ejpmr, 2020,7(11), 153-160

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

METHOD DEVELOPMENT AND VALIDATION FOR ELEMENTAL IMPURITIES ANALYSIS OF MAGNESIUM STEARATE USP BY ICP-OES

ABM Mahfuz ul Alam[1]*, Shahana Shilpi[2] and M. I. R. Mamun[3]

[1]Quality Operations Department, ACI Health Care Limited, Treepordi, Sonargaon, Narayangonj, Bangladesh.
[2]Quality Control Department, Navana Pharmaceuticals Limited, Rupsi, Rupgonj, Narayangonj, Bangladesh.
[3]Department of Chemistry, University of Dhaka, Dhaka, Bangladesh.

***Corresponding Author: ABM Mahfuz ul Alam**

Quality Operations Department, ACI Health Care Limited, Treepordi, Sonargaon, Narayangonj, Bangladesh.

Article Received on 12/09/2020 **Article Revised on 02/10/2020** **Article Accepted on 22/10/2020**

ABSTRACT

Method of analysis for determination of CADMIUM, LEAD & NICKEL in magnesium stearate USP was developed in inductively coupled plasma - optical emission spectrometry (ICP-OES). The Methods were found to be highly sensitive, selective, rapid, precise, accurate and affordable which can be followed by pharmaceutical industries. The method in ICP-OES was achieved at wavelength Cd (214.439 nm), Ni (231.604 nm) Pb (220.353 nm), with a measurement condition of Read time (s): 5, RF power (kW): 1.20, Stabilization time (s): 15, Nebulizer flow (L/min): 0.70, Plasma flow (L/min): 12.0, Aux flow (L/min): 1.00, Make up flow (L/min): 0.00, Viewing mode: Radial, Viewing height (mm): 8, Use multiple conditions: 2, Viewing mode: Axial. The method was validated as per ICH guidelines for Accuracy, Precision, Ruggedness, LOD and LOQ which showed that proposed method was simple, sensitive, and highly robust for routine analysis.

KEYWORDS: ICP-OES, Magnesium Stearate, Elemental Impurities, Method Validation.

INTRODUCTION

Safety and quality of every drug product is very important. Level of Impurities in pharmaceutical products is an important quality parameters which are came from drug substances, excipients, manufacturing steps, storage and other contact surfaces. To ensure the safety and quality every manufacturer have to ensure impurities within the acceptable level to ensure quality of its manufactured product. Moreover, Major regulatory bodies are US FDA, EMA, WHO come up with regulation to control elemental impurities.

Elemental impurities include catalysts and environmental contaminants that may be present in drug substances, excipients, or drug products.[3] Regulatory bodies and Pharmacopoeia defined acceptable level of these impurities in drug products.

ICH Q3D (R1) on elemental impurities placed these into three classes based on their toxicity (PDE) and likelihood of occurrence in the drug product. The likelihood of occurrence is derived from several factors including: probability of use in pharmaceutical processes, probability of being a co-isolated impurity with other elemental impurities in materials used in pharmaceutical processes, and the observed natural abundance and environmental distribution of the element.

Class 1: The elements, As, Cd, Hg, and Pb, are human toxicants that have limited or no use in the manufacture of pharmaceuticals. Their presence in drug products typically comes from commonly used materials (e.g., mined excipients). Because of their unique nature, these four elements require evaluation during the risk assessment, across all potential sources of elemental impurities and routes of administration. The outcome of the risk assessment will determine those components that may require additional controls which may in some cases include testing for Class 1 elements.

Class 2: A elements have relatively high probability of occurrence in the drug product and thus require risk assessment across all potential sources of elemental impurities and routes of administration (as indicated). The class 2A elements are: Co, Ni and V.

Because elemental impurities do not provide any therapeutic benefit to the patient, their levels in the drug product should be controlled within acceptable limits. In some cases, lower levels of elemental impurities may be warranted when levels below toxicity thresholds have been shown to have an impact on other quality attributes of the drug product (e.g., element catalyzed degradation of drug substances).[1]

Magnesium stearate is the most commonly used Lubricant for oral solid dose product development in pharmaceuticals worldwide. This metallic salt contains stearic acid and palmitic acid at nearly equivalents composition and magnesium ion. Due to its low cost, stability and high melting point this excipient is widely used in drug development. Maximum permitted potency of magnesium stearate/unit dose of oral tablet is 400.75 mg, oral capsule is 256.4 mg and oral suspension is 57.56 mg/5 ml.[2]

The analytical procedures suggested in the USP are based on inductively coupled plasma techniques being much more specific and sensitive than the procedure used in <231> Heavy Metals. Chapter <232> Elemental Impurities – Limits states limit concentrations of a number of target elements in oral, parenteral and inhalational drug formulations (drug products), expressed as maximum daily doses (g element/day).[4]

Magnesium stearate is a commonly used excipients of oral tablet, capsules and suspension. Presence of elemental impurities in magnesium stearate plays significant role for the overall elemental impurities in these dosage form. Present study is designed to develop a suitable method using inductively coupled plasma - optical emission spectrometry (ICP-OES) to identify class 1 (Cd & Pb) and 2A (Ni) elements in magnesium stearate.

