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Determination of tungsten in bulk drug substance and intermediates by ICP-AES and ICP-MS

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Abstract

A quick and sensitive method has been developed and validated for the determination of tungsten in bulk drug substance and intermediates using either Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES) or Inductively Coupled Plasma Mass Spectrometry (ICP-MS). Sample preparation is by direct dissolution with a 80:20 (v/v) concentrated nitric acid:deionized water mixture and avoids labor intensive and potentially hazardous digestion techniques. Excellent agreement was found between ICP-AES and ICP-MS results and between Merck results and Microwave Induced Plasma Mass Spectrometry (MIP-MS) results provided by an independent raw material vendor.

Keywords: Tungsten analysis; Bulk drug substance and intermediates; Inductively coupled plasma atomic emission spectroscopy; Inductively coupled plasma mass spectroscopy

1. Introduction

Tungsten containing catalysts, such as sodium tungstinate, may be employed in organic synthesis to make bulk pharmaceutical chemicals. Since the toxicological properties of tungsten have not been thoroughly investigated, and little information is available relating to normal routes of occupational exposure, close monitoring of residual tungsten levels in process intermediates and final drug substance is needed.

Tungsten is not widely analyzed by spectroscopic methods as are many other elements [1–16], and only one recent paper reported tungsten content in biological fluids, hair, and nails [1]. The majority of the others were on tungsten in rocks and minerals [4,6,13], and ores and concentrates [8,11,12,14,15]. Very little literature is available on tungsten in pharmaceuticals [16]. Much of the early work was performed using N_2O acetylene flame Atomic Absorption Spectrometry, which suffers from poor sensitivity. More recent work was done by Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES) and/or inductively coupled plasma mass spectrometry (ICP-MS). Most of these analyses involved sample decomposition using heated acid mixtures. These procedures can be long and tedious, and most of

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the analysis time is used to convert the solid samples into liquid form before the actual spectroscopic measurement.

This paper presents an ICP-AES and ICP-MS method for the determination of tungsten content in intermediates and bulk drug substances combined with a simple and straight forward sample preparation procedure which involves direct dissolution of the samples with a 80:20 (v/v) concentrated nitric acid, deionized water mixture. Spectral interferences were monitored by using two W lines in ICP-AES, and by using three different isotopes in ICP-MS. Excellent agreements were found between ICP-AES and ICP-MS results and between results obtained by an independent laboratory using Microwave Induced Plasma Mass Spectrometry (MIP-MS).

2. Experimental

2.1. Reagents and materials

Concentrated nitric acid (70%, trace metal grade) was purchased from Seastar (Sidney, B.C., Canada). NIST traceable tungsten stock standard solution (1000 ± 3 μg ml in 2% HNO_3 and 1% HF), was purchased from High-Purity Standards (Charleston, SC). Deionized water was prepared by passing distilled water through a Milli-Q water system (Millipore Corporation, Bedford, MA). The bulk drug substance and intermediates were obtained from Merck Research Laboratories (Merck & Co., Inc., Rahway, NJ), and from an independent raw material vendor. The structures of the intermediates and bulk drug substance are not provided in this paper and are not relevant to the analysis being conducted.

2.2. Preparation of standards

80:20 (v/v) concentrated nitric acid:deionized water mixture was used as calibration blanks for both ICP-AES and ICP-MS. Working standards of 0.10, 0.50, and 1.0 μg ml^{-1} for ICP-AES were prepared by diluting directly the 1000 μg ml^{-1} certified tungsten stock solution with 80:20 (v/v) concentrated nitric acid:deionized water mixture. Working standards of 0.010, 0.020, and 0.040 μg ml^{-1} for ICP-MS were prepared by diluting a 10 μg ml^{-1} intermediate standard made by diluting the 1000 μg ml^{-1} certified tungsten stock solution. Since heat is released when concentrated nitric acid and water are mixed, it is important to point out the importance of diluting to the final volume after the mixture is cooled to room temperature.

2.3. Preparation of samples

Weigh approximately 0.02 g (ICP-MS) to 0.1 g (ICP-AES) of sample into a 10 ml volumetric flask, dilute to volume with premixed and cooled 80:20 (v/v) concentrated nitric acid:deionized water mixture. With shaking, bulk drug and intermediate samples were readily soluble, and in most cases, ready for analysis without further dilution.

