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Development and validation of ICPMS methods for simultaneous determination of elemental impurities in topical cream containing ximenynic acid

Rakesh Shivatare[1*], Sarita Jangra[2], Asmita Gaikwad[3], Shailesh Kewatkar[4], Neetin Bhutale[1], Dhanaji S. Suryavanshi[5] and Harshal Tare[6]

Abstract

Background These days, the presence of simple impurities in pharmaceuticals is a major cause for worry. This is because some contaminants are dangerous on their own, and even small impurities can make a drug less stable and shorten its shelf life. The goal of this study was to see if creams with ximenynic acid could be tested with inductively coupled plasma-mass spectrometry to find out how much arsenic, mercury, lead, cadmium, vanadium, cobalt, and nickel were in them. The best way to do things would be one that was quick, accurate, sensitive, and very productive (ICP-MS). The method included both inductively coupled plasma mass spectrometry (ICP-MS) and microwave digestion.

Results Seven of the seven linearity correlation coefficient ('*R*') value were more than 0.99. LOD values were calculated using 33% of the 0.25 J threshold. Six LOQ responses (0.25 J level) were taken after considerable discussion. Calculated and reported %RSD for six LOQ copies. All elemental impurities Vanadium (V), Cobalt (Co), Nickel (Ni), Arsenic (As), Cadmium (Cd), Mercury (Hg), and Lead (Pb) were recovered between 83.33% and 115.97%, within acceptability limits. RSD% for procedure precision and intermediate precision data never exceeded 5%. The available evidence shows that the ICP-MS technique is a good way to measure these components.

Conclusion The statistical analysis showed that the developed ICP-MS method for measuring elements in Topical Cream with Ximenynic Acid is selective and accurate. Since this ICPMS method is good at estimating several elements simultaneously, it could be used to check for elemental contaminants in the formulation.

Keywords ICPMS, MWAD, Elemental impurities, Validation, Topical cream containing ximenynic acid

*Correspondence:
Rakesh Shivatare
rakeshshivatareprs@gmail.com
Full list of author information is available at the end of the article

Background

Research and development in the current pharmaceutical industry is preoccupied with three primary concerns: quality, safety, and effectiveness [1, 2]. At each stage of the manufacturing process for pharmaceuticals beginning with raw materials and progressing through intermediates, active pharmaceutical ingredients (API), excipients, and finally the finished drug product [3, 4] it is essential to keep a close eye on the amount of inorganic impurities that are present and to take steps to reduce this amount. As a consequence of this, a technique that is very exact and sensitive is necessary in order to determine the quantity of metal that is contained in therapeutic compounds. This is very necessary in order to guarantee the drugs' effectiveness and safety [5].

Up to the year 2010, the USP, BP, EP, and JP all used a colorimetric analytical method that included the precipitation of a metal sulphide in a sample and comparison to a lead standard (USP231> and Ph, Eur) [6]. This method was referred to as the "precipitation method." In response to the Guideline for Elemental Impurities (Q3D) that was published in 2010 by the International Conference on Harmonization (ICH), the United States Pharmacopeial Convention (USP) planned to publish three new General Chapters [7–12]. This was done in order to ensure the safety of consumers and the integrity of the marketplace. Daily exposure limits (PDE) are given in USP 232> [13, 14] for a number of different inorganic pollutants that are considered to be elements. Only two examples of the analytical procedures for determining elemental impurities are presented and discussed in chapter 233. These procedures are known as microwave acid digestion (MW-AD) for sample preparation and inductively coupled plasma mass spectrometry (ICP-MS) [10] for identifying the impurities. Both of these procedures can be found in the chapter.

Inductively coupled plasma mass spectrometry (also known as ICP-MS) is now the technology that is most often used for analysing trace elements. In addition to possessing very low detection limits in the sub-parts-per-trillion (ppt) ranges, it may measure at high parts-per-million (ppm) levels [15]. This technology allows for the detection of several components, and it also has a wide linear range, high sensitivity and accuracy, and an easy approach to link with separation techniques such as liquid chromatography [16–18]. These are just some of the numerous benefits that this technology offers.

There is no such thing as an analytical technique that does not first need the step of sample preparation as a requirement. Due to the fact that matrix and spectrum interferences may substantially distort ICP-MS results, this is an essential component for every ICP-MS analysis. Irradiation with microwaves provides a different approach to heating the processes involved in chemical reactions [19]. It is important for digests to have a low acidity and a low amount of residual carbon so that ICP-MS observations are not impacted and the analytical signal is not masked (RCC). When compared to traditional acid digestion, microwave acid digestion (MW-AD) is superior in terms of accuracy and repeatability, while at the same time reducing the amount of heat lost to the environment (Fig. 1).

Ximenynic acid is a natural conjugated acetylenic fatty acid that is mostly found in plants in the order Santalales. Studies done in vitro and in vivo have shown that this unique fatty acid is good for the body. Here, we explain what ximenynic acid does to fight inflammation, cancer, bacteria, and worms. With ximenynic acid, doctors may have a unique chance to treat diseases that cause inflammation. It also includes the breakdown of long-chain fatty acids, which may control insulin release and reduce insulin resistance. Ximenynic acid has a lot of market potential because it is used a lot in the makeup business. Because of the many molecular roles that have been found for ximenynic acid, its demand is growing quickly. The purpose of this research article is to develop and validate a single method for simultaneous determination of Elemental Impurities in Topical Cream Containing Ximenynic Acid by ICP-MS [20].

