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METHOD DEVELOPMENT AND VALIDATION OF ELEMENTAL IMPURITIES IN AMITRIPTYLINE HYDROCHLORIDE TABLETS BY ICP/MS

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ABSTRACT

An Inductively Coupled Plasma Mass Spectrometry (ICP-MS) method was developed for determination of elemental impurities in Amitriptyline Hydrochloride tablets as per ICH Q3D. New US FDA and EMA regulations came into effect from Jan 2018 as industry standard requirements for the determination of inorganic elemental impurities using ICP-OES or ICP-MS analytical techniques. The method development was optimized for the determination of the class 1 and class 2A elemental impurities listed in ICH Q3. The proposed method was validated for System suitability, Specificity, Linearity, LOD and LOQ determination, Recovery, Precision, and Range. All the parameters were found within the acceptable limits as per ICH Q3D. The Linearity of elemental impurities was in the range of LOQ to 200% of specification level as per ICH Q3D. ICP/MS method was specific, accurate, precise and suitable for the analysis of elemental impurities in Amitriptyline Hydrochloride tablets.

KEYWORDS

Inductively Coupled Plasma Mass Spectrometry (ICP-MS), Elemental (Inorganic) impurities, Permitted daily exposure (PDE), ICH guideline Q3D and Method validation guideline Q2(R1).

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INTRODUCTON

Elemental impurities pose toxicological concerns and do not provide any therapeutic benefit to the patient, their levels in drug products should be controlled within acceptable limits. In general, FDA recommends that the manufacturer of any U.S. marketed drug product follow ICH Q3D[1]. recommendations to establish appropriate procedures for identifying and controlling elemental impurities in the drug product based on risk assessment and product-specific considerations, unless the drug product must comply with USP<232>requirements[2].

An elemental impurity in drug product arises from several sources; they may be added intentionally in the synthesis of drug product component (e.g. Catalysts) or may be present as a contamination and subsequently detected in drug product.

The development of an analytical methodology for elements of interest should be free of chemical interferences and possesses an allowable linear dynamic range of the instrument. Validation is the method of demonstration that an analytical procedure is suitable for its intended purpose of measurement. Analytical procedures for both risk assessments and routine quality control testing shall be validated, and validation criterion (e.g., accuracy, precision, detection limits) should suffice the intended purpose. The analytical method validation has to accompany as per USP[3-6] and ICH Methodology guidance[7]. ICP-MS used for either single or multi-element analysis with good sensitivity over an extended linear dynamic range.

Material manufactures have to authenticate that the analytical methods to employ during the risk assessment control characteristics (e.g., precision, specificity, accuracy) such that the manufacturers are reasonably sure at 95% confidence level that the measurement is reliable for routine testing of materials in the control strategy.

Control of elemental impurities is one part of the overall control strategy for a drug product that assures that elemental impurities do not exceed the PDEs. When the level of an elemental impurity may exceed the control threshold, additional measures should be implemented to assure that the level does not exceed the PDE. Approaches that an applicant can pursue include but are not limited to:

Modification of the steps in the manufacturing process that result in the reduction of elemental impurities below the control threshold through specific or non-specific purification steps.

Implementation of in-process or upstream controls, designed to limit the concentration of the elemental impurity below the control threshold in the drug product.

Establishment of specification limits for excipients or materials (e.g., synthetic intermediates).

Establishment of specification limits for the drug substance.

Establishment of specification limits for the drug product.

Selection of appropriate container closure systems.

SPECIFICATION LIMIT

The limit of below elemental impurities is taken ICH Q3D, Option 1: Common permitted concentration limits of elements across drug product components for drug products with daily intake of NMT 10grams.

METHOD DEVELOPMENT

Plastic ware

Use PFA (Perfluoroalkoxy alkane) /polypropylene or polystyrene volumetric flask/ Tube measuring cylinder for solution preparations in the study.

Preparation of Diluent

Accurately measured and transfer 30.0mL of Concentrated Nitric acid and 10.0mL of Concentrated hydrochloric acid into a 500mL volumetric flask containing about 200mL of LC-MS grade water and then make up the volume with LC-MS grade water and mix thoroughly.

Preparation of Internal standard stock solution

Accurately pipette out 0.1mL of each Scandium, Yttrium and Bismuth standard solution (about 1000ppm) into a 50mL volumetric flask and then make up the volume with diluent and mix thoroughly.

Preparation of Gold standard stock solution

Use 1000ppm gold standard solution as such.

Add 0.05mL of Gold standard stock solution and 0.125mL internal standard stock solution in to each level of calibration standard before make up to the volume with diluent.

Standard Check Solution (150% Level)

Accurately pipette and transfer 1.50mL of Standard stock solution-2 into 25mL volumetric flask/Tube, add 0.050mL gold standard stock solution and 0.125mL internal standard stock solution and dilute to volume with diluent. Or use Calibration standard solution level 150% as standard check solution.