2.4. Instrumentation

A Spectro-Flame-EOP Inductively Coupled Plasma Emission Spectrometer (SPECTRO Analytical Instruments, Fitchberg, MA) and a Perkin-Elmer Elan 6000 Inductively Coupled Plasma mass spectrometer equipped with an AS-91 autosampler were used throughout this study. The instrumental conditions and general method parameters are listed in Table 1, and Table 2, respectively.

Table 1
Spectro-Flame EOP instrument conditions and method parameters

RF power	1200 W
Coolant argon flow	15 l min^{-1}
Auxiliary argon flow	0.8 l min^{-1}
Nebulizer argon flow	1.0 l min^{-1}
Nebulizer	Modified Lichte
Operating frequency	27.12 MHz
Observation height, above the load coil	N/A (Axial configuration)
Sample delivery rate	2 ml min^{-1}
Flush time	35 s
Integration time	3.0 s
Wavelength	224.875 nm, 220.448 nm

Table 2
Elan 6000 instrumental conditions and method parameters

RF Power	1300 W
Coolant argon flow	15.0 l min^{-1}
Auxiliary argon flow	1 l min^{-1}
Nebulizer argon flow	0.90–0.95 l min^{-1}
Sample introduction system	Cross flow nebulizer with Scott spray chamber
Operating frequency	40 MHz
Sample uptake rate	1.5 ml min^{-1}
Detector mode	Dual mode
Sampler/skimmer cones	Platinum
Scanning mode	Peak hopping
Number of points per peak	1
Dwell time	40 ms
Sweeps per reading	50
Tungsten isotopes used	182, 184, 186
Internal standard used	^{209}Bi

3. Results and discussion

3.1. Sample preparations

For most atomic spectroscopic methods, it is necessary to solubilize the solid samples in a suitable solvent before it can be introduced into the instrument. In many cases, this proves to be the most crucial, challenging and time-consuming step. The intermediates and bulk drug substance evaluated in this study are all non-water soluble. Samples prepared by microwave digestion techniques in the initial stage of this study using mixed-acid yielded either incomplete digestion or non-reproducible results. Some explosion hazard was encountered while digesting these materials using acid mixtures.

Although these materials are soluble in some organic solvents (e.g. acetonitrile), extremely high melting and boiling points of tungsten carbide formed in the furnace make measurements by graphite furnace atomic absorption spectrometry difficult. ICP or ICP-MS analysis of metals in organic matrices are also not routine. Normally, organic solvents cannot be aspirated into the ICP without extinguishing it, thus making special accessories, such as a spray chamber chiller and oxygen connection to the torch assembly, indispensable. In addition, standard-matching organic solvents is also quite burdensome. It was found by the authors that all the materials involved are readily soluble in concentrated nitric acid. The 20% deionized water was employed to reduce the viscosity of the solution and to minimize nitric acid consumption. It was also observed that more than 20% deionized water in the solution would result in a slow reprecipitation of the dissolved material.

The direct dissolution approach not only dramatically shortens sample preparation by avoiding digestion and keeping sample handling to a minimum, but also reduces the chance for cross-contamination. A sample can be weighed directly into an autosampler tube, and after adding 8.0 ml of concentrated nitric acid, 2.0 ml of deionized water, and vortex mixing, is ready for analysis. The complete sample preparation step for a sample takes about 1–2 min compared to 1–2 h for digestion procedures.

3.2. Method validation

3.2.1. Matrix effect and spectral interferences

Matrix effects were minimized by making the calibration blanks and standards in the same 80:20 concentrated nitric acid:deionized water matrix as the sample. The absence of a matrix effect is evidenced by the excellent spike recoveries as shown in the discussion of accuracy (Section 3.2.4). Spectral interference was monitored by using the 224.875 nm and 220.448 nm W-lines simultaneously in ICP-AES, and by measuring three tungsten isotopes (^{182}W, ^{184}W, and ^{186}W) in ICP-MS. The agreement in results as shown later in Table 7, between the two tungsten lines in ICP-AES and between the three isotopes in ICP-MS ensures the absence of spectral interferences.

