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Research Article

ESTIMATION OF HEAVY METALS IN DIFFERENT BRANDS OF AMLODIPINE BESYLATE TABLET DOSAGE FORMS BY INDUCTIVELY COUPLED PLASMA-MASS SPECTROMETRY (ICP-MS)

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ABSTRACT

The aim of this study is to estimate heavy metals in different brands of amlodipine besylate tablet dosage forms by inductively coupled plasma-mass spectrometry (ICP-MS). In many laboratories around the world as the instrument of choice for performing trace metal analysis is ICP-MS. ICP-MS using Kinetic Energy Discrimination (KED) mode was used. Samples are assimilated using multi-wave sample digestion system. Each element standards of conc. 1000 mg/l was prepared and followed by serial dilution with 2% nitric acid. The validation was performed as per USP232 standards for the different brands of commercially available samples. Parameters such as linearity, accuracy, precision, Limit of detection (LOD), Limit of Quantification (LOQ) were evaluated. Calibration curves were linear and co-relation co-efficient (r^2) was 0.995 for all elements. LOD is divided into two components, method detection limit (MDL) and instrumental detection limit (IDL). The MDL limits (in ppb) of ^{75}As, ^{111}Cd, ^{208}Pb, ^{202}Hg, ^{52}Cr, ^{60}Ni were found to be 8.55, 0.15, 1.35, 1.5, 1.95 and 5.4 respectively. The IDL limits (in ppb) of ^{75}As, ^{111}Cd, ^{208}Pb, ^{202}Hg, ^{52}Cr, ^{60}Ni were found to be 0.005, 0.003, 0.003, 0.003, 0.0018, and 0.0021 respectively. In three different brands of amlodipine besylate tablets, elements like ^{75}As, ^{111}Cd, ^{208}Pb, ^{202}Hg, ^{52}Cr, ^{60}Ni were estimated by a validated method of ICP-MS. The obtained results show us that this method could be used in the laboratory for the estimation of trace elements in amlodipine besylate in tablet dosage form using ICP-MS.

Keywords: Inductively coupled plasma-mass spectrometry, Amlodipine besylate, multi-wave sample digestion system, trace elements, validation.

INTRODUCTION

Inductively coupled plasma mass spectrometry (ICP-MS) is capable of detecting metals and several non-metals at lower concentrations (part per quadrillion, ppq). This is achieved by ionizing the sample with inductively coupled plasma and then using a mass spectrophotometer to separate and quantify those ions. ICP-MS is applicable to the determination of sub-microgram per litre concentrations of a large number of elements in water samples and in waste extracts or digests[1-2]. When dissolved constituents are required, samples must be filtered and acid-preserved prior to analysis. No digestion is required prior to analysis for dissolved elements in water samples. Acid digestion prior to filtration and analysis is required for groundwater, aqueous samples, industrial wastes, soils, sludge's, sediments and other solid wastes for which total (acid-soluble) elements are required[3]. ICP-MS has been applied to the determination of over 60 elements in various matrices.

ICP MS is used in different fields such as geochemistry, environmental and life sciences, food, chemical, semiconductor, nuclear industries, forensic science and archaeology[4]. Most of the manufacturers produce reliable and robust instruments with very low detection limits (parts per trillion ppt) and high spectral resolution (10000) for multi-element analysis[5-6]. ICPMS has also become the method of choice in elemental analysis[7-8], covering a field of covalently bound elements, coordinated metals, metalloids and organometallic metabolites[9]. In the pharmaceutical industry, ICP-MS is used for detecting inorganic impurities in pharmaceuticals and their ingredients[10].