MATERIALS AND METHODS

Reagents and Chemicals

For the method development and validation following reagents and standard solution were used.

Name	Manufacturer	Grade/Potency	Batch No.
Magnesium Stearate	Valtris Specialty Chemicals	Mg Stearsate VG EP 125 Lb Orm	011209699
Sulphuric Acid	Merck	GR	K46603331
Hydrochloric Acid	Merck	ACS	K46915817
Cadmium nitrate tetrahydrate	Sigma-Aldrich	AR	MKCF3933
Nickel	AccuStandard	1000 ppm	217055079
Lead	AccuStandard	1000 ppm	216105044
Nitric Acid	Merck	ISO Emsure	K47457156
Water	In-house by Labconco water purifier	Ultra-pure	N/A

Instrumentation

Development and validation analysis was performed with ICP-OES manufactured by Agilent, USA. For sample preparation analytical, semi microbace of Sartor ius and muffle furnace of Falc were used. Other instruments used are shaking water batch by Memmert, Magnetic stirrer of Witeg. The ICP-OES operating conditions are summarized.

ICP Configuration

Auto sampler	:	Ok
Elements	:	Cadmium
Elements	:	Nickel
Elements	:	Lead

Conditions

Label (Wavelength nm)	Type	Background Correction	Number of Pixels	Condition Set
Cd (214.439 nm)	Analyte	Fitted	6	2
Ni (231.604 nm)	Analyte	Fitted	6	2
Pb (220.353 nm)	Analyte	Fitted	6	2

Common Conditions

Replicates	:	3
Pump speed (rpm)	:	12
Uptake delay (s)	:	25 (Fast pump selected)
Rinse time (s)	:	30 (Fast Pump selected)

Measurement conditions

Read time (s)	:	5
RF power (kW)	:	1.20
Stabilization time (s)	:	15
Nebulizer flow (L/min)	:	0.70
Plasma flow (L/min)	:	12.0
Aux flow (L/min)	:	1.00
Make up flow (L/min)	:	0.00
Viewing mode	:	Radial
Viewing height (mm)	:	8
Use multiple conditions	:	2
Viewing mode	:	Axial

Standards Correlation coefficient limit: 0.99.

Solution Label	Rack: Tube	Cd	Ni	Pb
		ppm	ppm	ppm
Blank	S1:1	0.0000	0.0000	0.0000
Standard 1	S1:2	0.0300	0.0500	0.1000
Standard 2	S1:3	0.0600	0.1000	0.2000
Standard 3	S1:4	0.1200	0.2000	0.4000

Calibration fit

Label (Wavelength nm)	Cd	Ni	Pb
Unit	ppm	ppm	ppm
Calibration Fit	Ok	Ok	Ok
Through Blank	Ok	Ok	Ok
Calibration Error	20 %	20 %	20 %

Samples and Calibration

Id	Rack: Tube	Solution Label	Solution Type	Weight (g)	Volume (mL)	Dilution
1	S1:1	Blank	Sample	1.0	1.0	1.0
2	1:1	Magnesium Stearate	Sample	X	50	1.0
3	S1:2	Bracketing Standard	Sample	1.0	1.0	1.0

Here, X = Weight of magnesium Stearate (in g)

Calculation

Calculate individually the amount of Cd, Pb and Ni by following,

$$\text{Amount (ppm)} = \frac{\text{Conc. in ppm} \times 50 \times 1}{1000} \times \frac{1000}{\text{Sample weight in g}}$$

Preparation of 5 % Nitric Acid (Blank/Diluent)

Dilute 38.5 mL of 65 % nitric acid in a 500 mL volumetric flask containing 250 mL of water. Volume up to the mark with water.

Preparation of standard stock solution of cadmium (1000 PPM) from cadmium nitrate tetrahydrate

Dissolve 2.8 g Cadmium nitrate tetrahydrate (Equivalent to 2.744 g of 100% Cadmium nitrate tetrahydrate) in 1000 mL volumetric flask with water and make up to the mark with the same solvent.