An ICP-MS method has recently been described for the purpose of analysing the component parts of a topical cream containing Ximenynic Acid for the very first time. In order to identify the presence of heavy metals in pharmaceutical compounds and, by extension, to ensure the safety and effectiveness of medicines that are meant for human consumption, a technique that is both more sensitive and more selective is necessary. This study details an improvement made to a microwave acid digestion (MW-AD) method for the simultaneous ICP-MS detection of arsenic, mercury, lead, cadmium, vanadium, nickel, and cobalt in a topical cream containing Ximenynic Acid [21].

Methods

Experimental

Chemical and laboratory reagents

The Pharma internal standard 1, ultrapure grade hydrogen peroxide (supplied by JT Baker), ICH/USP target element standard A (supplied by Merck), and ICH/USP target element standard B (supplied by Merck) are all products that may be purchased from trustworthy vendors (Merck). The guidelines found on the supplier's certificate of analysis

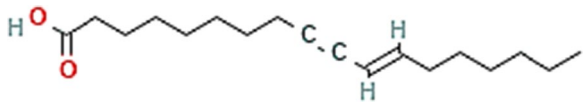

Fig. 1 Structure of ximenynic acid

about the proper storage of the test materials were followed. The temperatures at which the test solutions were kept were the same as those employed during the testing. In each and every one of the volumetric flasks that were used for the procedures, polymethyl pentene (PMP) and polypropylene (PP) were both used.

Instrumentation

An Agilent 7800 ICP-MS was used in the gathering of each and every reading. The typical method of sample introduction was replicated with this apparatus by using a Micromist concentric nebulizer, a quartz spray chamber, and a quartz flame that was outfitted with a 2.5 mm id injector. All of these components were included into its construction. Ni fashioned them by hand all by himself (with a Ni-plated Cu-core sampler). In order to stop the build-up of salt on the nebulizer, an Agilent argon gas humidifier was attached to the gas that was being carried by the carrier. The helium mode demonstrates the degree to which the elements are sensitive at the USP levels. During the validation process, both the conventional and the cutting-edge high-energy helium (He) mode were used.

Method development [22, 23]

When determining which digestion technique to use, many factors, including the sample, the analyte, the availability of reagents, and the capabilities of the equipment, all play a part. This is due to the fact that they direct the selection of settings that are ideal for extracting the greatest amount of metals from the sample. The circumstances of the ICPMS, the diluent used in the preparation of the sample, the programmed of the microwave digester, and the settings of the instrument are all examples of aspects that may be optimized.

Selection of ICPMS conditions

On the basis of the most recent and accurate information and the accumulated knowledge at the time, the following criteria were set for each metal: (Table 1).

Table 2 Instrument parameters

Pre run	
Uptake speed	:50 s
Uptake time	:0.5 rps
Stabilize	:40 s
Post run (probe rinse)	
Rinse speed (nebuliser pump)	: 0.30 rps
Rinse at rinse port (sample)	: 10 s
Rinse at rinse port (standard)	: 10 s
Post run (rinse)	
Rinse vial 1 (2% nitric acid)	: 1
Rinse speed	: 0.10 rps
Rinse at rinse vial	: 60 s

Selection of diluents for digestion of sample

The sample matrix and the metals of interest are taken into consideration while selecting the digestion reagents to use. Because of their strong oxidizing capabilities, HCl, H_2SO_4, HF, and HNO_3 are the most effective acids for breaking down inorganic and organic compounds, respectively. This is the case for both inorganic and organic substances. In addition to hydrochloric acid and nitric acid, other combinations of concentrated acids with either thirty percent or fifty percent hydrogen peroxide were put through their paces throughout the testing process. It is not typical practice to make use of certain acids since it is difficult to reclaim volatile substances once digestion has taken place. In three different trials, we combined 1 mL of hydrogen peroxide with 5 mL of concentrated nitric acid, 4 mL of concentrated hydrochloric acid with 4 mL of water, and 5 mL of concentrated nitric acid with 1 mL of hydrochloric acid.

Instrument parameters

In order to get started on the job, the following ICPMS parameters were used, which were chosen based on previous knowledge and experience (Table 2).

Table 1 ICPMS conditions

Element	Element (amu)	Element (amu)	Type	Internal standard (amu)
1	Mass of vanadium	51	Analyte	Scandium (45)
2	Mass of cobalt	59	Analyte	Scandium (45)
3	Mass of nickel	60	Analyte	Scandium (45)
4	Mass of arsenic	75	Analyte	Germanium (72)
5	Mass of cadmium	111	Analyte	Tellurium (125)
6	Mass of mercury	201	Analyte	Bismuth (209)
7	Mass of lead	208	Analyte	Bismuth (209)

Selection of microwave digestion system programme

During the digesting process, the length of time that the matrix is exposed to the oxidizing acid is also an extremely important factor. Prolonged exposure has the potential to hasten the exothermic reactions that occur, which in turn makes it easier for the metal of interest to dissolve from the biological matrix and then be released into the air. The following procedure for digesting the samples was devised after the preliminary testing according to the findings of the following tests (Table 3).