The primary reasons for the growing popularity of ICP-MS can be summarized in a few points:

- Instrument detection limits are at or below the single part per trillion (ppt) levels for much elements of the periodic table
- Analytical working range is nine orders of magnitude
- Productivity is unsurpassed by any other technique
- Isotopic analysis can be achieved readily

Monitoring and control of metal impurities in medicinal preparations is of importance to the pharmaceutical industry as drug production and formulation processes often involve either direct addition of metals (as catalysts) or non-intentional addition via contaminated reagents or contact of the pharmaceutical ingredients with metal surfaces during production[11-12]. Analysis of trace elements in pharmaceutical formulations is an important task which includes the analysis of metal impurities in pharmaceutical dosage forms. Presence of toxic elements even at low concentrations has an inherent toxic effect on human health.

Hence it is important to determine the level of toxic metal impurities in pharmaceutical formulations and to ensure the quality of finished pharmaceutical dosage form is within USP 232 regulations[13-14]. The objective of USP 232 is to set limits on the amounts of elemental impurities in pharmaceuticals[15].

ICP-MS is recognized by the USP as the preferred technique for the detection of trace elements in pharmaceutical products, offering considerable advantages over the more traditional precipitation-based methods. Overall, the methods offer exceptional analytical performance, sensitivity and speed for multi-elemental measurements in complex matrices. In the present work, the following toxic and trace elements As, Hg, Pb, Cd, Cr and Ni were determined in different brands of amlodipine besylate tablet dosage forms. Inductively coupled plasma mass spectrometry (ICP-MS) was used throughout the study.

Drug profile

Amlodipine Besylate is chemically 3-Ethyl-5-methyl (±)-2-[(2-amino ethoxy) methyl]-4-(2-chloro phenyl)-l, 4-dihydro-6-methyl-3, 5-pyridine dicarboxylate, monobenzene sulphonate with a molecular weight of 567.05. It is a white to half-white crystalline powder, slightly soluble in water and propanol, freely soluble in methanol, sparingly soluble in ethanol. It acts as anti-hypertensive, vasodilator, calcium channel blocker, anti-anginal drug and available in the form of tablets with different doses like 2.5, 5 and 10 mg.

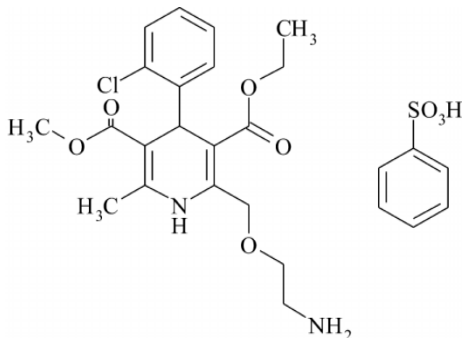

Figure 1: Structure of amlodipine besylate

MATERIAL AND METHODS

Chemicals

Materials used are amlodipine besylate standard, tablets of three different brands, HNO_3, H_2O_2, HF, Milli-Q water, Balance, Multi wave 3000 digestion system and NexIon Tuning Solution.

Instrument details

Perkin Elmer - NexION - 300D ICP-MS with NexION software, quadrupole analyser and photo multiplier tube detector were used in the analysis.

Instrument configuration/conditions

NexION 300D ICP-MS, using Kinetic Energy Discrimination (KED) mode was used for analysis. Extended Dynamic Range (EDR) was utilized to enable the simultaneous analysis of trace and toxic elements which are present at very low levels (ppm). Hg, Pb, Cd are the metals that are analysed at very low levels (ppb) in all samples. Table 1 shows the cell parameters and Table 8 shows the instrumental conditions used.

Table 1: NexION 300D instrumental operating parameters

Sample uptake Rate	0.5 ml/min
Peristaltic pump tubing	Tygon
Flush delay	30 sec
Read delay	15 sec
Wash	45 sec
Scanning mode	Peak hopping
Detector mode	Dual
Plasma gas flow	15 l/min
Auxiliary gas flow	1.2 l/min
Nebulizer gas flow	1.06 l/min
Nebulizer	Glass, concentric
Spray Chamber	Glass, cyclonic
Injector	2 mm quartz
Rf power	1400W
Dwell time	50ms
Sweeps/Readings	30
Replicates	3
Mode	KED (He)
Sample run time	3 min/sample