Preparation Blank

Accurately Pipette and transfer 0.25mL of internal standard stock solution and 0.10mL gold standard

stock solution into a 50mL volumetric flask and dilute to volume with diluent.

Preparation Sample blank Solution

Prepare as same as sample solution preparation without adding sample.

Preparation Sample Solution

Take 10 tablets and crushed these tablets with the help of clean and dry mortal and pistol. Then weigh the sample.

Accurately weigh and transfer about 0.200g of sample in to sample digestion vessel, add 1.0mL hydrogen peroxide, 4.0mL nitric acid, gradually add 2mL hydrochloric acid and 0.10mL gold standard stock solution and keep at least 30 min for pre digestion. Then close the digestion vessel, place in microwave sample digestion system, digest the sample by using Sample digestion program for Microwave Digestion System.

After completion of digestion cycle, open the digestion vessel slowly after cool down up to the room temperature and the remove gases, then transfer digested sample in 50.0mL volumetric flask/Tube, add 0.250mL internal standard stock solution and dilute to volume with water (Some milky solution may appear). Centrifuge the sample solution at 4000RPM for 10 min. After complete cycle of centrifuge keep the sample steady at least 30min. There after take the supernatant (Clear solution) part of sample solution and filter through 0.45µm PTFE syringe filter and filtered solution shall be use for analysis.

Preparation of Spike Sample Solution: [At specification limit]

Weigh accurately and transfer about 0.200g of sample in sample digestion vessel, add 1.0mL hydrogen peroxide, 4.0mL nitric acid, gradually add 2.0mL hydrochloric acid, 0.10mL gold standard stock solution, 2.0mL of standard stock solution-2 and keep at least 30min. for pre digestion. Then close the digestion vessel, place in microwave sample digestion system, digest the sample by using Sample digestion program for Microwave Digestion System.

After completion of digestion cycle, open the digestion vessel slowly after cool down up to the room temperature and the remove gases, then transfer digested sample in 50.0mL volumetric flask/Tube, add 0.250mL internal standard stock solution and dilute to volume with water (Some milky solution may appear). Centrifuge the sample solution at 4000RPM for 10 min. After complete cycle of centrifuge keep the sample steady at least 30min. Thereafter take the supernatant (Clear solution) part of sample solution and filter through 0.45µm PTFE syringe filter and filtered solution shall be use for analysis.

Preparation of Spike Sample Solution: [At LOQ level]

Weigh accurately and transfer about 0.200g of sample in sample digestion vessel, add 1.0mL hydrogen peroxide, 4.0mL nitric acid, gradually add 2.0mL hydrochloric acid, 0.10mL gold standard stock solution, 0.5mL of standard stock solution-2 and keep at least 30min. for pre digestion. Then close the digestion vessel, place in microwave sample digestion system, digest the sample by using Sample digestion program for Microwave Digestion System.

After completion of digestion cycle, open the digestion vessel slowly after cool down up to the room temperature and the remove gases, then transfer digested sample in 50.0mL volumetric flask/Tube, add 0.250mL internal standard stock solution and dilute to volume with water (Some milky solution may appear). Centrifuge the sample solution at 4000RPM for 10 min. After complete cycle of centrifuge keep the sample steady at least 30min. Thereafter take the supernatant (Clear solution) part of sample solution and filter through 0.45µm PTFE syringe filter and filtered solution shall be use for analysis.

Preparation of Spike Sample Solution: [At 150% of specification limit]

Weigh accurately and transfer about 0.200g of sample in sample digestion vessel, add 1.0mL hydrogen peroxide, 4.0mL nitric acid, gradually add 2.0mL hydrochloric acid, 0.10mL gold standard stock solution, 3.0mL of standard stock solution-2 and keep at least 30min for pre digestion. Then close the digestion vessel, place in microwave sample digestion system, digest the sample by using Sample digestion program for Microwave Digestion System.

After completion of digestion cycle, open the digestion vessel slowly after cool down up to the

room temperature and the remove gases, then transfer digested sample in 50.0mL volumetric flask/Tube, add 0.250mL internal standard stock solution and dilute to volume with water (Some milky solution may appear). Centrifuge the sample solution at 4000RPM for 10 min. After complete cycle of centrifuge keep the sample steady at least 30min. Thereafter take the supernatant (Clear solution) part of sample solution and filter through 0.45µm PTFE syringe filter and filtered solution shall be use for analysis.

System suitability acceptance criteria

Correlation coefficient of calibration standard solution should not be less than 0.995 for each element.

% drift variation of standard check Solution-After and before should be within ± 20% for each element.

% Drift Calculation

$$\%\ \boldsymbol{Drift} = \left(\frac{\mathbf{A}}{\mathbf{B}}\boldsymbol{X}\ \mathbf{100}\right) - \mathbf{100}$$

Where,

A= Concentration (ppb) of 150% level calibration Standard After sample introduction.