Preparation of standard solution of cadmium, Lead & Nickel from reference standard

Cadmium standard stock solution

Transfer 1.0 mL of Cadmium Reference Standard (1000 ppm) in a 100 mL volumetric flask and make up to mark with 5% nitric acid. Thus the stock solution is 10 ppm Cadmium standard.

Lead standard stock solution

Transfer 1.0 mL of Lead Reference Standard (1000 ppm) in a 100 mL volumetric flask and make up to mark with 5 % nitric acid. Thus the stock solution is 10 ppm Lead standard.

Nickel standard stock solution

Transfer 1.0 mL of Nickel Reference Standard (1000 ppm) in a 100 mL volumetric flask and make up to the mark with 5 % nitric acid. Thus the stock solution is 10 ppm Nickel.

Standard 1

Transfer 0.3 mL of Cadmium standard stock solution (10 ppm), 1.0 mL of lead standard stock solution (10 ppm) and 0.5 mL of nickel standard stock solution (10 ppm) in a 100 mL volumetric flask and make up to the mark with 5 % nitric acid. Thus the final strength of the solution is 0.03 ppm of Cadmium, 0.1 ppm of Lead and 0.05 ppm of Nickel.

Standard 2
Transfer 0.6 mL of Cadmium standard stock solution (10 ppm), 2.0 mL of Lead standard stock solution (10 ppm) and 1 mL of Nickel standard stock solution (10 ppm) in a 100 mL volumetric flask and make up to the mark with 5% nitric acid. Thus the final strength of the solution is 0.06 ppm of Cadmium**,** 0.2 ppm of lead and 0.1 ppm of nickel.

Standard 3
Transfer 1.2 mL of Cadmium standard stock solution (10 ppm), 4.0 mL of Lead standard stock solution (10 ppm) and 2 mL of Nickel standard stock solution (10 ppm) in a 100 mL volumetric flask and make up to the mark with 5 % nitric acid. Thus the final strength of the solution is 0.12 ppm of Cadmium, 0.4 ppm of lead and 0.2 ppm of nickel.

Test solution
Weigh about 1.0 g of sample into a silica crucible. Add about 2 mL of Sulfuric acid to moisten the sample and burn on burner until white fume fully evaporated. Then add more 2 mL Sulfuric acid in the same crucible sample and follow the same procedure. Ignite the sample at 600 ℃ for 3 hours in a muffle furnace and allow to cool. Transfer the residue in a beaker and rinse the crucible with 15 mL of hydrochloric acid and transfer the solution in the beaker. Introduce 5 mL of 65 % nitric acid to the sample solution and keep the solution on hot plate to heat until the yellow fume disappears. Transfer the solution in a 50 mL volumetric flask and make up to the mark with 5% nitric acid.

Method validation
System Suitability
To verify that the analytical system is working properly and can give accurate and precise result, the system suitability parameters were set and separately each of calibration standard solution were injected. Correlation of Coefficient was calculated and it was found 1.00 for Cd, Pb and Ni. Individual results are shown in Table: 1 and plot are presented in Figure 1:

Table 1: System suitability study.

Sample Name	Cadmium Concentration (ppm)	Lead Concentration (ppm)	Nickel Concentration (ppm)
Blank	0.00000	0.00000	0.00000
Standard 1	0.03112	0.10233	0.05016
Standard 2	0.05969	0.20083	0.09826
Standard 3	0.11998	0.39941	0.20035
Correlation coefficient	1.00 (figure 1a)	1.00 (figure 1b)	1.00 (figure 1c)

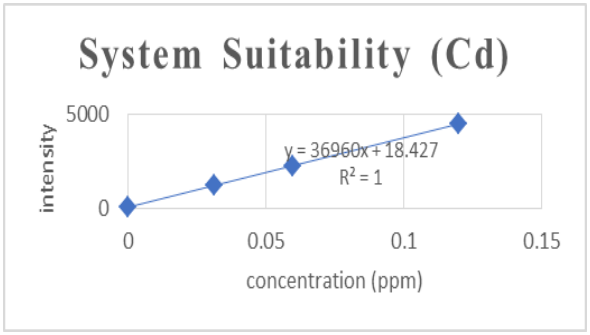

Figure: 1a.