Table 2: Universal cell conditions

Cell mode	Element with mass	Cell gas	Gas flow (ml/min)	Rpa	Rpq
KED	Hg 202	Helium	3	0	0.25
	Pb 208	Helium	3	0	0.25
	As 75	Helium	3	0	0.25
	Cd 111	Helium	3	0	0.25
	Cr 52	Helium	3	0	0.25
	Ni 60	Helium	3	0	0.25

Sample preparation

Samples are assimilated using multi-wave sample digestion system. This vessel is a closed digestive system which ensures all sample dissolved with the help of acids also it avoids loss of volatile elements like As, Hg. The samples are digested and analysed to confirm the results.

About 0.5 g of sample was weighed and taken in reference vessel. 5 ml nitric acid, 1 ml hydrogen peroxide solution, 0.5 ml hydrogen fluoride were added and the solution was mixed well to let the total wetting of the sample. Similarly blank solution is prepared. After closing all vessels, it should be kept undisturbed for 5-10 minutes for the reaction takes place, then put it into the microwave and run a program given below.

Table 3: Microwave digestion program

Step	Power (W)	Ramp (Min)	Hold (Min)	Fan
1	600	10	10	1
2	800	10	10	1
3	0	0	20	3

P: 0.5 bar/s, temp: 220 ^{0}C, P: 55 bar

After sample digestion was completed samples were transferred to 50 ml Tarsons tubes. Final volume was made up to 25 ml with ASTM type I water (Milli Q Water). The blank was also prepared in similar way.

Standard preparation

Single element standards of conc. 1000 mg/l was prepared and followed by serial dilution with 2% nitric acid to produce 1, 10, 50 µg/l concentrations of working standard. Blank was prepared.

RESULTS AND DISCUSSION

Results of system validation (ICP-MS)

Table 4: System validation

Analyte	Mass number	Intensity limits	Mode
Beryllium	9.0	> 3000	Standard
Magnesium	24.0	> 2000	Standard
Indium	114.9	> 5000	Standard
Uranium	238.1	> 4000	Standard
Cesium oxide	155.9	<= 0.025	Standard
Cesium	139.9	>0	Standard
Ce^{++}	70.0	<= 0.03	Standard
Background	220.0	<= 1	Standard

Oxide interferences (Ceo/ Ce^{++})

The low level of MO+ (typically CeO/ Ce is measured since the CeO bond is very strong and CeO is stable in the plasma) is a highly desirable property in an ICP-MS instrument. The CeO/ Ce ratio is often referred to as a measure of plasma robustness in ICP-MS. More robust plasma (lower CeO/ Ce) reduces interference correction equations, and also makes interference removal techniques – such as CRCs – more efficient.

Method validation

Method validation was according to ICH and USP < 233 > guidelines.

A. **Linearity**

The linearity of calibration curves (Mass V_s concentration) in standard solution was checked over the concentration range of about 1-25µg/l. The regression line relating standard concentrations of drug using regression analysis, the calibration curves were linear in the studied range and co-relation co-efficient (r^2) > 0.995 for all elements. The slope and correlation coefficient of standard curves (n = 3) were tabulated. The represented data was shown in Table 5.

Table 5: Linearity plot

Analyte	Mass	Curve type	Slope	Correlation coefficient
As (Arsenic)	74.922	Linear Thru Zero	903.76	0.999667
Cd (Cadmium)	110.904	Linear Thru Zero	11807.90	0.999850
Pb (lead)	207.977	Linear Thru Zero	78264.00	0.999173
Hg (Mercury)	201.971	Linear Thru Zero	34546.34	0.999999
Cr (Chromium)	51.941	Linear Thru Zero	7068.85	0.999475
Ni (Nickel)	59.933	Linear Thru Zero	2797.19	0.999533

B. Accuracy (Recovery)

Accuracy of the method was determined by recovery studies. To the three samples, the reference standard concentrations between 50-150% were added. The recovery studies were performed three times and the percentage recovery and percentage relative standard deviation of the recovery were calculated for drugs and shown in Table 7-9.