B= Concentration (ppb) of 150% level calibration Standard Before sample introduction.

Concentration of the analyte in the sample:

$$\text{Conc'n of elemental in sample (ppm)} = \frac{(C_S - C_{RB})}{1000} \times DF$$

Where,

CS = Observed concentration in ppb of individual elemental impurity in sample.

CRB = Observed concentration in ppb of individual elemental impurity in Sample blank.

DF = Dilution factor {Ratio of Diluent Volume (mL) /Sample wt. (g)}.

VALIDATION PARAMETERS

Limit of detection (LOD) and Limit of quantitation (LOQ)

It is the smallest amount or concentration of an analyte that can be estimated with acceptable reliability. The limit of detection is determined by aspirating appropriate number of diluted standards using regression plot of residual against linearity concentration of diluted standard.

Plotted a graph of response of analyte (at Y-axis) versus Concentration (at X-axis). Measured the residual standard deviation of response and slope through regression technique from the linearity data. Calculate the limit of detection by using the following formula.

$$\text{LOD (in ppb)} = \frac{3.3 \times \text{Residual standard deviation}}{\text{Slop}}$$

Calculate the limit of quantitation by using the following formula.

$$\text{LOQ (in ppb)} = \frac{10 \times \text{Residual standard deviation}}{\text{Slop}}$$

Preparation of diluent, internal standard stock solution, calibrations standard solution, Blank and standard check Solution as per methodology. Prepared solutions were aspirated on system.

System suitability as specified under methodology is complying with Acceptance criteria. The detection limit and quantitation limit for each elemental impurity in Amitriptyline Hydrochloride Tablets, refer Table No.1.

Precision at detection limit and quantitation limit

Each elemental impurity is detected reliably in six aspirations at LOD level solution. Hence obtained concentration can be considered LOD for each elemental impurity. The %RSD of intensity/ratio should be less than 33%.

%RSD of intensity/ratio for each elemental impurity in six aspirations of LOD precision solution was found within limit. For details, refer Table No.2.

The Quantitation limit is generally determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be quantified with acceptable accuracy and precision.

The limit of quantification is determined by establishing the six aspirations of LOQ level solution. Aspirate the blank sample and the spiked sample at LOQ level in six aspirations and calculate intensity/ratio at LOQ level. The % RSD of intensity/ratio for six aspirations of LOQ precision solution for each elemental impurity should not be more than 20.0%.

%RSD of intensity/ratio for each elemental impurity in six aspirations of LOQ precision solution was found within limit. For details, refer Table No.3.

Specificity

Specificity is an ability to assess the analyte unequivocally in the presence of matrix components. The specificity of the method is determined in terms of at particular mass of ions, response, abundance and potential interference of other elements and blank at the mass of analyte element.

To demonstrated the specificity of the method, aspirate the blank for 10 times with the linear calibration standards. The intensity of analyte in blank at particular mass should not be more than the intensity of analyte in LOD level in standard solution at particular mass.

The intensity of analyte in blank at particular mass found less than the intensity of analyte in LOD level standard solution at particular mass, refer Table No.4.

Precision

System precision

System precision was determined by aspirating blank and six replicates of standard solution at specification level (100% level standard solution) as per methodology. The %RSD was calculated for elemental impurities intensity.

The % RSD of intensities for six replicate aspiration of Standard preparation should not be more than 20.0.

The %RSD of obtained intensities of Standard solution for each element were found within acceptance criteria, refer Table No.5.

Method Precision

Method precision was determined by analyzing six spiked sample preparations at specification level as per the method representing a single batch.

Determined the results of these samples and evaluate the precision of the method by computing the %RSD results for elemental impurities. The %RSD for elemental impurities from six set of test preparation (Spike 100% level) should be NMT 20.0.

Prepared blank, spiked sample and standard solution as per description of analytical method, prepared solutions were aspirated on ICP/MS system.

The %RSD for result of elemental impurities of six spiked sample were found within limit. For details, refer Table No.6.

Intermediate Precision

Intermediate precision was determined by analyzing six spiked sample at specification level preparations as per the method representing a single batch by different analyst on different day.

% RSD for elemental impurities results were calculated.

Prepared blank, standard solution and sample solution as per description of analytical method and aspirated on ICP/MS system. Results of intermediate precision refer Table No7.

Cumulative % RSD for results of 12 spiked sample preparation for method precision and intermediate was found within acceptance criteria for each element.

Linearity

A linear relationship should be evaluated across the range of the analytical procedure. It may be demonstrated directly on the analyte by dilution of a standard stock solution using the proposed procedure. Linearity should be evaluated by visual inspection of a plot of signals as a function of analyte concentration or content. If there is a linear relationship, test results should be evaluated by appropriate statistical methods by calculation of a regression line. The correlation coefficient, y-intercept, slope of the regression line should be calculated.