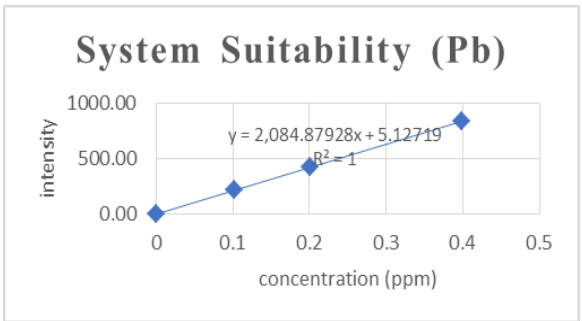

Figure: 1b.

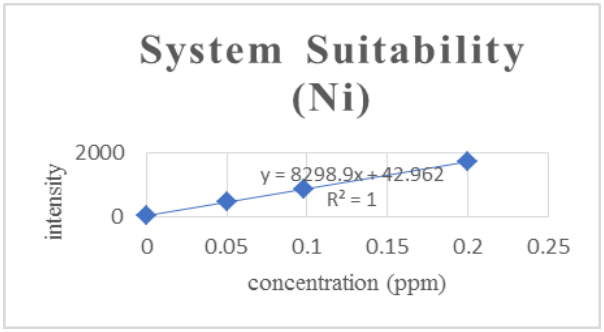

Figure: 1c.

Figure 1: Correlation of coefficient for system suitability.

System precision
Standard solutions containing Cadmium (Cd), Lead (Pb) & Nickel (Ni) in six replicates were analyzed. % RSD of the intensity of concentration of Standard-2 were calculated. Obtained results are given in table 2.

Table 2: System precision study.

Sample Name	Cadmium Concentration (ppm)	Lead Concentration (ppm)	Nickel Concentration (ppm)
Standard 1	0.06017	0.20293	0.09850
Standard 2	0.05991	0.20467	0.10095
Standard 3	0.06019	0.20235	0.09995
Standard 4	0.06041	0.2031	0.10119
Standard 5	0.06029	0.2013	0.10002
Standard 6	0.06027	0.20058	0.10150
Average	0.06020	0.20250	0.10040
Standard deviation	0.0002	0.0014	0.0011
% RSD	0.3	0.7	1.1

Method precision

In method precision, a homogeneous sample were analyzed six times. Magnesium Stearate sample was spiked with Cadmium (Cd), Lead (Pb) & Nickel (Ni) in six individual preparations and were analyzed in six replicates. The percentage RSD for the content of Cadmium (Cd), Lead (Pb) & Nickel (Ni) from six sample preparations was calculated. Obtained results are given in table 3.

Table 3: Method precision study.

Sample Name	Cadmium Concentration (ppm)	Lead Concentration (ppm)	Nickel Concentration (ppm)
Spiked sample 1	0.05116	0.16594	0.11185
Spiked sample 2	0.05146	0.16720	0.11049
Spiked sample 3	0.05172	0.17477	0.11103
Spiked sample 4	0.05153	0.16946	0.11732
Spiked sample 5	0.05085	0.1653	0.10800
Spiked sample 6	0.05172	0.16581	0.11424
Average	0.05140	0.16810	0.11220
Standard deviation	0.00030	0.00360	0.00320
% RSD	0.7	2.1	2.9

Intermediate precision

The intermediate precision was carried out to ensure that the analytical results remain unaffected with change in analyst and day. Magnesium Stearate sample was spiked with Cadmium (Cd), Lead (Pb) & Nickel (Ni) at specification limit concentration in six individual preparations and analyzed in six replicates. % RSD for the content of Cadmium (Cd), Lead (Pb) & Nickel (Ni) from six spike sample preparations were calculated. Obtained results are given in table 4A, 4B & 4C.

Table 4A: Intermediate precision study for Lead.

Sample Name	Analyst 1	Analyst 2
	Concentration (ppm)	Concentration (ppm)
Spiked sample preparation-1	0.16594	0.16570
Spiked sample preparation-2	0.16720	0.16940
Spiked sample preparation-3	0.17477	0.17000
Spiked sample preparation-4	0.16946	0.11250
Spiked sample preparation-5	0.16530	0.16570
Spiked sample preparation-6	0.16581	0.16790
Average	0.1681	0.1585
Standard deviation	0.0036	0.0226
% RSD	2.1	14.3

Table 4B: Intermediate precision study for Cadmium.

Sample Name	Analyst 1	Analyst 2
	Concentration (ppm)	Concentration (ppm)
Spiked sample preparation-1	0.05116	0.0507
Spiked sample preparation-2	0.05146	0.0508
Spiked sample preparation-3	0.05172	0.05100
Spiked sample preparation-4	0.05153	0.03250
Spiked sample preparation-5	0.05085	0.05070
Spiked sample preparation-6	0.05172	0.05130
Average	0.0514	0.0478
Standard deviation	0.0003	0.0075
% RSD	0.7	15.7

Table 4B: Intermediate precision study for Nickel.