Final methodology

Sample and standard preparation

Preparation of 2%V/V nitric acid and 1% v/v hydrochloric acid (diluent) Putting 50 mL of water to a volumetric flask with a 100 mL capacity. Add 2.0 mL concentrated nitric acid and 1.0 mL hydrochloric acid after that. Then, until the volume reached a total of 100 mL for the experiment, add some water to it.

Preparation of standard stock solution Standard A: Transferred 1 mL of the target element (As 15 ppm, Cd 5 ppm, Hg 30 ppm, Pb 5 ppm), and *Standard B* (Ag 150 ppm, Co 50 ppm, Ni 200 ppm, Se 150 ppm, Tl 8 ppm, V 100 ppm) from the ICH/USP target element to each individual 50 mL volumetric flask. When the diluent was used, the volume was at a level that was satisfactory.

Internal standard preparation Pharma internal standard-1 solution, 1 ml, was transferred to a 50 mL volumetric flask, and the volume was made up with diluent.

Sample diluent

1 mL of concentrated hydrochloric acid and 5 mL of concentrated nitric acid were combined.

Preparation of sample blank

This digesting tank was supplied with 5 mL of concentrated nitric acid as well as 1 mL of concentrated hydrochloric acid. The timetable for the digestion was adhered to. Following the chilling process, the sample was transferred into a volumetric flask of 50 mL, which was then filled with water.

Table 3 Digestion programme

Step	Temperature	Pressure (Bar)	Ramp (min)	Hold (min)	Energy (*P*%)
1	150	70	2	5	50
2	190	75	2	10	60
3	210	80	2	15	65
4	50	80	1	10	0

Preparation of sample solution

The Ximenynic acid Cream was then administered to the digestion vessel once the appropriate quantity had been determined using the measurement device. This digestion vessel was predigested for fifteen minutes with five mL of concentrated nitric acid and one mL of concentrated hydrochloric acid. The digestion process has been finished without any problems. After the liquid had cooled, the sample was transferred to a volumetric flask of 50 mL and the remainder of the space was filled with water.

Preparation of sample solution at 30% level of specification limit (0.25 J)

The Ximenynic acid Cream was then administered to the stomach once the appropriate quantity had been determined using the measurement device. This digestion vessel was predigested for fifteen minutes with five mL of concentrated nitric acid and 1 mL of concentrated hydrochloric acid. Following that, 0.25 mL of the stock solution that served as the gold standard was added. The digestion process has been finished without any problems. After the liquid had cooled, the sample was transferred to a volumetric flask of 50 mL and the remainder of the space was filled with water.

Preparation of sample solution at 100% level of specification limit

The Ximenynic acid Cream was then administered to the stomach once the appropriate quantity had been determined using the measurement device. This digestion vessel was predigested for fifteen minutes with five mL of concentrated nitric acid and one mL of concentrated hydrochloric acid. After that, one mL of the stock solution was put in. The digestion process has been finished without any problems. After the liquid had cooled, the sample was transferred to a volumetric flask of 50 mL and the remainder of the space was filled with water.

Method validations [10, 11, 23]

In line with the recommendations that came out of the International Conference on Harmonization (ICH), the method that has been determined to be the most effective for concurrently measuring seven different elements is ICPMS (R1). We investigated the suitability of the system, linearity, recovery, optimization of LOD and LOQ, method precision, and intermediate precision.

Linearity and range

The ability to get results that are proportionate to the quantity of analyte that was employed in the test is

what is meant by the term "linearity". In order to evaluate the linearity, seven distinct concentrations ranging from the lower limit of quantification (LOQ) to 250% of the specification level were aspirated. The correlation between the analyte's reaction and the ISTD's response was displayed versus the concentration. The calibration curve was used as the basis for the calculation of the slope, intercept, and correlation. If the correlation coefficient ('R') value is more than 0.99, this indicates that the data reasonably well match the regression line.

Limit of detection and limit of quantitation

The limit of detection (LOD) refers to the lowest possible concentration of an analyte that may be determined from a sample under the conditions of the experiment. The lowest acceptable concentration (LOQ) of an analyte is specified as the lowest concentration of the analyte that still provides a credible measurement under the conditions of the experiment. A blank sample was made and aspirated ten times before being evaluated. We used the linear regression equation to determine the LOD and LOQ for each element. This equation requires two inputs the standard deviation of the intercept, and the slope in order to function properly.

$$\mathrm{LOD} = 3.3 * \sigma/\mathrm{s},\ \mathrm{LOQ} = 10 * \sigma/\mathrm{s}$$

where σ = standard deviation of Ratio of analyte response to ISTD response of sample blank, s = slope of calibration curve.

Precision at limit of quantitation

In order to guarantee that the LOQ answer is accurate, six duplicates of it were created (0.25 J level). For the purpose of illustrating LOQ accuracy, relative standard deviation (%RSD) was used; at the LOQ level, the RSD value should be either less than or equal to 20.0.

Specificity

The specificity of the ICPMS technique was discovered via the study that investigated how the calibration blank influenced the recovery research at the LOQ level. These steps were taken to remove any possible impact that might have been caused by the excipients in the formulations. In order to assess the degree of accuracy, a calibration blank was made and then sucked a total of ten times. The mean percentage recovery at the LOQ level should be between 50.0 and 150%, and the average significant interference of the calibration blanks should be lower than that of the calibration standard solution1.