The total number of five concentration LOQ to 200% of specification limit considered and aspirate the linearity solution of each concentration level to define a calibration graph. The acceptable value of the correlation coefficient (r2) should be more than 0.99 for each elemental impurity.

Correlation coefficient for the linearity curve of each elemental impurity in Amitriptyline Hydrochloride Tablets found >0.99. The method is found linear from LOQ to 200 % of sample Concentration, for details, refer Figure No.1-3.

Recovery

Recovery means the percentage of the true concentration of a substance recovered during the analytical procedure. Recovery assessed using a minimum of 3 preparations over a minimum of 3 concentration levels (3 concentrations/3 replicates each level). % recovery was calculated for each level.

Acceptable limits for a recovery result during validation should be within the range of 70% - 130%. However, the lower recovery may be acceptable if the results are consistent (i.e. good precision).

Prepared blank, sample and standards solution as per methodology. Injected blank, sample and standards solution and checked the acceptance criteria for system suitability. Accuracy was carried out for each elemental impurity at QL level, 100% and 150% of specification limit.% Accuracy for each level was found within acceptance criteria refer Table No.8.

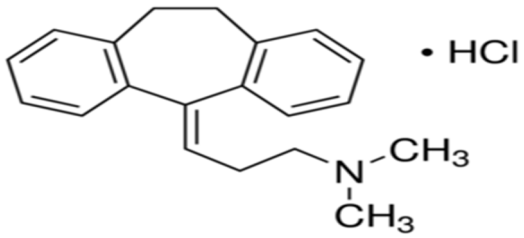
Range

Range of each elemental impurity in Amitriptyline hydrochloride tablets are linear, precise, and accurate from LOQ to 150% at specification limit.

DISCUSSION

This method involves demonstrating specificity, which is the ability of the method to accurately measure the each elemental impurity response in the presence of all potential sample components. The mass spectroscopy parameters were fixed and IPC/MS system was studied for suitability of elemental analysis. The developed method was performed for linearity, precision, Accuracy, specificity, range, LOD and LOQ.

Chemical structure of amitriptyline hydrochloride

Amitriptyline *Hydrochloride* **Chemical Name**: 3-(10, 11-dihydro-5H-dibenzo [a, d] cycloheptene-5-ylidene)-N, N-dimethylpropan-1-amine; hydrochloride **Molecular weight:** 313.9 g/mol. **Molecular Formula***:* $C_{20}H_{24}ClN$	

Details of Instruments, Chemicals, Standard and Sample used for Validation

Table No.1: The following reagents and chemicals were used during the validation study

S.No	Name of the materials	Grade	Make
1	Nitric Acid	Trace metal grade	Fisher Chemical
2	Hydrochloric Acid	Trace metal grade	Fisher Chemical
3	Hydrogen peroxide	OPTIMA	Fisher Chemical
4	Water	LC-MS	J.T Baker

Table No.2: The following instruments and equipment were used during the validation study

S.No	Instrument / Equipment Name	Make
1	ICP-MS	Perkin Elmer
2	Microwave Digester	Perkin Elmer
3	Balance	Mettler Toledo
4	Micropipette	Eppendorf
5	Centrifuge	Remi

Table No.3: The following standard and sample were used during the validation study

S.No	Name of Material	Make	Concentration (ppm)
1	Cadmium	Inorganic Ventures	1000
2	Lead	Inorganic Ventures	1000
3	Arsenic	Inorganic Ventures	1000
4	Mercury	Inorganic Ventures	1000
5	Cobalt	Inorganic Ventures	1000
6	Vanadium	Inorganic Ventures	1000
7	Nickel	Inorganic Ventures	1000
8	Scandium	Inorganic Ventures	1000
9	Yttrium	Inorganic Ventures	1000
10	Bismuth	Inorganic Ventures	1000
11	Gold	Inorganic Ventures	1000
12	**Sample:** Amitriptyline Hydrochloride Tablets USP 150mg Tablets USP 150mg		

S.No	Name of standard	Limit (ppm)
1	Cadmium	NMT 0.5ppm
2	Lead	NMT 0.5ppm
3	Arsenic	NMT 1.5ppm
4	Mercury	NMT 3ppm
5	Cobalt	NMT 5ppm
6	Vanadium	NMT 10ppm
7	Nickel	NMT 20ppm

Table No.4: Preparation of standard stock solutions-1

S.No	Name of the standard	Volume of Standard (mL)	Make up volume with diluent (mL)	Label
1	Arsenic (1000ppm)	0.3	Up to 20mL	Standard Stock solution-1
2	Cadmium (1000ppm)	0.1		
3	Lead (1000ppm)	0.1		
4	Mercury (1000ppm)	0.6		
5	Cobalt (1000ppm)	1.0		
6	Vanadium(1000ppm)	2.0		

