f1]	0.3	0.6	2.6	0.5
Zn	66	4.3	<0.1	1.6	1.6	0.3	0.6	2.6	0.5
Zn	67	3.7	<0.1	1.6	2.0	0.3	0.5	2.6	0.5
Ga	69	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06
Ge	72	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
As	75	0.1	<0.1	<0.1	0.1	<0.1	<0.1	<1[g1]	<0.1
Se	77	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<3[h1]	<0.5
Se	82	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5
Rb	85	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Sr	88	0.19	<0.05	0.16	0.21	0.09	0.14	0.08	0.05
Y	89	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Zr	90	0.16	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Nb	93	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Mo	95	<0.07	<0.07	<0.07	0.08	<0.07	<0.07	<3[i1]	<0.2[i1]
Ru	101	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Rh	103	0.29	<0.07	0.31	1.18	<0.07	<0.07	<0.07	<0.07
Pd	105	37.0	1.3	38.8	118	<0.1	<0.1	<0.1	<0.1
Ag	107	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Cd	111	0.3	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1

Table 12 (*Continued*)

Element	Isotope	Sample #1	Sample #2	Sample #3	Sample #4	Sample #5	Sample #6	Sample #7	Sample #8
In	115	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Sn	118	0.35	<0.06	0.34	2.10	<0.06	<0.06	<0.06	<0.06
Sn	120	0.37	<0.06	0.36	2.15	<0.06	<0.06	<0.06	<0.06
Sb	121	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06
Te	125	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2
Cs	133	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
Ba	137	0.2	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
La	139	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Ce	140	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Pr	141	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Nd	146	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Sm	147	<0.07	<0.07	<0.07	<0.07	<0.07	<0.07	<0.07	<0.07
Eu	153	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Gd	157	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Tb	159	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Dy	163	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Ho	165	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Er	166	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Tm	169	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Yb	172	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Lu	175	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Hf	178	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Ta	181	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
W	182	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Re	185	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Os	189	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5
Ir	193	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Pt	195	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Au	197	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2
Hg	202	<0.7	<0.7	<0.7	<0.7	<0.7	<0.7	<0.7	<0.7
Tl	205	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Pb	208	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Bi	209	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Th	232	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
U	238	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03

[a] Signal saturated.
[b] $^{35}Cl^{16}O$ interference.
[c] $^{40}Ar^{12}C$ interference.
[d] $^{37}Cl^{16}O$ interference.
[e] $^{40}Ar^{23}Na$ interference.
[f] $^{32}S^{16}O_2$ and/or $^{32}S_2$ interference.
[g] $^{40}Ar^{35}Cl$ interference.
[h] $^{40}Ar^{37}Cl$ interference.
[i] $^{79}Br^{16}O$ interference.

Table 13
Results (μg/g) for eight samples in 80% HNO_3 solution

Element	Isotope	Sample #9	Sample #10	Sample #11	Sample #12	Sample #13	Sample #14	Sample #15	Sample #16
Li	7	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5
Be	9	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
B	11	<25	29	<25	<25	<25	<25	<25	<25
Na	23	63	629	14	41	197	3	<1	605
Mg	24	3	3	<1	3	10	<1	<1	<1
Al	27	<20	<20	<20	<20	<20	<20	<20	<20
Si	28	S[a1]	S[a1]	S[a1]	10200	5080	24700	<120	595
P	31	<800	<800	<800	<800	<800	<800	<800	<800
K	39	<4	<4	<4	<4	8	<4	<4	<4
Ca	44	2710	703	1090	190	155	357	69	49
Sc	45	17	4	9	<4	<4	<4	<4	<4
Ti	48	<1	2	<1	<1	<1	<1	<1	S[a1]
Ti	49	<1	1	<1	<1	<1	<1	<1	S[a1]
V	51	<0.08	0.09	<0.08	0.10	0.09	<0.08	<0.08	<0.5[b1]
Cr	52	<6[c1]	<4[c1]	<5[c1]	<2[c1]	<2[c1]	<2[c1]	<0.2	<8[c1]
Cr	53	<2[d1]	<2[d1]	<1[d1]	<1[d1]	<1[d1]	<1[d1]	<0.3	<2[d1]
Mn	55	<0.09	<0.09	<0.09	<0.09	<0.09	<0.09	<0.09	<0.09
Fe	57	<4	<4	<4	<4	<4	<4	<4	<4
Co	59	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Ni	58	<8	<8	<8	<8	<8	<8	<8	<8
Ni	60	<5	<5	<5	<5	<5	<5	<5	<5
Cu	63	0.7	0.8	0.2	0.4	0.6	0.6	<0.2	<80[e1]
Cu	65	0.7	0.8	0.3	0.3	0.6	0.6	<0.3	<150[f1]
Zn	64	<20	<20	<20	<20	<20	<20	<20	<3725[g1]
Ga	69	0.17	0.06	0.16	<0.05	<0.05	0.06	<0.05	<0.05
Ge	72	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
As	75	<1	<1	<1	<1	<1	<1	<1	<2[h1]
Se	77	<2	<2	<2	<2	<2	<2	<2	<9[i1]
Se	82	<3	<3	<3	<3	<3	<3	<3	<3
Rb	85	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Sr	88	0.15	0.14	0.15	0.13	0.49	0.09	0.08	<1.5[j1]
Y	89	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Zr	90	0.06	0.06	0.29	0.03	0.06	0.04	0.06	<0.3[k1]
Nb	93	<0.07	<0.07	<0.07	<0.07	<0.07	<0.07	<1[l1]	<0.3[m1]
Mo	95	0.13	0.10	<0.08	<0.08	0.10	<0.08	<71[n1]	<0.2[o1]
Ru	101	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04
Rh	103	52.3	53.6	8.54	0.78	0.44	3.84	<0.03	<0.03
Pd	105	440	498	483	9.11	12.4	80.3	<0.08	<0.08
Ag	107	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Cd	111	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<12[p1]	<0.1
In	115	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04
Sn	118	1080	464	238	0.69	0.41	74.1	<0.05	0.48
Sn	120	1090	467	236	0.69	0.40	72.1	<0.05	0.47

