Development and Validation of a Simple and Sensitive ICP-MS Method for the Quantification of Elemental Impurities in Propafenone Hydrochloride Drug Substance

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ABSTRACT

Elemental impurities are substances present in drug products, excipients, or drug formulations. They may be formed by the presence of catalysts and environmental contaminants. Elemental impurities can be detected by a sophisticated method such as Inductively Coupled Plasma Mass Spectrometry (ICP–MS). ICP-MS is an advanced method to detect elemental impurities in drug substances. In this study Propafenone hydrochloride drug was used, Propafenone Hydrochloride is an antiarrhythmic medication belonging to class 1C used to prevent supraventricular and ventricular arrhythmias. The present study was aimed to develop and validate inductively coupled plasma mass spectroscopic (ICP–MS) method for detection of elemental contaminants, i.e., Class 1, Cd, Pb, As, Class 2A, Hg, Co, V, and Class 2B impurities such as Ni, T1, Se, Ag, Au, Pd, Ir, Os, Rh, Ru, and Pt. Total 17 elemental impurities were detected in Propafenone Hydrochloride and this method was employed for the regular sample analysis of 17 elemental impurities in Propafenone Hydrochloride for pharmaceutical use. The instrument conditions were set using RF power of 1550 W, auxiliary gas of 0.5 L/min, and nebulizer flow of 1.01 L/min nebulizer pump pressure was 0.10 rps, spray chamber temperature was 2°C, and mode used was He, He flow rate was 4.3 mL/min and the energy discrimination rate was 3.0 V. The technique is sensitive and may identify desirable elemental impurities within permissible regulatory limits when additional elements are present. The proposed ICP-MS approach has been found to be accurate, precise, linear, rugged, robust, and convenient for the quality control of the drug substance propafenone hydrochloride. The linearity results for each impurity were 0.9990. The methods were validated according to USP requirements and International Council for Harmonization ICH guidelines. The suggested approach is an excellent quality control tool for the concurrent quantitative assessment and detection of elemental contaminants at low levels in the drug substance propafenone hydrochloride.

Keywords: Elemental Impurities, ICP-MS, Propafenone Hydrochloride, Validation.

INTRODUCTION

Elemental impurities are substances found in pharmaceuticals, excipients, and drug formulations. They may be produced as a result of the presence of one or more catalysts and environmental contaminants. These impurities can occur naturally or may be intentionally introduced. Interactions with equipment and containers can produce these impurities.[1] The chemical entity of Propafenone hydrochloride is 1-[2-[2-hydroxy-3-(propylamino) propoxy] phenyl]-3-phenylpropan-1-one. Fig 1 It is an antiarrhythmic medication of class 1C that is used to prevent supraventricular and ventricular arrhythmias. It also has anaesthetic properties on a local level. It works as an anti-arrhythmic agent. It contains propafenone (1+). It is a very effective

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antiarrhythmic medication for ventricular arrhythmias. Additionally, its beta-blocking effects are modest.[2]

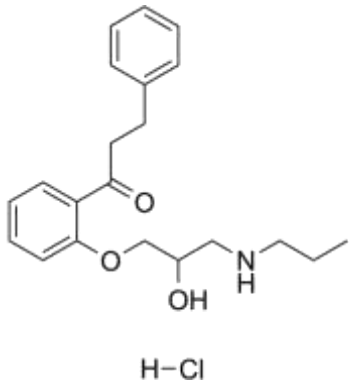

Fig 1 Chemical Structure of Propafenone Hydrochloride

Elemental impurities are categorized into Class 1, 2A & 2B impurities. Class 1 elements are proven human toxins with little to no application in the development of drugs. Their inclusion in drug products often results from elements that are widely used. These four components should be evaluated due to the inherent hazards they carry. Class 1 impurities include As, Cd, Hg, and Pb.[3]

Due to the relatively high possibility of Class 2A elements which may be present in the pharmaceutical drug products, it is necessary to assess their risk across all potential sources of elemental impurities and administration routes. Impurities that are specified in Class 2A include Co, Ni, and V. Class 2B elements have a lower possibility of being in the therapeutic product due to their low abundance and limited possibilities for co-isolation with other materials. Therefore, they can be excluded from the risk evaluation unless they are purposefully included during the production of drug ingredients, excipients, or other parts of the drug product. Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se, and TI are class 2B impurities.[4,5]

Few elements such as arsenic, cadmium, mercury and lead are known to produce toxic effects in humans (often through a variety of different mechanisms), and are therefore should be measured to estimate exposure. ICP-MS has several advantages, it is a multi-element technique with a broad analytical range and a low detection limit, it has high sample throughput, a low sample volume, it requires little sample preparation and it has high resolution. From a laboratory point of view, ICP-MS method has many advantages over other methods perhaps the most significant advantage of is its multi-element analysis, it can measure multiple elements simultaneously in a single analysis. Coupled with simple sample preparation and short analysis time, very high sample throughput is the major advantage of ICP-MS in the laboratory.[6]