Table No.5: Preparation of standard stock solutions-2

S.No	Name of the standard	Volume of Standard (mL)	Make up volume with diluent (mL)	Label
1	Nickel (1000ppm)	0.1	Up to 50mL	Standard stock solution-2
2	Standard stock Solution-1	0.5		

Table No.6: Preparation of Calibration standard solutions

S.No	Name of element	Concentration (in ppb)	Final Volume (mL)	Concentration (in ppb)				
				Calibration standard				
				Std-1	Std-2	Std-3	Std-4	Std-5
				Add volume of standard stock Solution -2 (mL)				
				0.250	0.50	1.00	1.50	2.00
				Level-25%	Level-50%	Level-100%	Level-150%	Level-200%
1	Cd	Concentration (in ppb)	Up to 25mL	0.5	1.0	2.0	3.0	4.0
2	Pb			0.5	1.0	2.0	3.0	4.0
3	As			1.5	3.0	6.0	9.0	12.0
4	Hg			3.0	6.0	12.0	18.0	24.0
5	Co			5.0	10.0	20.0	30.0	40.0
6	V			10.0	20.0	40.0	60.0	80.0
7	Ni			20.0	40.0	80.0	120.0	160.0

Table No.7: Sample digestion program for Microwave Digestion System

S.No	Temperature [°C]	Pressure [bar]	Ramp (Min.)	Hold	Power [%]
1	150	30	10	0	80
2	200	30	10	30	80
3	50	30	0	0	0

Table No.8: Instrument Parameters

S.No	Instrument Parameter	Condition / Input
1	Instrument	Perkin Elmer NexION 2000 B
2	Carrier Gas	Argon
3	Timing Parameters	Sweeps / Reading : 40 Readings/Replicate : 1 Number of Replicates : 3
4	Mode	KED, Cell Gas 4.0, for all Selected elements
5	Set Internal Standard	**Sc For:** V, Co and Ni
		Y For: As and Cd
		Bi For: Hg and Pb
6	Sample unit	ppb
7	Standard Unit	ppb
8	Dwell time	**50.0ms:** For- All element
9	Processing Parameter	Default input
10	Equation Parameters	Default input
11	Calibration Parameters	Mass of analyte, Mass
12	Curve type	Linear thru Zero
13	Sampling Device	Manual

Method Calibration

Table No.9: Linearity values for elemental impurities as mentioned below

Elements Standard Concentration in ppb							
	V	Co	Ni	As	Cd	Hg	Pb
STD-1	10	5	20	1.5	0.5	3	0.5

STD-2	20	10	40	3	1	6	1
STD-3	40	20	80	6	2	12	2
STD-4	60	30	120	9	3	18	3
STD-5	80	40	160	12	4	24	4

Table No.10: Mass values for elemental impurities as mentioned below

S.No	Mass of Elements Standard						
	V	Co	Ni	As	Cd	Hg	Pb
1	51	59	60	75	111	202	208

Table No.11: Mass values for internal standard as mentioned below

S.No	Mass of Internal standard		
	Sc	Y	Bi
1	45	89	209

Sampling Parameters

Table No.12: Default setting mentioned below

S.No		Time (Sec)	Speed (+ / - rpm)
1	Sample flush	35	-42
2	Read Delay	15	-35
3	Analysis	-	-35
4	Wash	45	-42

Table No.13: LOD and LOQ values

S.No	Name of Element	LOD	LOQ
		ppm	
1	Vanadium	0.833	2.50
2	Cobalt	0.416	1.25
3	Nickel	1.666	5.00
4	Arsenic	0.125	0.375
5	Cadmium	0.042	0.125
6	Mercury	0.250	0.750
7	Lead	0.042	0.125

Table No.14: Precision at LOD level

S.No	LOD Solution (ppb)						
	V	Co	Ni	As	Cd	Hg	Pb
1	2.694	1.678	6.711	0.434	0.167	1.028	0.170
2	2.672	1.670	6.638	0.442	0.166	1.037	0.170
3	2.686	1.673	6.674	0.437	0.164	1.016	0.170
4	2.661	1.647	6.695	0.442	0.168	1.028	0.170
5	2.661	1.677	6.675	0.443	0.168	1.016	0.170
6	2.645	1.649	6.582	0.425	0.167	1.035	0.171
Average	2.670	1.666	6.646	0.437	0.167	1.027	0.170
SD	0.018	0.014	0.050	0.007	0.002	0.009	0.000
% RSD	0.7	0.8	0.8	1.6	0.9	0.9	0.2