The spike recoveries for each repeat of all three samples at the 0.5 J, J and 1.5 J spike levels are shown in Table 6.

Table 6: Sample spike levels

Element	Component limit (µg/ml or ppm)	0.5 J (ppm)	J (ppm)	1.5 J (ppm)
^{75}As	1.5	0.75	1.5	2.25
^{202}Hg	1.5	0.75	1.5	2.25
^{208}Pb	1	0.5	1	1.5
^{111}Cd	0.5	0.25	0.5	0.75
^{63}Cu	250	125	250	375
^{52}Cr	25	12.5	25	37.5
^{60}Ni	25	12.5	25	37.5

J-Component Limit

USP 233 states that the acceptance criteria for this test are recoveries of between 50 and 150% for the mean of three repeat analyses of each sample at above spike levels. Table 7-9 shows that these criteria are easily achieved using the Perkin Elmer NexION 300D ICP-MS, with average recoveries at both spike levels ranging from 80 to 120%.

Table 7: Recovery studies of sample 1

Elements	Added amount (ppm)	Recovery (%)	% RSD
^{52}Cr	12.5	99	2.6
	17	106	3
	37.5	110	1.2
^{60}Ni	12.5	106	4.6
	25	96	3.5
	37.5	104	5.8
^{75}As	0.75	91	2.6
	1.5	97	3.2
	2.25	105	4.7
^{202}Hg	0.75	98	0.7
	1.5	87	3.1
	2.25	92	2.5
^{206}Pb	0.5	106	0.7
	1	112	1.3
	1.5	110	1.9
^{111}Cd	0.25	83	2.6
	0.5	92	2.5
	0.75	85	2

Table 8: Recovery studies of sample 2

Elements	Added amount (ppm)	Recovery (%)	% RSD
^{52}Cr	12.5	108	2.7
	25	92	3.0
	37.5	112	5.2
^{60}Ni	12.5	104	2.5
	25	106	3.5
	37.5	87	7.2
^{202}Hg	0.75	101	2.7
	1.5	106	2.6
	2.25	112	2.8
^{206}Pb	0.5	103	1.2
	1	98	0.6
	1.5	108	6.3
^{111}Cd	0.25	91	2.6
	0.5	97	3.2
	0.75	105	4.7
^{75}As	0.75	101	2.7
	1.5	106	2.6
	2.25	112	2.8

Table 9: Recovery studies of sample 3

Elements	Added amount (ppm)	Recovery (%)	% RSD
^{52}Cr	12.5	106	1.5
	17	97	2.7
	37.5	92	3.9
^{60}Ni	12.5	93	1.7
	25	105	4.6
	37.5	110	6.5
^{75}As	0.75	98	1.3
	1.5	92	2.9
	2.25	88	4.1
^{202}Hg	0.75	98	3
	1.5	95	1.8
	2.25	86	2.4
^{206}Pb	0.5	108	2.4
	1	102	1.5
	1.5	110	1
^{111}Cd	0.25	84	4.2
	0.5	89	1.9
	0.75	98	0.4

C. **Precision**

The sample was replicated three times (n = 3) using concentrations of 1 (LQC), 10 (MQC), 25 (HQC) for all elements. Computation of the coefficient of variations (C.V) for these three samples was done. All elements were calibrated with standard curve concurrently prepared on the day of analysis. The results were illustrated in the Table 10-12.

Results for the analysis of three independent aliquots of all samples (ppb) were shown in following tables.