Table 13 (*Continued*)

Element	Isotope	Sample #9	Sample #10	Sample #11	Sample #12	Sample #13	Sample #14	Sample #15	Sample #16
Sb	121	<0.08	<0.08	<0.08	<0.08	<0.08	<0.08	<4[q1]	<0.08
Te	125	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6
Cs	133	<0.02	<0.02	<0.02	0.09	<0.02	<0.02	<0.02	<0.02
Ba	137	0.11	0.56	0.30	0.07	0.10	0.07	0.18	0.18
La	139	0.03	<0.03	0.03	<0.03	<0.03	<0.03	0.03	0.04
Ce	140	0.15	0.12	0.15	0.08	0.09	0.10	0.13	0.23
Pr	141	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Nd	146	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Sm	147	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Eu	153	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
Gd	157	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06
Tb	159	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Dy	163	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04
Ho	165	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Er	166	<0.09	<0.09	<0.09	<0.09	<0.09	<0.09	<0.09	<0.09
Tm	169	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Yb	172	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04
Lu	175	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04
Hf	178	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04
Ta	181	<0.07	<0.07	<0.07	0.11	0.12	<0.07	<0.07	0.10
W	182	0.2	<0.2	0.2	0.2	<0.2	<0.2	<0.2	<0.2
Re	185	0.17	<0.05	0.15	<0.05	<0.05	0.14	<0.05	<0.05
Os	189	4.7	2.1	<0.7	<0.7	<0.7	<0.7	<0.7	<0.7
Ir	193	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Pt	195	<0.07	<0.07	<0.07	<0.07	<0.07	<0.07	<0.07	<0.07
Au	197	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Hg	202	0.3	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2
Tl	205	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Pb	208	0.33	0.36	0.31	0.25	0.30	0.24	0.39	0.42
Bi	209	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04
Th	232	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
U	238	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02

[a] Signal saturated. [b] $^{35}Cl^{16}O$ interference. [c] $^{40}Ar^{12}C$ interference. [d] $^{37}Cl^{16}O$ interference. [e] $^{47}Ti^{16}O$ interference. [f] $^{49}Ti^{16}O$ interference. [g] $^{48}Ti^{16}O$ interference. [h] $^{40}Ar^{35}Cl$ interference. [i] $^{40}Ar^{37}Cl$ interference. [j] $^{40}Ar^{48}Ti$ interference. [k] $^{40}Ar^{50}Ti$ interference. [l] $^{81}Br^{12}C$ interference. [m] $^{46}Ti^{47}Ti$ interference. [n] $^{79}Br^{16}O$ interference. [o] $^{48}Ti^{47}Ti$ interference. [p] $^{79}Br^{16}O_2$ interference. [q] $^{81}Br^{40}Ar$ interference.

lytical problems, its application to more mundane uses is simply good resource management. We have found that the extensive use of ICP-MS for this metal survey analysis does not degrade its capability for even more challenging tasks.

4. Conclusion

The proposed method uses direct dissolution of the samples either in 1 or 80% nitric acid solutions and uses ICP-MS as the analytical tool to survey

metals of pharmaceutical interest and in fact almost all the elements in the periodic table. Excellent spike recoveries were achieved for all the samples used in this study. The availability of ICP-MS in the laboratory provides a rapid, sensitive, precise, simple, and element-specific, from semi-quantitative to quantitative alternative to the USP and EP heavy metals tests.

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