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Using AAS to analyze Cadmium, Lead, Arsenic and Mercury in Pharmaceutical Products

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ABSTRACT

Purpose: this poster demonstrates that with AAS, the required detection limits for arsenic, cadmium, lead and mercury as described in the USP Chapters 232 and 233 are achieved.

Methods: An Atomic Absorption Spectrometer with Zeeman Graphite Furnace and Autosampler were used for the Cd, Pb and As analysis. This system was chosen because both Zeeman and Deuterium background correction can be utilized for graphite furnace analysis. This provides the capability to perform accurate analysis with almost any matrix. With the addition of a vapor generation accessory the Atomic Absorption Spectrometers are capable of performing the Hg analysis.

Results: this poster shows that AAS is a cost effective alternative to ICP-AES /ICP-MS when only a small number of elements are to be considered, whilst meeting validation and data security requirements.

INTRODUCTION

The United States Pharmacopeia (USP) has recently introduced two new chapters (232 and 233) dealing with elemental impurities in pharmaceutical products. Permissible limits are given in Chapter 232 for a number of elements. These limits were revised in Feb–2016 (Table 1).
Chapter 233 defines two standard methods (ICP-AES and ICP-MS) but these do not have to be used provided an alternative method meets the validation requirements specified. There are two levels of validation depending on whether the method only indicates that the samples are above or below the limit (Limit Procedure) or gives a concentration (Quantitative Procedure). Both procedures were carried out for Cadmium, Lead, Arsenic and Mercury in an oral electrolyte formulation.

MATERIALS AND METHODS

Instrumentation

The Thermo Scientific™ iCE™ 3500 Atomic Absorption Spectrometer with GFS35Z Zeeman Graphite Furnace and Autosampler (Figure 1) were used for the analysis of Cd, Pb and As. The Thermo Scientific™ iCE™ 3300 Atomic Absorption Spectrometer combines with Thermo Scientific™ VP100 vapor generation system (Figure 2) was used for analysis of Hg. The unique VP100 vapor generation accessory uses a continuous flow system to produce a steady-state signal and provides excellent analytical precision. The continuous flow of reagents ensures that the system is self-cleaning, reducing memory effects and increasing sample throughput. The VP100 vapor generation accessory is entirely controlled by the Thermo Scientific™ SOLAAR Software, meaning that developing a method and running an analysis is extremely simple.

Figure 1. iCE™ 3500 AAS.

Figure 2. VP100 vapor generation system.

Sample Preparation

The maximum dose for the oral electrolyte formulation is 5 sachets a day (corresponding to approximately 25 g in total). From Table 1 it can be seen that the maximum daily intake must not exceed 15 µg of Arsenic, 5 µg of Cadmium, 5 µg of Lead and 30 µg of Mercury. The stock sample solutions were made up of 12.5 g of the formulation in 0.5 l 1% nitric acid and deionized water. The J value (target concentration) was thus 15 $\mu g \cdot kg^{-1}$ for arsenic, 5 $\mu g \cdot kg^{-1}$ for Cadmium, 5 $\mu g \cdot kg^{-1}$ for lead and 30 $\mu g \cdot kg^{-1}$ for mercury. All solutions were freshly prepared before each test within standards from Fisher Scientific. The regulations state that for a solid sample the volume of solvent can be chosen to ensure that the analyte concentration is in a range compatible with the sensitivity of the instrument.

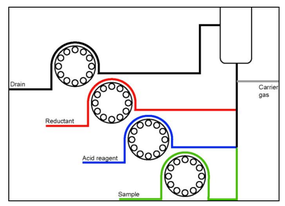
Table 1. Elemental impurities for drug products (from USP Chapter 232).

Element	Class	Oral Daily Dose PDE(µg/day)	Parenteral Daily Dose PDE(µg/day)	Inhalational Daily Dose PDE(µg/day)
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

VP100 vapor generation accessory reagent preparation

The VP100 vapor generation accessory requires both a reductant and an acid solution to perform the reactions that form the gaseous mercury (Figure 3). For this application the reductant was a solution of 0.5% $NaBH_4$ stabilized in 0.1% NaOH. The acid solution was 20 %. The parameters used for the VP100 vapor generation accessory are shown in Table 2.

Figure 3. Schematic of the VP100 vapor generation accessory showing how the sample, acid and reductant are mixed.



Method Development

Automatic Ash Atomize optimization plots were run for arsenic, cadmium and lead in the sample matrix to ensure an optimal furnace temperature program was achieved. Prior to carrying out the optimization the drying phase of the cycle was setup by watching the sample behavior using the graphite furnace television (GFTV) feature. The GFTV allows the inside of the graphite furnace cuvette to be viewed on screen via a camera and is a standard feature of the iCE 3500 AA.

Table 2. VP100 Vapor Generation Accessory Parameters.