Accuracy (recovery)

The accuracy of an analytical technique may be evaluated by contrasting the expected value with the actual value that was achieved. This number may be obtained by calculating the proportion of recovered elements, denoted as R%. The tried-and-true ICPMS method was put to the test in this circumstance by repeatedly (n = 3) analysing spiked samples at four different concentrations (LOQ, 50%, 100%, and 150% of the LOD). Using the formula [% Recovery = (Recovered content of analyte/Actual spike content of analyte) 100], the experimental data were subjected to a statistical analysis in order to establish the level of recovery achieved by the method as well as its overall validity. The average recovery at the LOQ level of any analyte must be between 50 and 150% for it to be considered acceptable, and the recovery at all other levels must likewise be between 70 and 150% for it to be considered acceptable (Table 4).

Precision

The degree to which distinct studies performed on numerous duplicates provide the same findings may be used to characterize the accuracy of a measurement technique. The system precision, the method precision, and the intermediate precision have all been investigated throughout the studies of precision. Testing the accuracy of the system assured that the results of repeated measurements would be reliable. On the System Precision Solution, the Calibration Blank, the Calibration Standards, and the Standard Check Solution, extractions and analyses were carried out. It is recommended that the correlation coefficient ('R') value of the calibration curve be less than 0.99 for each analyte. In order to evaluate the accuracy of the procedure, the Specification Level produced three samples that were left "as is" and six samples that were "spiked" (1 J). The preparation and aspiration of three as-is samples and six individual spike samples at the specification level required a large number of analysts who worked on various days. This was done in order to achieve intermediate accuracy. The relative standard deviation (%RSD) was the metric that was used to evaluate how well the method performed in general. The relative standard deviation (RSD) over all six Spike at Specification level solution preparations should not exceed 15%. In order to prevent RSD readings from being more than 15%, it is necessary to have a high level of both method accuracy and intermediate precision for each analyte.

Results

Method development

During the course of this inquiry, a number of concerns were examined, and a solution was found for each one. To be more specific, the analysis matrix did not make it possible to find certain things. Some of the acids that have been used include concentrated hydrochloric acid, nitric

Table 4 Preparation of samples for accuracy

Sr. no	Sample name	Weight of sample (g) accurately	Volume of HNO_3 + HCl (mL)	Volume of stock-B solution (mL)	Microwave digestion	Final volume make up with type-I water (mL)
1	As such sample	0.2000	5.0 + 1.0	NA	Perform microwave digestion till the sample was clear	50
2		0.2000	5.0 + 1.0			50
3		0.2000	5.0 + 1.0			50
1	LOQ	0.2000	5.0 + 1.0	0.250		50
2		0.2000	5.0 + 1.0			50
3		0.2000	5.0 + 1.0			50
1	Spike at 50%	0.2000	5.0 + 1.0	0.500		50
2		0.2000	5.0 + 1.0			50
3		0.2000	5.0 + 1.0			50
1	Spike at 100%	0.2000	5.0 + 1.0	1.000		50
2		0.2000	5.0 + 1.0			50
3		0.2000	5.0 + 1.0			50
1	Spike at 150%	0.2000	5.0 + 1.0	1.500		50
2		0.2000	5.0 + 1.0			50
3		0.2000	5.0 + 1.0			50

acid, and acid mixed with either thirty percent or fifty percent hydrogen peroxide. Other acids that have been used include: It is not typical practice to make use of certain acids since it is difficult to reclaim volatile substances once digestion has taken place. In order to dissolve the material, 5 mL of nitric acid and 1 mL of hydrogen peroxide were utilized. It was imagined to perform a microwave-accelerated digestion process by employing 5 mL of nitric acid and 1 mL of hydrochloric acid as diluents. We performed spike recoveries of arsenic, mercury, lead, cadmium, vanadium, cobalt, and nickel to demonstrate that the stabilizing combination is effective for a variety of chemicals and to take into account the fact that recovery varies from sample to sample. In addition, we did this to account for the fact that recovery varies from sample to sample. The elemental recoveries varied from 80 to 105%, which is within the USP's acceptable range of 70–150%.

Linearity and range

When plotted against the ratios of analyte response to ISTD response, concentrations formed a line that was continuous throughout the whole analysis. The results of the regression analysis are shown in Table 5. The correlation coefficient ('*R*') value used to assess linearity were more than 0.99, which demonstrates that the technique follows a linear pattern (Fig. 2).

Limit of detection and limit of quantitation

We were successful in determining both the LOD and LOQ by making use of the slope of the calibration curve as well as the standard deviation of the ratio of the analyte response to the ISTD response in the sample blank over a period of ten aspirations. Because the values predicted for the LOQ were lower than 0.25 J, that value was selected to serve as the LOQ for any further testing that may take place (Table 6).

Specificity

In order to determine the specificity of the test, the calibration blank was aspirated ten times, whereas the calibration standard level 1 was only done once. The calibration blanks were not allowed to cause any significant interference, and the average mass of each analyte had to be lower than that of the calibration standard solution-1 (Table 7).

Accuracy (recovery)

The recovery testing was what led to the determination of its accuracy. The three samples that were used in the recovery tests were generated with the LOQ concentration, 50% concentration, 100% concentration, and 150% concentration, respectively. It was determined how much of each analyte could be recovered on average across all of the different levels. On the basis of the data that was collected, it was determined that the standard medication mean recoveries were correct (Table 8, Fig. 3).

Precision

In terms of system precision, method precision, and intermediate precision, the precision analysis reveals that the designed approach is dependable and reproducible.