3.2.2. Linearity of the methods

The linearity of both the ICP-AES and ICP-MS methods was evaluated by calibrating both instruments with a blank and the standards listed in Section 2.2, and ensuring that the correlation coefficients of the calibration curves were better than 0.995. Then a series of standards above the upper calibration range of increasing concentrations were analyzed as samples. The linear dynamic range was defined as being the concentration for which the results (in concentration units) were within $\pm 10\%$ of the true value (prepared value). The results are listed in Table 3 and Table 4, for the ICP-AES, and ICP-MS, respectively. For simplicity, only the results obtained with the 224.875 nm W line in ICP-AES, and the results obtained using ^{184}W in ICP-MS are listed, but similar results were obtained with the other wavelength and other isotopes. Table 3 demonstrates that the ICP-AES can measure up to 3.0 μg ml^{-1} W in solution without dilution (92% recovery of the designated value), and Table 4 shows that the ICP-MS can analyze at least to 5.0 μg ml^{-1} W in solution without dilution (96% recovery of the prepared value), which is equivalent to 300 ppm and 2500 ppm W in original solid bulk drug substance, and intermediate samples, respectively. The reason for the wider ICP-MS linear dynamic range than for the ICP-AES is the dual detector mode that is available on the Elan 6000 which was used to extend the linear range by using the analog mode of the detector in conjunction with pulse counting. A detector cross-calibration was performed for all three isotopes of tungsten during initial instrument set up.

Table 3
Linearity of the ICP-AES

Measured value (μg ml^{-1})	Designated value (μg ml^{-1})	Recovery (%)
2.10	2.0	105
2.77	3.0	92
3.39	5.0	68

Table 4
Linearity of the ICP-MS

Measured value (μg ml^{-1})	Designated value (μg ml^{-1})	Recovery (%)
0.094	0.100	94
0.477	0.500	95
0.956	1.000	96
1.93	2.000	96
4.92	5.000	98

3.2.3. LOD/LOQ

Limit of detection (LOD) and limit of quantitation (LOQ) were determined by analyzing ten replicate aliquots of the spiked calibration blanks as samples (with rinsing between samples) at concentrations between two to five times the estimated limits of detection (based on the standard deviation of ten replicate blanks). The spiked levels in these calibration blanks are 0.05 μg ml^{-1} for ICP-AES, and 0.0005 μg ml^{-1} for ICP-MS. The LOD is defined as three times the standard deviation of the ten measurements, and the LOQ is ten times the standard deviation. The results are listed in Table 5, only results obtained using the 224.875 nm W line in ICP-AES, and results obtained using ^{184}W in ICP-MS are given. As shown in Table 5, when using the 224.88 nm W line in ICP-AES, the LOQ of the method is 0.06 μg ml^{-1} W in solution, which corresponds to 6.0 ppm W in the original solid sample, and when using W isotope 184 in ICP-MS, the LOQ of this method is 0.000246 μg ml^{-1} W in solution, which corresponds to 0.12 ppm W in the original solid sample.

3.2.4. Accuracy of the methods

Since no relevant standard reference materials (SRM's) are available at this time, accuracy of the methods was evaluated by the recoveries of known amounts of W spiked (prior to sample dissolution) into one bulk drug sample and one intermediate sample at 5.0 and 10.0 ppm levels (5.0 ppm was the initial control level for tungsten in the drug substance and intermediates), and also by spiking another intermediate sample at 5.0 and 50.0 ppm levels. Table 6 summarizes the excellent recovery results for both the ICP-AES and ICP-

Table 5
LOD/LOQ study

Number of run	ICP-AES		ICP-MS	
	In solution (μg ml^{-1})	In solid sample (ppm)	In solution (μg ml^{-1})	In solid sample (ppm)
1	0.0581	5.81	0.000514	0.26
2	0.0672	6.72	0.000509	0.26
3	0.0602	6.02	0.000539	0.27
4	0.0504	5.04	0.000493	0.25
5	0.0529	5.29	0.000490	0.25
6	0.0492	4.92	0.000473	0.24
7	0.0544	5.44	0.000487	0.23
8	0.0504	5.04	0.000458	0.23
9	0.0484	4.84	0.000479	0.24
10	0.0504	5.04	0.000464	0.23
Average	0.0542	5.42	0.000491	0.25
STD	0.0060		0.0000246	
LOD (3 × STD)	0.018	1.8	0.0000738	0.04
LOQ (10 × STD)	0.06	6	0.000246	0.12

Table 6
Recovery study

Sample ID	Drug substance	Drug substance	Intermediate #1	Intermediate #1	Intermediate #2	Intermediate #2
Spiked level	5.0 ppm	10.0 ppm	5.0 ppm	10.0 ppm	5.0 ppm	50.0 ppm
ICP-AES Recovery (%)		101		111		112
ICP-MS Recovery (%)	101	98	107	99	104	106