Sample 1

Table 10: Sample 1 concentrations in ppb

Element	^{75}As	^{111}Cd	^{206}Pb	^{202} Hg	^{52}Cr	^{60}Ni
Sample 1	2.18	0.01	0.007	-0.04	0.071	1.63
SD	0.090	0.001	0.000	0.001	0.005	0.019
%RSD	4.1	6.0	0.7	3.9	1.6	1.2

Sample 2

Table 11: Sample 2 concentrations in ppb

Element	^{75}As	^{111}Cd	^{206}Pb	^{202} Hg	^{52}Cr	^{60}Ni
Sample 2	2.110	0.013	0.011	-0.05	4.81	1.92
SD	0.020	0.001	0.002	0.001	0.057	0.042
%RSD	0.9	7.7	1.8	1.4	1.2	0.3

Sample 3

Table 12: Sample 3 concentrations in ppb

Element	^{75}As	^{111}Cd	^{206}Pb	^{202} Hg	^{52}Cr	^{60}Ni
Sample 3	2.110	0.013	0.105	-0.047	4.809	11.920
SD	0.020	0.001	0.002	0.001	0.057	0.042
%RSD	0.9	7.7	1.8	1.4	1.2	0.3

D. **Repeatability**

Repeatability provides short-term variation in measurement results and is used to estimate the likely difference between results obtained in a single batch of analysis. The repeatability standard deviation, variance, probability distribution function, etc must be determined with at least 6 degrees of freedom (DF). This can be achieved for example, by analyzing 7 times in a series with one test item (DF = 6), 4 times in a series with 2 test items (DF = 6), 3 times in a series with 3 test items (DF = 6) etc.

Instrumental repeatability may be determined by the injection of the standard solutions that are used to prepare the working calibration curve as well as an incurred or fortified sample at each of the spike levels 7 times. These injections should be done in random order to minimize bias. Calculate mean, standard deviation and percent relative standard deviation.

Method repeatability may be determined by preparing pools of sample material with levels of the analyte (s) at or near the concentrations used for method recovery studies. This may be done by using incurred material or by fortifying material (blank or incurred) with the required amount of the analyte (s). Replicate extracts are prepared of each of these samples and analyzed by one analyst on the same day. Calculate mean, standard deviation and percent relative standard deviation.

E. **Limit of Detection (LOD)**

For most modern analytical methods the LOD may be divided into two components, method detection limit (MDL) and instrumental detection limit (IDL).

1. **Method detection limit (MDL)**

The MDL can be defined as the smallest amount or concentration of an analyte that can be reliably detected from the background for a particular matrix (by a specific method). It is applied for the analysis of specific analytes within a matrix. All matrix interferences must be taken into account. The MDL limits (in ppb) of ^{75}As, ^{111}Cd, ^{208}Pb, ^{202}Hg, ^{52}Cr, ^{60}Ni were found to be 8.55, 0.15, 1.35, 1.5, 1.95 and 5.4 respectively.

Method detection limits (MDL) calculated from 3 * the standard deviation of the mean of the 10 separate consecutive blanks. Method detection limits (in µg, relative to the original 0.5 g sample)

2. **Instrumental detection limit (IDL)**

Instrument detection limit (IDL) defined as the smallest amount of an analyte that can be reliably detected or differentiated from the background on an instrument (i.e. instrumental noise). As the instrument sensitivity increases, the IDL decreases and vice versa.

The Instrument detection limits (IDL) for the target elements, calculated from 3 * standard deviation of the blank (for the original undiluted samples). The IDL limits (in ppb) of ^{75}As, ^{111}Cd, ^{208}Pb, ^{202}Hg, ^{52}Cr, ^{60}Ni were found to be 0.005, 0.003, 0.003, 0.003, 0.0018, and 0.0021 respectively.

F. **Limit of Quantification (LOQ)**

Quantification limits based on 10 separate consecutive blanks were measured. These were calculated from 10 * the standard deviation of the mean and The limits (in ppb) of ^{75}As, ^{111}Cd, ^{208}Pb, ^{202}Hg, ^{52}Cr, ^{63}Cu, ^{60}Ni were found to be 28.5, 0.5, 4.5, 5, 6.5, 25.5 and 18 respectively.