Table 5 Linearity table of 7 elements

Linearity level	Vanadium (V)		Cobalt (Co)		Nickel (Ni)		Arsenic (As)		Cadmium (Cd)		Mercury (Hg)		Lead (Pb)	
	Conc. In ppb	Ratio	Conc. in ppb	Ratio	Conc. In ppb	Ratio	Conc. in ppb	Ratio	Conc. in ppb	Ratio	Conc. in ppb	Ratio	Conc. in ppb	Ratio
Linearity Level-1 (25%)	10.00	2.1902	5.00	2.5707	20.00	2.8737	1.50	0.1455	0.50	0.2031	3.00	0.0237	0.50	0.0485
Linearity Level-2 (50%)	20.00	4.2902	10.00	5.0613	40.00	5.6086	3.00	0.2855	1.00	0.4169	6.00	0.0469	1.00	0.0944
Linearity Level-3 (100%)	40.00	8.0322	20.00	9.4614	80.00	10.459	6.00	0.5347	2.00	0.7596	12.00	0.0887	2.00	0.1729
Linearity Level-4 (150%)	60.00	12.296	30.00	14.572	120.00	16.083	9.00	0.8138	3.00	1.1418	18.00	0.1361	3.00	0.267
Linearity Level-5 (200%)	80.00	15.593	40.00	19.266	160.00	20.655	12.00	1.0409	4.00	1.5426	24.00	0.1753	4.00	0.3397
Linearity Level-6 (250%)	100.00	20.164	50.00	25.031	200.00	26.927	15.00	1.3474	5.00	1.9344	30.00	0.2279	5.00	0.441
Slope		0.197		0.493		0.132		0.088		0.382		0.007		0.086
y-Intercept		0.252		−0.074		0.167		0.015		0.013		0.001		0.005
Correlation coefficient r		0.999		0.999		0.999		0.999		1.000		0.999		0.999
Squared correlation coefficient (r2)		0.999		0.999		0.999		0.999		0.999		0.999		0.999

Conc. in ppb—Concentration of standard (ppb), *Ratio*—ratio of analyte response to ISTD response

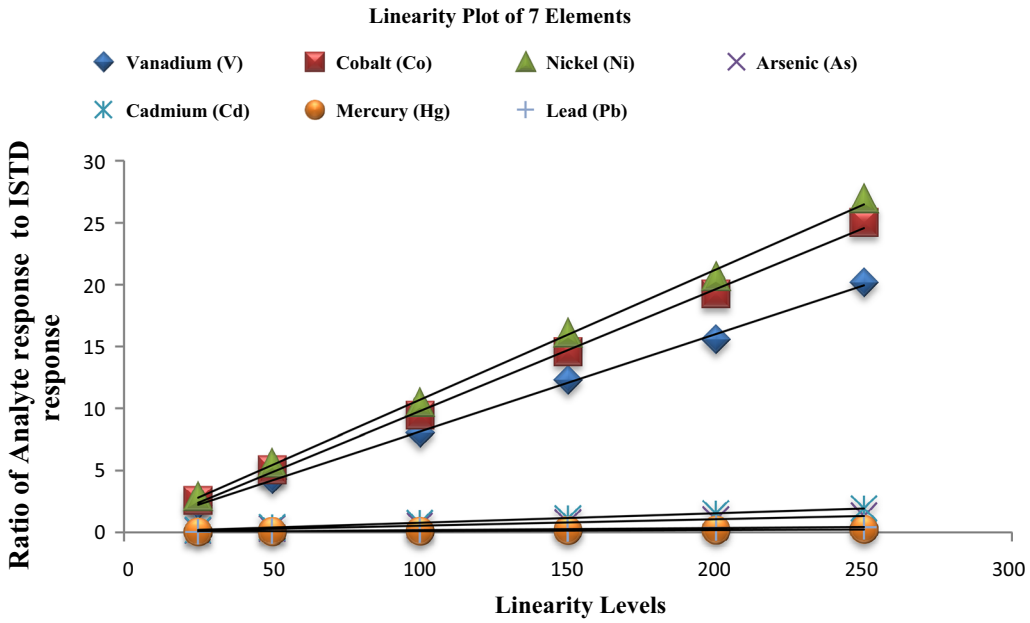

Fig. 2 Linearity plot for 7 elements. This figure contain linearity plot of Vanadium (V), Cobalt (Co), Nickel (Ni), Arsenic (As), Cadmium (Cd), Mercury (Hg), and Lead (Pb)

Table 6 Table for precision at LOQ

Sample	Analyte content in the sample						
	V	Co	Ni	As	Cd	Hg	Pb
1	1.5506	1.9353	2.3087	0.1010	0.1453	0.0146	0.0346
2	1.5346	1.9240	2.2596	0.1020	0.1513	0.0146	0.0337
3	1.5508	1.9177	2.2869	0.1009	0.1495	0.0149	0.0337
4	1.5431	1.9117	2.2731	0.1007	0.1471	0.0147	0.0342
5	1.5455	1.9250	2.2921	0.1014	0.1531	0.0144	0.0344
6	1.5515	1.9308	2.2843	0.1010	0.1491	0.0148	0.0342
Mean	1.5460	1.9241	2.2841	0.1012	0.1492	0.0147	0.0341
SD	0.00650	0.00860	0.01670	0.00050	0.00280	0.00020	0.00040
%RSD	0.42	0.45	0.73	0.49	1.88	1.36	1.17