Sample Name	Analyst 1	Analyst 2
	Concentration (ppm)	Concentration (ppm)
Spiked sample preparation-1	0.11185	0.10940
Spiked sample preparation-2	0.11049	0.11150
Spiked sample preparation-3	0.11103	0.11160
Spiked sample preparation-4	0.11732	0.0678
Spiked sample preparation-5	0.10800	0.10940
Spiked sample preparation-6	0.11424	0.11100
Average	0.1122	0.1035
Standard deviation	0.0032	0.0175
% RSD	2.9	16.9

Specificity

Blank solution, Calibration standard solutions, sample preparation and sample spiked with Cadmium (Cd), Lead (Pb) & Nickel (Ni) were prepared and analyzed separately. Obtained results are given in table 5. Concentration has increased as per spiked concentration.

Table 5: Specificity study.

Name	Sample type	Concentration (ppm)
Cadmium	Unspiked sample	0.00014
	Spiked sample	0.05109
Nickel	Unspiked sample	0.03084
	Spiked sample	0.11293
Lead	Unspiked sample	0.00505
	Spiked sample	0.16403

Limit of Quantification (LOQ) and Limit of Detection (LOD)

The aim of this study was to verify the lowest amount of an analyte in a sample that can be quantified (LOQ) with acceptable precision and accuracy under the stated experimental conditions and to verify the lowest amount of analyte that can be detected. The LOQ value and the LOD value 3 time lower than the LOQ value has been established. Obtained results are given in table 6.

Table 6: Limit of Quantification (LOQ) and Limit of Detection (LOD) study.

Established Parameter Name	Cadmium Concentration (ppm)	Intensity	Lead Concentration (ppm)	Intensity	Nickel Concentration (ppm)	Intensity
Blank	0.00	18.42937	0	9.23794	0.000	43.21257
LOD	0.06	245.54447	0.02	49.09089	0.010	124.68481
LOQ	0.02	565.88086	0.05	103.59531	0.025	250.18580

Precision at QL

Quantitation Limit was confirmed by performing the precision at Quantitation Limit level. Obtained results are given in table 7.

Table 7: Precision at QL study.

Sample Name	Cadmium Concentration (ppm)	Lead Concentration (ppm)	Nickel Concentration (ppm)
Precision at QL solution-1	0.01431	0.04753	0.02336
Precision at QL solution-2	0.01435	0.04709	0.02325
Precision at QL solution-3	0.01416	0.04541	0.02395
Precision at QL solution-4	0.01429	0.04486	0.02336
Precision at QL solution-5	0.01422	0.04566	0.02368
Precision at QL solution-6	0.01439	0.04674	0.02411
Average	0.0143	0.0462	0.0236
Standard deviation	0.0001	0.0011	0.0004
% RSD	0.6	2.3	1.5

Accuracy

To determine the accuracy of the method, 3 replicate solutions at LOQ level, 100% and 150% of target Conce ntration were prepared and analyzed. Obtained results are given in table 8A, 8B & 8C.

Table 8A: Accuracy study for Cadmium.

S/N	Sample Name	Spiked amount (ppm)	Concentration (ppm)	Recovery (%)	Average	%RSD
1	Accuracy solution at LOQ level-1	0.015	0.01209	80.6	80	1.5
2	Accuracy solution at LOQ level-2		0.01206	80.4		
3	Accuracy solution at LOQ level-3		0.01177	78.5		
4	Accuracy solution at 100 % level-1	0.06	0.04884	81.4	81	0.6
5	Accuracy solution at 100 % level-2		0.04842	80.7		
6	Accuracy solution at 100 % level-3		0.049	81.7		
7	Accuracy solution at 150 % level-1	0.09	0.07323	81.4	82	0.3
8	Accuracy solution at 150 % level-2		0.07371	81.9		
9	Accuracy solution at 150 % level-3		0.07362	81.8		

Table 8B: Accuracy study for lead.