Pump Speed	40 rpm
Gas Flow	200 $ml \cdot min^{-1}$
Acid Reagent	20 % HCl
Reductant	0.5 % $NaBH_4$ in 0.1% NaOH
Measurement Delay	70 s

The optimal furnace program was determined to be the same for cadmium and lead, the furnace parameters are shown in the table 3, for arsenic the optimal furnace program is shown in the table 4.

RESULTS

Limit procedure results

Arsenic passes the test as the Spike 1 corrected value is within 15% of the standard value (95.6%) and Spike 2 is less than the standard value.

Cadmium passes the test as the Spike 1 corrected value is within 15% of the standard value (107%) and Spike 2 is less than the standard value.

Lead passes the test as the Spike 1 corrected value is within 15% of the standard value (112%) and Spike 2 is less than the standard value.

Mercury passes the test as the Spike 1 corrected value is within 15% of the standard value (103%) and Spike 2 is less than the standard value.

The results are presented in Table 5.

Table 3. Optimized Graphite Furnace program for cadmium and lead.

Temp (°C)	Time (s)	Ramp (°C/s)	Gas Type	Gas Flow (l/min)	Read	Temp control
100	30	10	Argon	0.2		
350	20	150	Argon	0.2		
1100	3	0	Argon	Off	√	√
2500	3	0	Argon	0.2		√

Table 4. Optimized Graphite Furnace program for arsenic.

Temp (°C)	Time (s)	Ramp (°C/s)	Gas Type	Gas Flow (l/min)	Read	Temp control
100	30	10	Argon	0.2		
1250	20	150	Argon	0.2		
2550	3	0	Argon	Off	√	√
2700	3	0	Argon	0.2		√

Table 5. Detectability test corrected data and as percentage of standard.

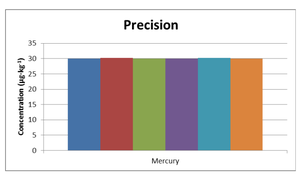
Element	Std (Abs)	Spike 1 (Abs)	Spike 2 (Abs)	Spike 1 (%Std)
Arsenic (As)	0.478	0.457	0.418	95.6%
Cadmium (Cd)	0.343	0.367	0.326	107%
Lead (Pb)	0.090	0.101	0.089	112%
Mercury (Hg)	0.112	0.115	0.090	103%

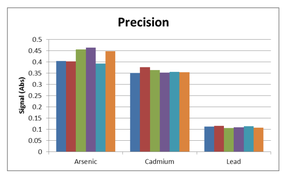
Precision test

All elements pass the test as their RSD is less than 20% (0.5% for mercury, 7.4% for arsenic, 2.7% for cadmium and 3.2% for lead). This is the same as the repeatability test for Quantitative Procedures.

The results are presented in Figure 4 and 5.

Figure 4. Precision test results.





Ruggedness

All elements pass having an RSD of less than 25%, see table 6.

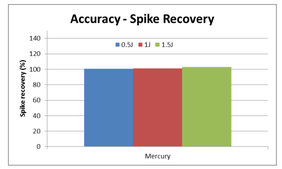
Table 6. Raw data from a sample run on different days.

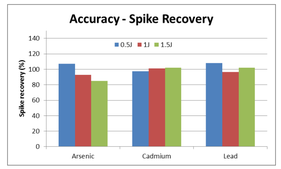
Element	Day 1 (Abs)	Day 2 (Abs)	Day 3 (Abs)	RSD
Arsenic (As)	0.478	0.421	0.435	6.7%
Cadmium (Cd)	0.375	0.378	0.372	0.8%
Lead (Pb)	0.112	0.106	0.100	5.6%
Mercury (Hg)	0.112	0.115	0.111	1.8%

Accuracy

All elements pass as the recoveries are in the range 70-150%.

Figure 5. Spike recovery at 0.5, 1.0 and 1.5 times J (the target concentration).





CONCLUSIONS

The Thermo Scientific iCE AAS Spectrometer Series with VP100 vapor generation accessory system and GFS35Z Zeeman Graphite Furnace provides a simple, low cost means of complying with the requirements of USP chapters 232 and 233. The CFR 21 Part 11 compliance of the Thermo Scientific™ SOLAAR*security* Software enables the system to be used in regulated laboratories. The instrument has sufficient sensitivity to be used for all the target elements. For the particular product that was tested it has been demonstrated that arsenic, cadmium, lead and Mercury meet the requirements of the alternative method validation procedure for both Limit and Quantitative Procedures.

REFERENCES

1. EPA, the CFR 21 Part 11.
2. USP chapters 232 and 233
3. Application Note 43381 – Using cold vapor generation atomic absorption to determine mercury impurities in pharmaceutical products.
4. Application Note 43384 – Using graphite furnace atomic absorption to meet the requirements of elemental impurity analysis in pharmaceutical products for arsenic, cadmium and lead.

TRADEMARKS

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