Table 7 Table for specificity

Sr. no.	Element	Mean ratio of 10 replicates of blank	Ratio of calibration standard level 1
1	Vanadium	0.0172	2.2352
2	Cobalt	0.0081	2.6828
3	Nickel	0.0737	3.0439
4	Arsenic	0.0016	0.1486
5	Cadmium	0.0005	0.2182
6	Mercury	0.0009	0.0261
7	Lead	0.0019	0.0512

The data were provided with an RSD%, and it never went beyond 5%, despite the fact that the greatest figure that is allowed within the range is 15%. To achieve a higher level of precision across the system, six time aspirations of the precision solution (1 J) were developed in accordance with the method described in Methodology (Tables 9, 10, 11, Fig. 4).

Intermediate precision

Toughness, or intermediate accuracy, is a measure of how frequently the same result can be obtained using

the same procedure, on the same material, by different personnel on various days in the same laboratory. The median accuracy of the present approach to determining trace metals was determined by calculating the proportion of metals recovered at three concentration levels (1.0, 100.0, and 1000.0 ppb) supplied by another analyst on a separate day using the same ICP-MS apparatus. The healing rate increased from 98.2 to 101.8%, which is extremely near to what the primary analyst discovered, proving the efficacy of the procedure (Fig. 5).

Reproducibility

Repeatability is the degree of similarity in test results obtained using the same technique on the same test substance in the same laboratory by the same operator with the same equipment over a brief period of time. It is computed using a minimum of nine determinations that

Table 8 Table for mean recovery

	Vanadium (V)	Cobalt (Co)	Nickel (Ni)	Arsenic (As)	Cadmium (Cd)	Mercury (Hg)	Lead (Pb)
LOQ Level	100.23	108.47	87.90	101.30	103.27	102.53	105.60
50% Level	101.53	109.97	85.83	100.67	101.23	104.03	106.77
100% Level	96.17	116.13	86.40	100.30	99.13	100.00	100.73
150% Level	97.53	115.97	83.33	100.20	96.77	100.20	100.40

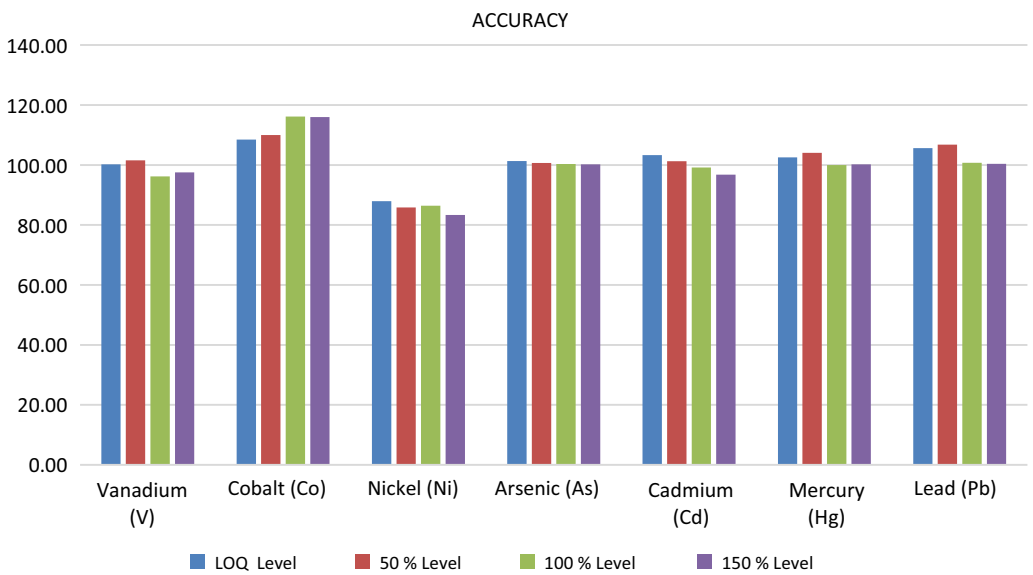

Fig. 3 Accuracy of 7 elements at four level. This figure contain recovery comparison of Vanadium (V), Cobalt (Co), Nickel (Ni), Arsenic (As), Cadmium (Cd), Mercury (Hg), and Lead (Pb) at four different levels

Table 9 System suitability for precision

Parameter →	Element	LOD LOQ optimisation	LOD LOQ Precision	Linearity, specificity and method precision	Accuracy	Intermediate precision
RSD for six replicates for 1.0 J	V	0.81	1.85	2.01	0.39	0.65
	Co	0.95	1.80	2.09	0.35	0.76
	Ni	1.06	1.63	2.25	0.31	0.75
	As	1.03	1.96	2.59	0.59	1.28
	Cd	3.08	1.43	1.62	1.17	1.50
	Hg	1.31	2.23	2.07	0.25	0.23
	Pb	0.57	1.95	1.73	0.37	0.83