S/N	Sample Name	Spiked amount (ppm)	Concentration (ppm)	Recovery (%)	Average	%RSD
1	Accuracy solution at LOQ level-1	0.05	0.03729	74.6	73	2.0
2	Accuracy solution at LOQ level-2		0.03613	72.3		
3	Accuracy solution at LOQ level-3		0.03597	71.9		
4	Accuracy solution at 100 % level-1	0.2	0.15385	76.9	80	4.4
5	Accuracy solution at 100 % level-2		0.15678	78.4		
6	Accuracy solution at 100 % level-3		0.16723	83.6		
7	Accuracy solution at 150 % level-1	0.3	0.23849	79.5	79	0.4
8	Accuracy solution at 150 % level-2		0.23879	79.6		
9	Accuracy solution at 150 % level-3		0.23713	79.0		

Table 8A: Accuracy study for Nickel.

S/N	Sample Name	Spiked amount (ppm)	Concentration (ppm)	Recovery (%)	Average	%RSD
1	Accuracy solution at LOQ level-1	0.025	0.01891	75.6	75	2.7
2	Accuracy solution at LOQ level-2		0.01923	76.9		
3	Accuracy solution at LOQ level-3		0.01822	72.9		
4	Accuracy solution at 100 % level-1	0.1	0.08057	80.6	79	1.9
5	Accuracy solution at 100 % level-2		0.07891	78.9		
6	Accuracy solution at 100 % level-3		0.07757	77.6		
7	Accuracy solution at 150 % level-1	0.15	0.11809	78.7	85	6.2
8	Accuracy solution at 150 % level-2		0.13308	88.7		
9	Accuracy solution at 150 % level-3		0.12975	86.5		

Linearity

Five different concentrations of Cadmium, Lead (Pb) & Nickel (Ni) standards spanning the range i.e. LOQ level, 50 % (0.05 ppm), 100 % (0.1 ppm), 150% (0.15 ppm) and 200% (0.2 ppm) of the test concentration were prepared and analyzed. Correlation coefficient between concentrations were calculated. Obtained results are given in table 9.

Table 9: Linearity study.

Sample Name	Cadmium Concentration (ppm)	Lead Concentration (ppm)	Nickel Concentration (ppm)
Standard solution (LOQ)	0.0144	0.04675	0.0238
Standard solution (75 %)	0.0288	0.09631	0.0487
Standard solution (100 %)	0.0580	0.19431	0.0972
Standard solution (150 %)	0.0878	0.29258	0.1462
Standard solution (200 %)	0.1167	0.39278	0.1967
Correlation coefficient	1.0 (figure 2a)	1.0 (figure 2b)	0.9999 (figure 2c)

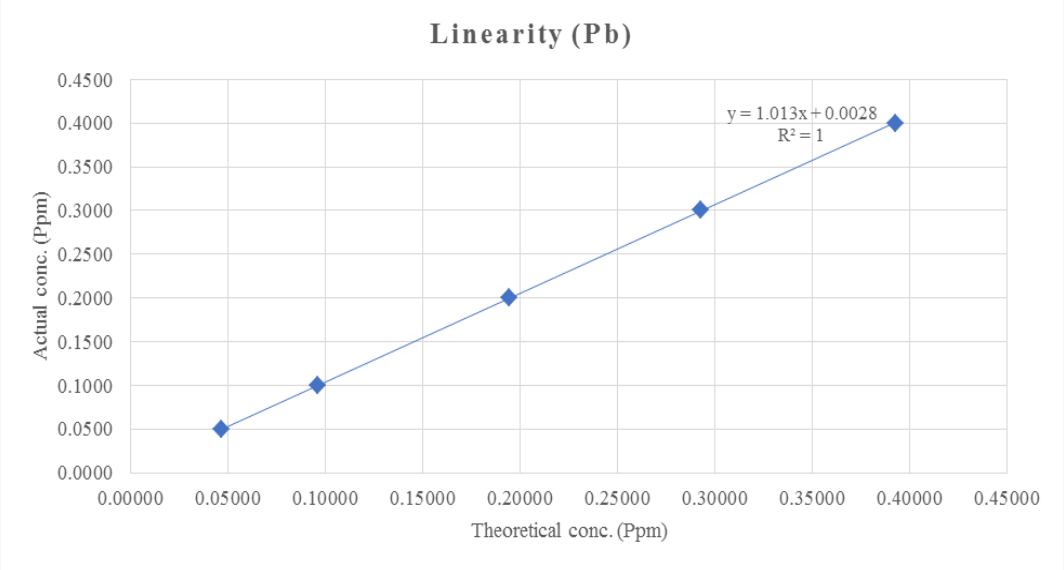

Figure: 2a.