G. **Sample analysis results**

The concentration determined from each target element in the pharmaceutical materials under investigation is shown in Table 13 below. The results shown here have been corrected for 50 x sample dilution and shown the concentrations measured in original 0.5 gm sample (in mg/l).

Table 13: Sample analysis results (final conc. in PPM)

Wt (per 0.5 ml)	^{75}As	^{111}Cd	^{208}Pb	^{202}Hg	^{52}Cr	^{60}Ni
Sample 1 (ppm)	0.109	n.d	n.d	n.d	0.0155	0.0815
Sample 2 (ppm)	0.105	n.d	0.0055	n.d	0.2405	0.096
Sample 3 (ppm)	0.1	0.0056	0.006	n.d	0.0225	0.0915

n.d = not detected

Table 13 shows that, above table shows that, in all three samples, most of the target elements were either present at low concentrations or not detected at all (i.e. present at concentrations lower than the detection limit). However, as was found to contain around 0.193, 0.1055, 0.1 µg of as in all samples respectively. Cd was not detected in the sample 1 and 2. In sample 3 however, was found to contain around 0.0056 µg of Cd (in 0.5 g of sample). The concentration of Pb was not detected in sample 1 and it was found to be 0.0055 and 0.006 µg of Pb in respective samples 2 and 3. These levels, although easily detectable with the NexION 300D ICP-MS.

Comparison with USP-232 guidelines

The USP 232 sets limits on the amounts of elemental impurities in pharmaceuticals. The USP 232 applies to drug substances, drug products (including natural-source and rDNA biologics) and excipients.

Table 14: Comparison with USP-232 limits

Element	Component limit (ppm)	Sample 1 (ppm)	Sample 2 (ppm)	Sample 3 (ppm)	Pass/Fail
^{75}As	1.5	0.1	0.1	0.1	Pass
^{202} Hg	1.5	-	-	-	Pass
^{208}Pb	1	-	0.005	0.006	Pass
^{111}Cd	0.5	-	-	0.0056	Pass
^{52}Cr	25	0.015	0.240	0.022	Pass
^{60}Ni	25	0.0815	0.096	0.0915	Pass

Table 14 shows all the specified USP-232 elements present in different brands of Amlodipine Besylate tablet dosage forms have been found to be within the acceptance criteria, indicating that all the three samples have passed the USP-232 component limits.

CONCLUSION

In the present work, the following toxic and trace elements As, Hg, Pb, Cd, Cr and Ni were determined in different brands of Amlodipine Besylate tablet dosage forms. Inductively coupled plasma mass spectrometry (ICP-MS) was used throughout the study. The examined samples were dissolved in a high-pressure microwave system using supra-pure nitric acid, hydrogen peroxide and hydrogen fluoride (HF) and the concentration of As, Hg, Pb, Cd, Cr and Ni were determined using ICP-MS. The effect of the carbon residue in the digest solution on the determination result was eliminated by this sample preparation technique.

The method was validated for all validation parameters as per USP 233 guidelines. The linearity ranges for specified USP-232 elements were 1-50 µg/l. Recovery for all elements in samples are within the required acceptance criteria of 80-120%. The correlation co-efficient was > 0.995 and excellent repeatability (< 10% RSD) for the spiked samples were obtained, illustrating the reliability of the tested method using the NexION 300D ICP-MS.

The results of analysis showed that the content of Ni in dosage form preparations ranged between 0.008 mg/l and 0.096 mg/l with the lowest content found in sample 1 and highest content was found in sample 3. The analysis of chromium content in dosage forms indicated that the mean value of chromium ranged between 0.015 mg/l and 0.240 mg/l. The lowest value of chromium was found in samples 1 and 2 and highest in sample 3. Arsenic was found in all three samples but below MDL. For lead, mercury, cadmium analysis, the intensity measurements for all samples were too low which means that the Cd, Hg concentrations were not detectable.

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