Table 10 Table for method precision

Aspirations	Ratio of analyte response to internal standard response						
	V	Co	Ni	As	Cd	Hg	Pb
1	9.4547	9.3576	22.0298	0.5218	0.8007	0.0926	0.1835
2	10.5279	10.3086	23.6646	0.5681	0.8581	0.1029	0.2018
3	9.6006	9.3929	21.7001	0.5205	0.7853	0.0938	0.1852
4	9.5205	9.3604	21.7120	0.5287	0.7915	0.0931	0.1845
5	9.5716	9.3646	21.4316	0.5273	0.8017	0.0928	0.1846
6	9.7889	9.4586	21.6740	0.5227	0.8178	0.0941	0.1858
Mean	9.7440	9.5405	22.0354	0.5315	0.8092	0.0949	0.1876
SD	0.40010	0.37820	0.82060	0.01820	0.02640	0.00400	0.00700
%RSD	4.11	3.96	3.72	3.42	3.26	4.21	3.73

Table 11 Table for cumulative RSD for method precision and intermediate precision

Element	Analyst	1	2	3	4	5	6	Mean	SD	%RSD
Vanadium	1	9.4547	10.5279	9.6006	9.5205	9.5716	9.7889	9.8782	0.3130	3.17
	2	10.1117	10.0616	10.1082	10.0434	9.8920	9.8567			
Cobalt	1	9.3576	10.3086	9.3929	9.3604	9.3646	9.4586	9.6747	0.3047	3.15
	2	10.0188	9.8334	9.8308	9.8461	9.6734	9.6516			
Nickel	1	22.0298	23.6646	21.7001	21.7120	21.4316	21.6740	22.3205	0.7052	3.16
	2	23.2205	22.9326	22.8481	22.4799	22.1422	22.0103			
Arsenic	1	0.5218	0.5681	0.5205	0.5287	0.5273	0.5227	0.5360	0.0139	2.59
	2	0.5474	0.5443	0.5426	0.5415	0.5390	0.5279			
Cadmium	1	0.8007	0.8581	0.7853	0.7915	0.8017	0.8178	0.8090	0.0194	2.40
	2	0.8200	0.8074	0.8045	0.8168	0.8151	0.7890			
Mercury	1	0.0926	0.1029	0.0938	0.0931	0.0928	0.0941	0.0947	0.0028	2.96
	2	0.0949	0.0949	0.0957	0.0943	0.0932	0.0937			
Lead	1	0.1835	0.2018	0.1852	0.1845	0.1846	0.1858	0.1876	0.0490	2.61
	2	0.1887	0.1883	0.1894	0.1886	0.1850	0.1862			

span the indicated range of the procedure (for example, three levels and three repetitions per determination). RSD should not exceed 1.5% when administering duplicate injections. By calculating the RSD of the responses (in cps) of six replicate injections of standard solutions of the seventeen metals with three concentrations (1.0, 100, and 1000.0 ppb), the repeatability of the current method for determining the seventeen metals was determined to be less than 1.5% for all metals at the three concentration levels. These results demonstrate the repeatability of the current method for determining metal concentrations.

Discussion

The United States Pharmacopoeia (USP) and International Conference on Harmonisation (ICH) have proposed new regulations and recommendations to manage the potential prevalence of heavy metals in pharmaceuticals [22]. USP 232> and ICH Q3D define 24 elemental contaminants and their concentration limitations in consideration of the permitted daily exposure (PDE) of multiple medication categories (oral, parenteral, and inhalation). While USP 233> provides more specifics on the method validation procedure and sample preparation, it is important to note that USP 233> is not a standard [23].

Based on the data, it is clear that the stabilizing mixture is the approach that provides the highest level of precision and dependability when it comes to evaluating the elemental impurities present in dissolved pharmaceutical products in accordance with regulatory criteria. In Linearity and Range the Seven of the correlation coefficient ('*R*') values used to assess linearity were more than 0.99. The LOD values were determined by utilizing 33% of the 0.25 J threshold in the calculation. After some deliberation, it was determined that six copies of the LOQ response would be taken (0.25 J level). The %RSD for six

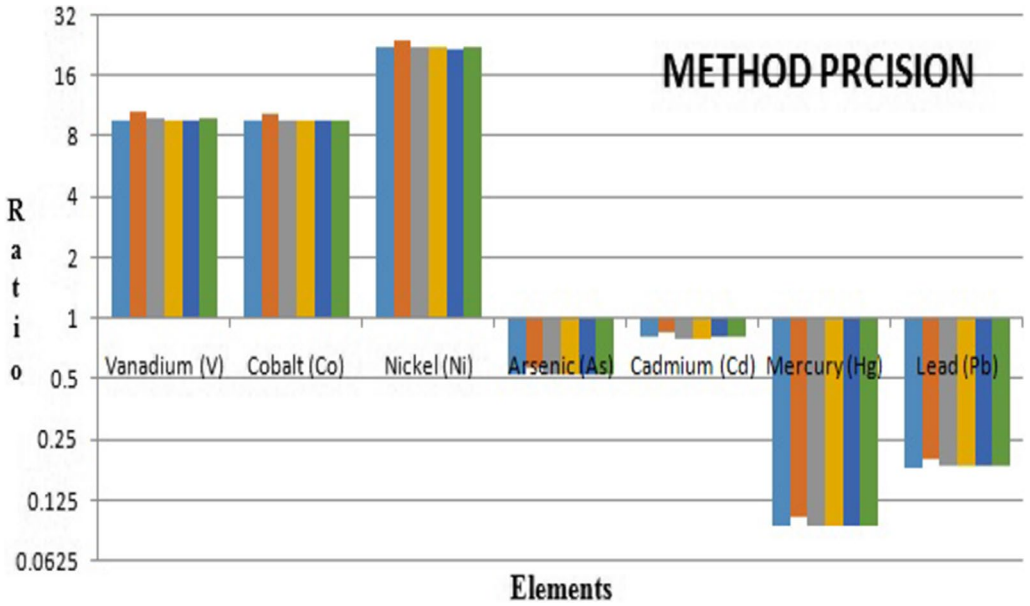

Fig. 4 Method precision. This figure contain Method precision of six samples for the analysis of Vanadium (V), Cobalt (Co), Nickel (Ni), Arsenic (As), Cadmium (Cd), Mercury (Hg), and Lead (Pb)