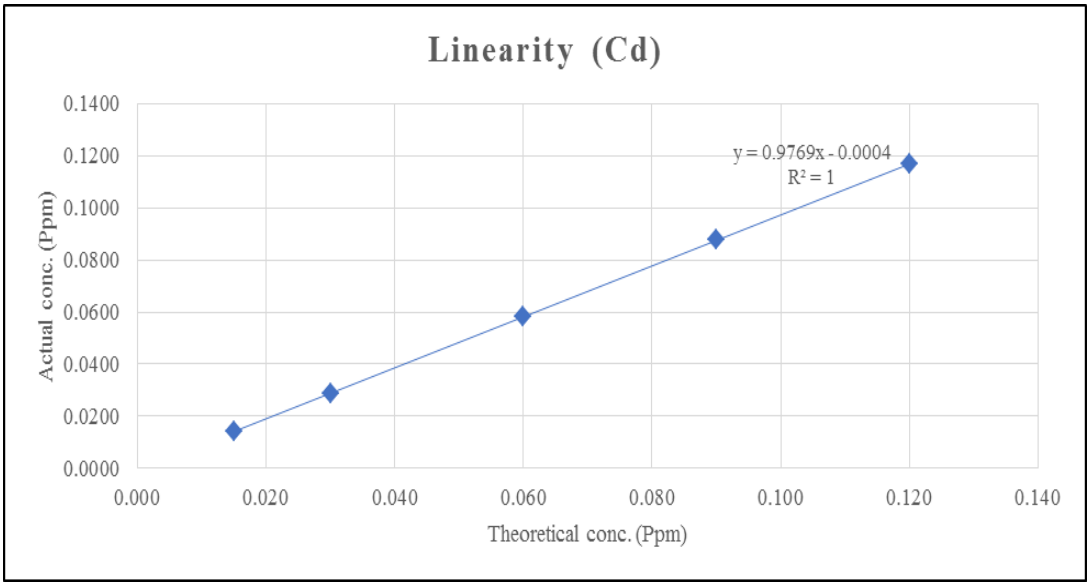

Figure: 2b.

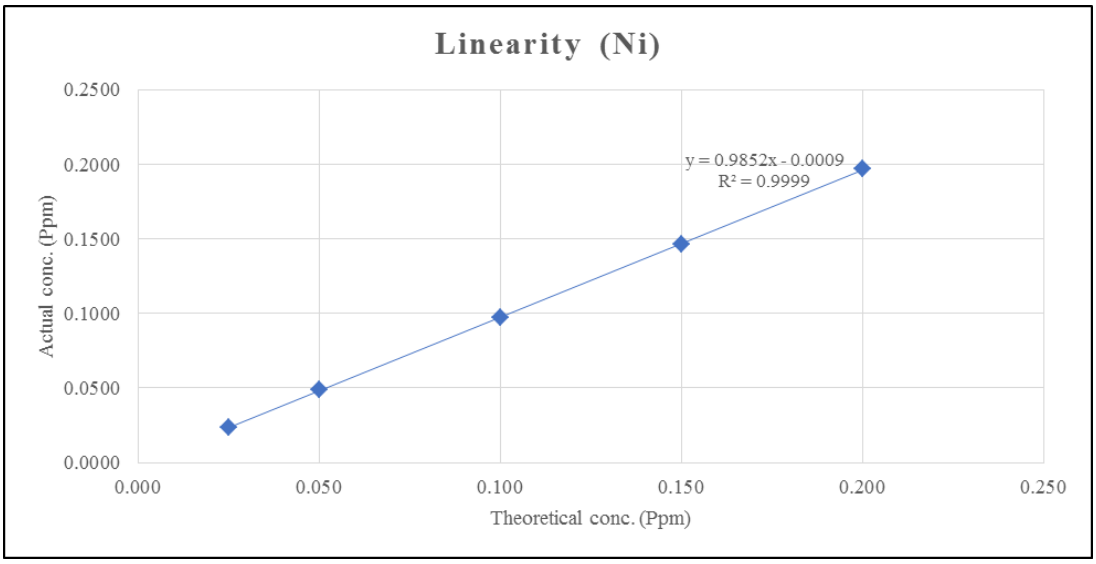

Figure: 2c.

Range

The range of analytical method is the interval between the upper and lower levels of analyte that has been demonstrated to be determined with a suitable accuracy and linearity. Obtained results are given below:

From Linearity test, the range of this analytical method has been determined as the interval of concentration between-

For Cadmium-the upper level (200 % which is 0.1167 ppm) and lower level (LOQ which is 0.0144 ppm).

For Lead-the upper level (200 % which is 0.39278 ppm) and lower level (LOQ which is 0.4675 ppm).

For Nickel-the upper level (200 % which is 0.1967 ppm) and lower level (LOQ which is 0.0238 ppm).