Table No.15: Precision at LOQ level

S.No	LOQ Solution (ppb)						
	V	Co	Ni	As	Cd	Hg	Pb
1	9.327	5.023	20.023	1.476	0.503	3.025	0.501
2	9.390	5.002	19.975	1.445	0.501	3.033	0.498
3	9.404	5.053	20.011	1.452	0.505	3.042	0.501
4	9.424	5.045	20.041	1.443	0.509	3.032	0.498
5	9.373	5.083	20.156	1.446	0.512	3.033	0.498
6	9.359	5.009	20.018	1.465	0.508	3.032	0.503
Average	9.380	5.036	20.037	1.455	0.506	3.033	0.500
SD	0.034	0.030	0.062	0.013	0.004	0.005	0.002
%RSD	0.4	0.6	0.3	0.9	0.8	0.2	0.4

Table No.16: Results of Specificity

S.No	BLANK	Elements						
		Intensity of LOD standard solution						
		V	Co	Ni	As	Cd	Hg	Pb
		71095	66335	69212	1467	1030	8193	10248
		Intensity of Specificity Blank						
1	Replicate-1	16216	144	323	461	9	283	218
2	Replicate-2	16112	143	319	439	7	278	228
3	Replicate-3	16000	133	310	448	8	267	217
4	Replicate-4	16169	137	321	439	8	263	227
5	Replicate-5	16067	128	325	439	7	242	222
6	Replicate-6	16206	123	314	448	8	248	225
7	Replicate-7	16339	117	315	443	6	232	223
8	Replicate-8	16456	129	309	431	6	222	211
9	Replicate-9	16348	118	301	447	7	220	220
10	Replicate-10	16623	116	313	422	6	197	227

Table No.17: System precision

S.No	Element	Standard Solution Replicate						%RSD
		1	2	3	4	5	6	
1	Vanadium	767973	766703	761423	762287	754784	754578	0.7
2	Cobalt	877150	87786	879155	868220	866184	861762	0.8
3	Nickel	881853	873094	876036	865220	869590	867462	0.7
4	Arsenic	15298	15156	15217	15099	15116	15153	0.5
5	Cadmium	13174	13081	13225	13076	12941	13009	0.8
6	Mercury	99064	982019	98720	98084	97173	97290	0.8
7	Lead	118794	119036	118296	117300	117358	118072	0.6

Table No.18: Method Precision

S.No	Element	Sample Solution Results (in ppm)						%RSD
		1	2	3	4	5	6	
1	Vanadium	10.087	9.954	10.119	9.998	10.055	9.979	0.6
2	Cobalt	4.970	4.948	4.997	4.974	4.954	4.941	0.4
3	Nickel	19.421	19.403	19.785	19.527	19.631	19.476	0.7
4	Arsenic	1.351	1.344	1.335	1.331	1.344	1.329	0.6
5	Cadmium	0.469	0.469	0.466	0.464	0.470	0.465	0.5
6	Mercury	2.961	2.987	2.970	2.921	2.954	2.917	0.9
7	Lead	0.562	0.562	0.572	0.566	0.570	0.565	0.7

Table No.19: Intermediate precision

S.No	Element	Sample Solution Results (in ppm)						%RSD
		1	2	3	4	5	6	
1	Vanadium	9.927	10.115	10.106	10.077	10.111	10.095	0.7
2	Cobalt	4.814	4.873	4.853	4.943	4.942	4.875	1.0
3	Nickel	19.304	19.681	19.521	19.648	19.749	19.650	0.8
4	Arsenic	1.420	1.406	1.409	1.395	1.399	1.425	0.8
5	Cadmium	0.469	0.471	0.475	0.476	0.478	0.474	0.7
6	Mercury	2.993	3.010	3.003	3.017	3.037	3.002	0.5
7	Lead	0.554	0.553	0.551	0.553	0.556	0.551	0.3

Table No.20: Accuracy (%Recovery)

S.No	Level (%)	Sample ID	V	Co	Ni	As	Cd	Hg	Pb
			% Recovery						
1	Control	Injection-1	ND	ND	ND	ND	ND	ND	ND
		Injection-2	ND	ND	ND	ND	ND	ND	ND
		Injection-3	ND	ND	ND	ND	ND	ND	ND
2	LOQ	Injection-1	93.6	96.5	95.0	86.7	93.6	97.3	103.2
		Injection-2	94.1	97.0	95.1	84.5	94.4	97.5	102.4
		Injection-3	94.0	96.2	95.7	87.5	94.4	98.1	102.4
Average % Recovery			**93.9**	**96.6**	**95.3**	**86.2**	**94.1**	**97.6**	**102.7**
3	100	Injection-1	99.3	96.1	94.1	94.7	92.0	99.8	104.0
		Injection-2	101.2	97.3	96.0	93.7	92.4	100.3	103.8
		Injection-3	101.1	96.9	95.2	93.9	93.2	100.1	103.4
Average % Recovery			**100.5**	**96.8**	**95.1**	**94.1**	**92.5**	**100.1**	**103.7**
4	150	Injection-1	100.9	96.7	94.1	94.3	92.5	100.0	102.7
		Injection-2	101.6	97.6	96.0	94.5	93.1	100.2	102.9
		Injection-3	101.4	98.8	95.2	94.0	93.5	100.1	103.3
Average % Recovery			**101.3**	**97.7**	**96.0**	**94.3**	**93.0**	**100.1**	**103.3**