MS. The accuracy of the methods is also evaluated by analyzing one bulk drug sample and 12 intermediate samples from different sources by both ICP-AES and ICP-MS. The results are summarized in Table 7. Results listed in reference value #1 were obtained by ICP-MS with the samples prepared by microwave digestion using an acid mixture, while results listed in reference value #2 came from the independent raw material vendor, who used a microwave induced plasma mass spectrometer combined with a completely different sample preparation method using an organic solvent. Excellent agreement was found between ICP-AES and ICP-MS results and between our results and the MIP-MS results.

3.2.5. Precision of the methods

Precision of the methods were determined by repeated analysis of a bulk drug substance sample spiked with 1.0 ppm W (ICP-MS) or 10.0 ppm W (ICP-AES), and two intermediate samples spiked with 1.0 ppm W (ICP-MS) or with 15.0 and 35.0 ppm W (ICP-AES), and by evaluating the degrees of the reproducibility in terms of standard deviation (SD) and relative standard deviation (RSD) among the replicate results from the same sample. As shown in Table 8, the SDs and %RSDs for spiked bulk drug substance and for spiked and unspiked intermediate samples are all less than 1.3, and 3.5, respectively. The results obtained with ICP-MS present particularly good SDs and

Table 7
Accuracy study

Sample ID	ICP-AES Result (ppm)		ICP-MS Result (ppm)			Reference Value #1 (ppm)	Reference Value #2 (ppm)
	W 224.875 nm	W 220.448 nm	^{182}W	^{184}W	^{186}W		
Drug substance	<6	<5	<0.12	<0.12	<0.12	<0.12	
Intermediate #1	<6	<5	0.74	0.72	0.74	<0.12	
Intermediate #2	17	17	16.0	16.1	15.9	16	
Intermediate #3	26	25	25.9	25.8	25.3	26	
Intermediate #4	12	13	10.9	11.0	11.0		
Intermediate #5			9.5	9.5	9.5		10
Intermediate # 6			12.8	12.9	12.9		14
Intermediate #7			9.5	9.6	9.6		9
Intermediate #8	17	17	15.8	15.9	15.9		17
Intermediate #9	28	28	29.2	29.6	29.5		30
Intermediate #10	17	17	16.8	17.1	17.1		18
Intermediate #11	15	16	16.5	16.5	16.5		16
Intermediate #12	17	18	20.2	20.6	20.5		22

RSDs due to the fact that it has superior sensitivity and an internal standard (Bi) was also used.

4. Conclusion

Either the ICP-AES or the ICP-MS method combined with the direct dissolution of the sample in 80:20 (v/v) concentrated nitric acid:deionized water mixture can be used for the determination of tungsten in bulk drug substance and intermediates, precisely, accurately, and rapidly. The LOD and LOQ were determined to be 1.8, and 6 ppm, respectively, in the solid samples for the ICP-AES using the 224.875 nm W line, and the LOD and LOQ were determined to be 0.04, and 0.12 ppm, respectively, in the solid samples for the ICP-MS using W isotope 184. The ICP-AES method covers the range up to 300 ppm tungsten in the solid samples, and the ICP-MS method covers the range at least up to 2500 ppm tungsten in the solid samples.

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Table 8
Precision study

Number of run	Drug substance		Intermediate #1		Intermediate #2	
	Spiked 10.0 ppm ICP-AES	Spiked 1.0 ppm ICP-MS	Spiked 15.0 ppm ICP-AES	Spiked 1.0 ppm ICP-MS	Spiked 35.0 ppm ICP-AES	Unspiked ppm ICP-MS
1	9.82	1.18	14.1	1.61	49.2	15.82
2	9.85	1.24	15.4	1.59	52.1	15.81
3	9.32	1.21	15.1	1.59	50.3	16.02
4	10.30	1.19	15.3	1.60	52.8	16.03
5	10.12	1.18	15.9	1.60	51.6	15.85
6	9.70	1.23	15.1	1.59	51.5	16.14
Mean	9.85	1.21	15.2	1.60	51.3	15.95
SD	0.34	0.026	0.59	0.0082	1.30	0.137
RSD (%)	3.46	2.15	3.90	0.51	2.53	0.86

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