RESULTS AND DISCUSSION

Optimized method was developed for sample preparation using different acid like Hydrochloric acid, Nitric acid and Sulfuric acid. Based on solubility sulfuric acid was best fit. ICP-OES method was achieved at wavelength Cd (214.439 nm), Ni (231.604 nm) Pb (220.353 nm), with a measurement condition of Read time (s) : 5, RF power (kW) : 1.20, Stabilization time (s) : 15, Nebulizer flow (L/min) : 0.70, Plasma flow (L/min) : 12.0, Aux flow (L/min) : 1.00, Make up flow (L/min) : 0.00, Viewing mode : Radial, Viewing height (mm) : 8, Use multiple conditions : 2, Viewing mode : Axial.

The developed method was validated in terms of accuracy, precision, linearity, specificity, LOD, LOQ and range. These validation results are presented in Table: 10.

Table 10: Results of method validation parameters.

Validation parameters	Observation
System suitability	Cd: 1.00, Pb: 1.00 and Ni: 1.00
System Precision	Cd: 0.3%, Pb: 0.7% and Ni: 1.1%
Method Precision	Cd: 0.7%, Pb: 2.1% and Ni: 2.9%
Intermediate Precision	Ni: % RSD (Analyst 1 - 2.9%, Analyst 2- 16.9%), Mean difference between Method precision and Intermediate Precision 7.8 % Cd: % RSD (Analyst 1 – 0.7%, Analyst 2- 15.7%), Mean difference between Method precision and Intermediate Precision 7.0 % Pb: % RSD (Analyst 1 - 2.1%, Analyst 2- 14.3%), Mean difference between Method precision and Intermediate Precision 5.7 %
Specificity	Concentration has increased as per spiked concentration Cd: Unspiked (0.00014 ppm) Spiked - 0.05109 (ppm) Ni: Unspiked (0.03084ppm) Spiked - 0.11293 (ppm) Pb: Unspiked (0.00505 ppm) Spiked - 0.16403 (ppm)
Limit of Detection and Limit of Quantification	Cd: LOD – 0.006 ppm, LOQ – 0.140 ppm Pb: LOD – 0.018 ppm, LOQ – 0.044 ppm Ni: LOD – 0.009 ppm, LOQ – 0.024 ppm
Precision at QL	Cd: 0.6%, Pb: 2.3%, Ni: 1.5%
Accuracy	Cd: Average Recovery – 81%, % RSD (average) – 0.8% Pb: Average Recovery – 77.3%, % RSD (average) – 2.3% Cd: Average Recovery – 80%, % RSD (average) – 3.6%
Linearity	Cd: 1.00, Pb: 0.9999, Ni: 0.9999
Range	From Linearity test, the range of this analytical method has been determined as the interval of concentration between- For Cadmium-the upper level (200 % which is 0.1167 ppm) and lower level (LOQ which is 0.0144 ppm). For Lead-the upper level (200 % which is 0.39278 ppm) and lower level (LOQ which is 0.4675 ppm). For Nickel-the upper level (200 % which is 0.1967 ppm) and lower level (LOQ which is 0.0238 ppm).

CONCLUSION

All the results of validation parameters are found within an acceptable limit. Therefore it was concluded that the proposed ICP-OES method was found to be simple, specific, precise, accurate, rapid and economical and can be used for the estimation of Cd, Pb, Ni as elemental impurities in magnesium stearate.

ACKNOWLEDGEMENT

The authors greatly acknowledge ACI HealthCare Limited for providing the reference sample, reagents and laboratory facility to carry out this work.

REFERENCES

1. ICH Q3D Guideline for Elemental Impurities, https://database.ich.org/sites/default/files/Q3D-R1EWG_Document_Step4_Guideline_2019_0322.pdf, 2, 2 March 2019.
2. Inactive Ingredient Database, US FDA, https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm?event=BasicSearch.page, Magnesium Stearate.
3. ELEMENTAL IMPURITIES <233>, USP, https://www.usp.org/sites/default/files/usp/document/our-work/chemical-medicines/key-issues/233_ElementalImpuritiesProcedures.pdf.
4. *(PDF) Development and validation of an ICP-OES method for quantitation of elemental impurities in tablets according to coming US pharmacopeia chapters*. Available from: https://www.researchgate.net/publication/249319622_Development_and_validation_of_an_ICP-OES_method_for_quantitation_of_elemental_impurities_in_tablets_according_to_coming_US_pharmacopeia_chapters [accessed Oct 20 2020].