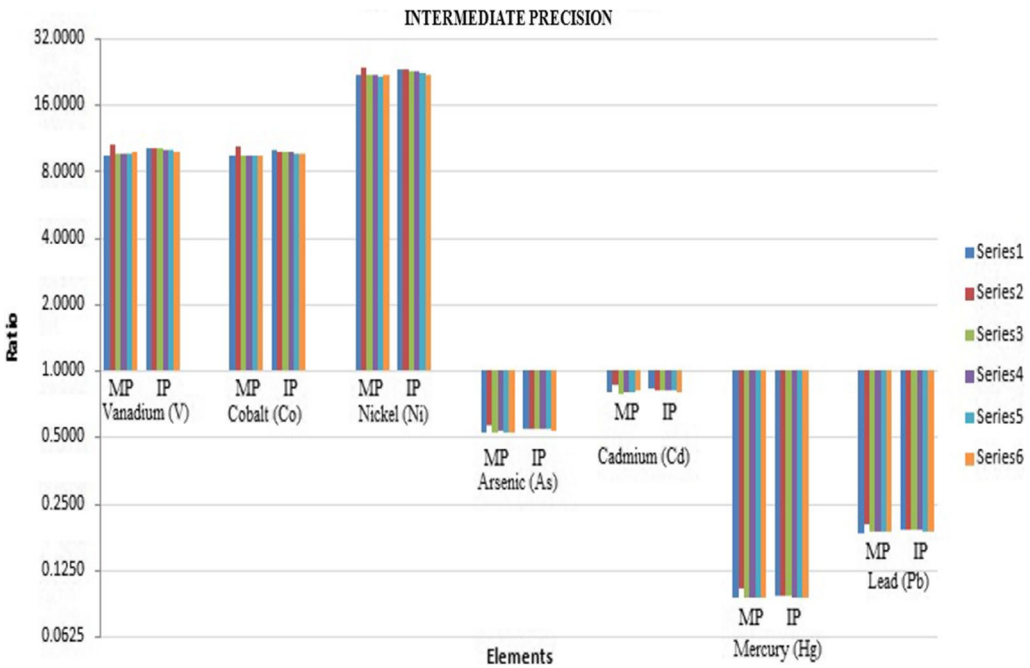

Fig. 5 Intermediate precision. This figure contain comparison between the method and Intermediate precision for the analysis of Vanadium (V), Cobalt (Co), Nickel (Ni), Arsenic (As), Cadmium (Cd), Mercury (Hg), and Lead (Pb)

different copies of LOQ was calculated and reported. The Recovery of all elemental impurities Vanadium (V), Cobalt (Co), Nickel (Ni), Arsenic (As), Cadmium (Cd), Mercury (Hg), Lead (Pb) was between 83.33% to 115.97% i.e. within acceptance limit. The method precision as well as intermediate precision data provided with an RSD%, and it never went beyond 5%. The established method was proved to be simple, sensitive and accurate. It successfully applied to the elemental impurity determination.

Conclusion

Extensive testing has shown that an analytical method for elemental impurities that complies with USP 232 and 233 is reliable in terms of its specificity, accuracy, repeatability, ruggedness, linearity, and solution stability. These qualities may be broken down as follows: For the purpose of providing accurate results, each and every sample and standard has to be made more complex and robust. In order to complexity the substance and ensure its stability, five mL of nitric acid and one mL of hydrochloric acid were mixed together. A single process using microwave digestion may be used to test whether or not all of the USP-mandated constituents are present in the finished product. On this page, you can find information that is specific on the inorganic components that make up Ximenynic Acid Topical Cream. The percentage of inorganic components that make up these materials may now be calculated. As a result of the fact that the ICP-MS method permits the simultaneous identification of inorganic components in such complex matrices, the suggested sample treatment was not only successful but also compatible with this method.

Abbreviations

ICPMS	Inductively coupled plasma mass spectrometry
MWAD	Microwave acid digestion
ICH	International Conference on Harmonization
LOD	Limits of detection
LOQ	Limit of quantitation
USP	United States Pharmacopeial Convention
mL	Millilitre
Minute	Min

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Author details

[1]Department of Pharmaceutical Sciences, JJT University, Jhunjhunu, Rajasthan, India. [2]Department of Pharmacy Practice, Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, India. [3]Department of Pharmaceutical Chemistry, Sharadchandra Pawar College of Pharmacy, Otur, Tal. Junnar, Maharashtra, India. [4]Department of Pharmacognosy, Rajarshi Shahu College of Pharmacy, Buldana, Maharashtra, India. [5]Department of Pharmaceutical Sciences, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune, Maharashtra, India. [6]Department of Pharmacognosy, Sharadchandra Pawar College of Pharmacy, Otur, Tal. Junnar, Maharashtra, India.

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