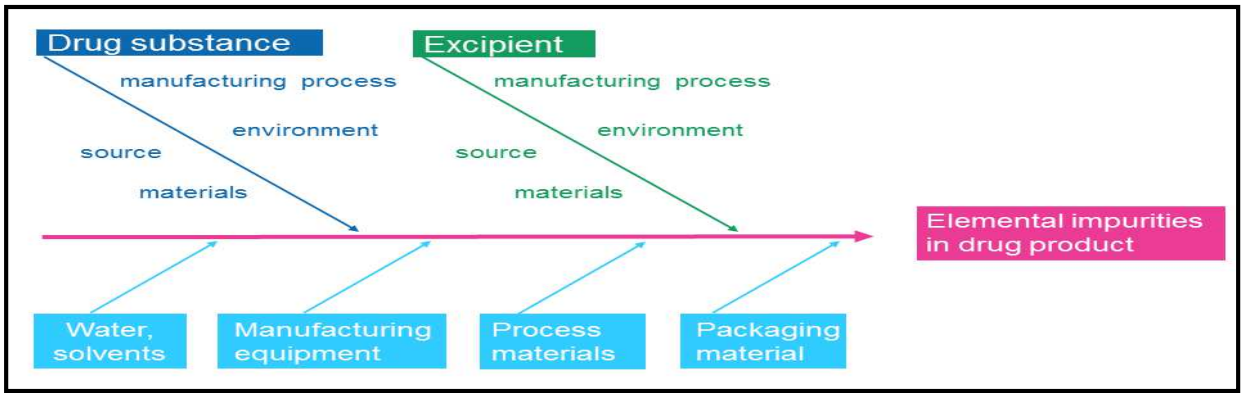


Figure No.1: Potential sources of elemental impurities

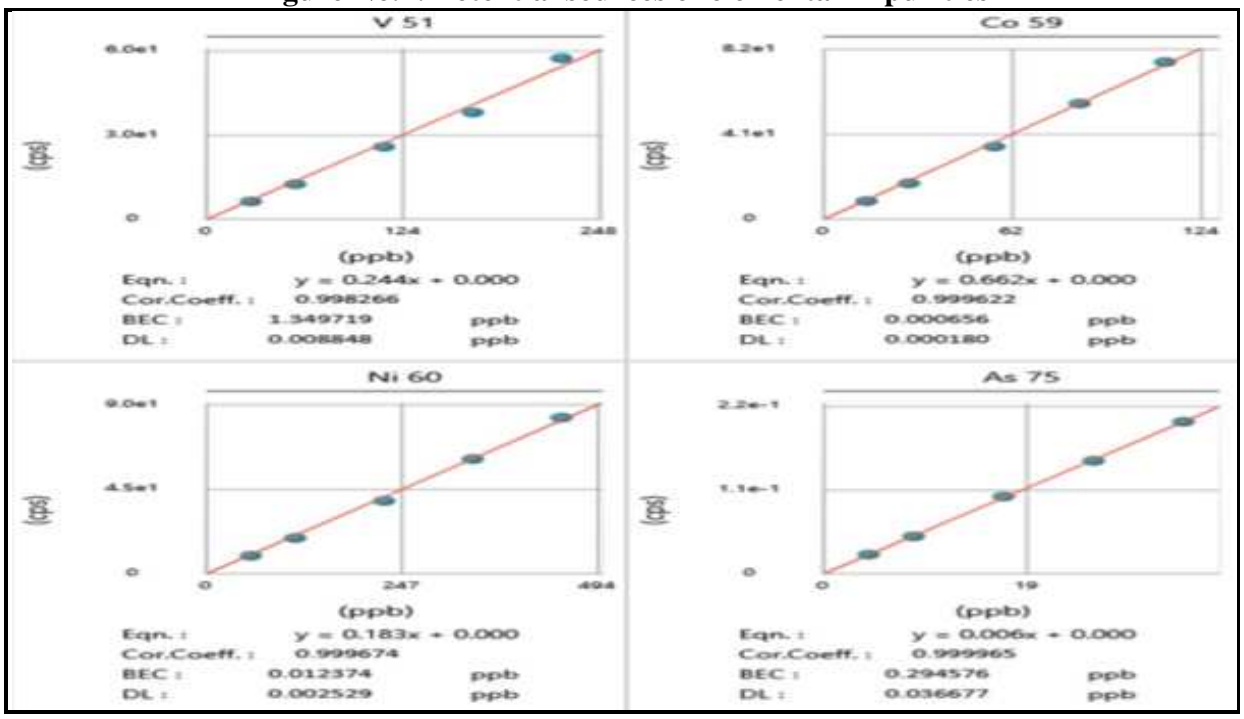


Figure No.2: Linearity Curve for Vanadium, Cobalt, Nickel and Arsenic

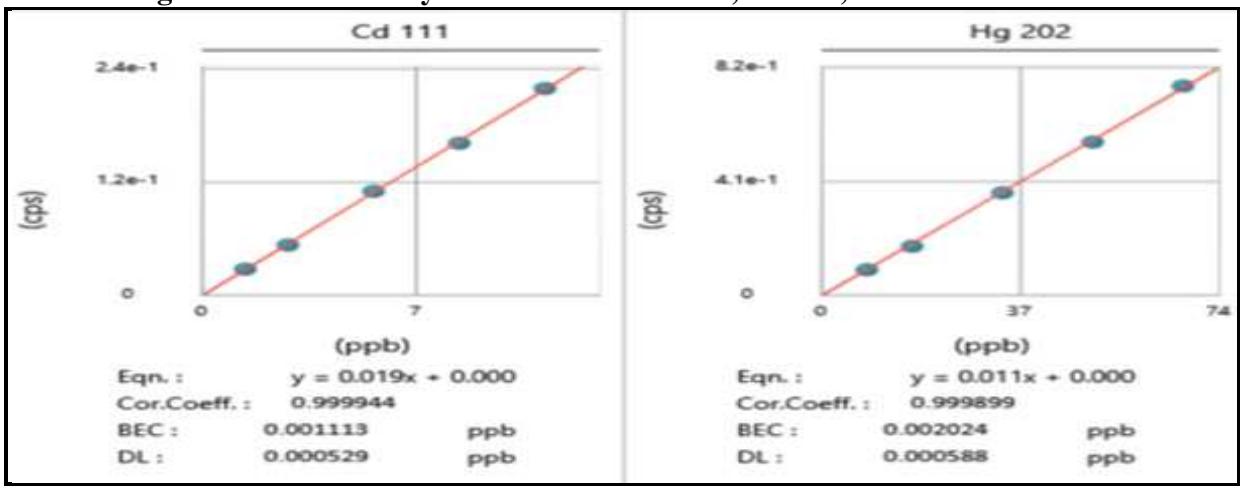


Figure No.3: Linearity Curve for Cadmium and Mercury

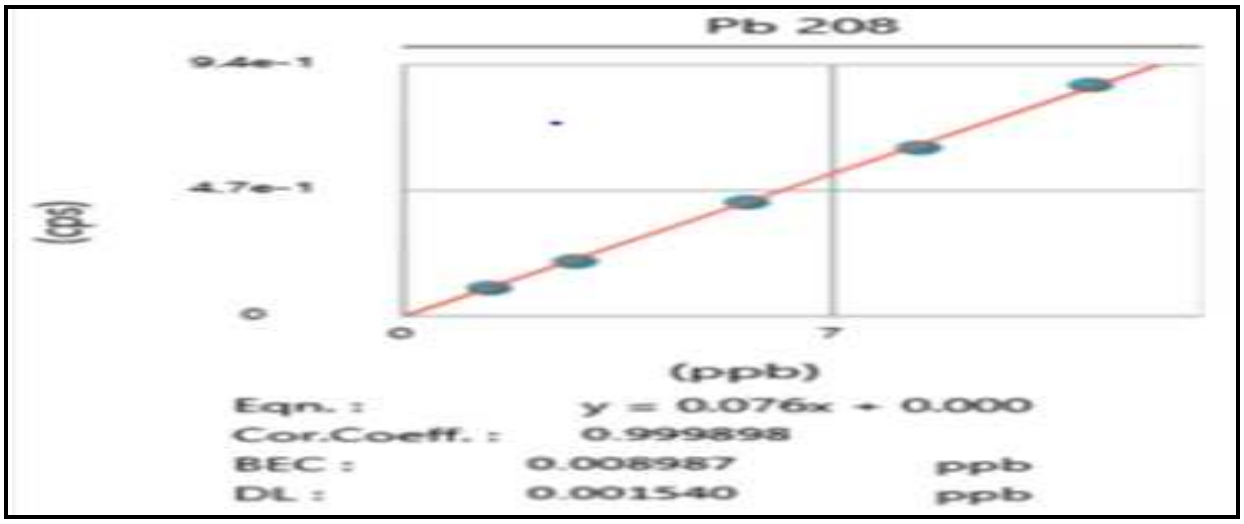


Figure No.4: Linearity curve for Lead

CONCLUSION

A simple and sensitive method for the determination elemental impurities in Amitriptyline hydrochloride Tablets by using ICP/MS was developed, validated and applied for the analysis of Amitriptyline hydrochloride Tablets samples. The sample of Amitriptyline hydrochloride Tablets was prepared with diluent. The method was validated to ensure the feasibility of the method for its application in routine analysis. The LOQs achieved through this method were lower than the 50% of specification limit of elemental impurities.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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