USP 232_ establishes PDE limits for a variety of inorganic (elemental) impurities, including Cd, Pb, As, Hg, Co, V, Ni, T1, Se, Ag, Au, Pd, Ir, Os, Rh, Ru, and Pt. The recommended maximum daily dose and daily exposure limits for elemental impurities must be scaled for the drug under investigations, so for a substance with a daily dose of 10 g, the elemental impurity level in the dosage form must be less than ten times than the limits shown. Modern instrumental techniques like ICP-MS, which are listed in USP 233, make it simple to measure the requisite limits directly. Currently, the management of elemental impurities in pharmaceutical products is changing from management based on concentrations in drug product components to management based on permissible daily exposures in drug products.[7-9] The developed method was validated according to International Council for Harmonization (ICH) (Q2A) guidelines.[10]

Few methods were developed by RP-HPLC and LC-MS according to literatures, A method was performed using HPLC equipped with a conventional octadecylsilyl silica column and ultraviolet detector Simultaneous determination of serum propafenone and its metabolites.[11] A reversed phase HPLC method was developed to stereoselectively determine enantiomers of propafenone in human plasma.[12] A simple, rapid, accurate, precise, robust and reproducible reverse phase high performance liquid chromatographic method was developed for the determination of Propafenone HCl in pure drug and pharmaceutical dosage form.[13] A simple, precise and accurate RP-UFLC method was developed for determination

of propafenone hydrochloride.[14] A simple, sensitive and rapid High performance liquid chromatography/positive ion electrospray tandem mass spectrometry method was to be developed and validated for quantification of propafenone (PPF) and its two major metabolite 5-hydroxy propafenone (5-OHP) and N-depropyl propafenone (NDP) in human plasma.[15] Another LC–MS/MS method was adopted to develop a novel sample preparation Hybrid SPE phospholipid technology to extract plasma samples for improved phospholipid removal.[16] A rapid spectrophotometric and chromatographic method was developed for the estimation of propafenone hydrochloride in tablet dosage form by Quality by Design (QbD) approach as per ICH Q8(R2) guidelines.[17] In another study a rapid and sensitive LC-MS/MS method was developed and validated for the quantification of propafenone (PPF) and its active metabolite 5-hydroxypropafenone (5-OHP) in human plasma.[18] In this study, a novel method for determining 17 elemental impurities in propafenone hydrochloride was developed and validated by ICP-MS.

MATERIALS AND METHODS

Chemicals and Reagents

The chemicals used were obtained from the following suppliers: Conc. Nitric acid (69%) obtained from (Honey well Trace analysis), Conc. Hydrochloric acid (35%) procured from (Fisher scientific Trace analysis), and Tuning solutions used were procured from (Inorganic ventures) ICP-MS grade. The standards such as Cadmium, Lead, Arsenic, Mercury, Cobalt, Vanadium, Nickel, Thallium, Palladium, Iridium, Osmium, Rhodium, Ruthenium, Selenium, Silver, Platinum were procured from (Inorganic Venture) and Gold standard belonging to (Acc standard). Propafenone Hydrochloride was obtained as a gift sample from Pharmazell India P. LTD

Instruments used

An Agilent ICP-MS 7800 series, an Analytical Balance Radwag AS 82/220.X2, Micropipette Brand 20µL, 200µL, 1000µL and a Microwave Digester Milestone ETHOSUP 17092516 was used for the study. Table 1 Illustrates Instrument parameters

Plasma Condition

The RF Power was 1550 W, the RF matching was found to be 1.80 V, the sample depth was 8.0 mm, nebulizer gas flow was streamed at 1.01 L/min, nebulizer pump pressure was 0.10 rps, spray chamber temperature was 2°C, and mode used was He, He flow rate was 4.3 mL/min and the energy discrimination rate was 3.0 V.

Acquisition Parameters

The acquisition mode was spectrum mode, the peak pattern was 3 points, 3 replicates were used for the study, the sweeps/replicate was found to be 100, the integration time/mass (sec) was observed in the range of 0.0999 sec and the number of masses used was 17.

Tuning solution:

The standard solution was prepared by taking 1 ppb mixture of Li, Y, Tl, Co & Ce as tuning solutions, the expected m/z was found in the range of 7, 89, 205, 58 & 140 for all the five tuning solutions and the % RSD limit was observed to be NMT 15 % for (Li, Y, Tl / Co).

Table 1 Instrument parameters

Parameter	Method Condition	Parameter	Method Condition
Plasma Condition		**Octopole Condition**	
RF Power	1550 W	Energy discrimination	3.0 V
RF Matching	1.80 V	**Acquisition Parameters**	
Sample Depth	8.0 mm	Acq Mode	Spectrum
Nebulizer Gas	flow 1.01 L/min	Peak Pattern	3 points
Nebulizer Pump	0.10 rps	Replicates	Sweeps/Replicate 100
Spray Pattern temperature	2°C	Sweeps/Replicate	100
Mode	He	Integration time mass	0.0999 sec
He Flow	On	Number of masses	17
He flow rate	0.43 ml/min		

Table 2 Specification Limit for the elements

Elements Class	Name of the impurity	Specification Limit in (ppm)	Elements Class	Name of the impurity	Specification Limit in (ppm)
Class - 1	Cadmium	NMT 0.5	Class – 2B	Thallium	NMT 0.8
	Lead	NMT 0.5		Gold	NMT 10
	Arsenic	NMT 1.5		Palladium	NMT 10
Class – 2A	Mercury	NMT 3		Iridium	NMT 10
	Cobalt	NMT 5		Osmium	NMT 10
	Vanadium	NMT 10		Rhodium	NMT 10
	Nickel	NMT 20		Ruthenium	NMT 10
				Selenium	NMT 15
				Silver	NMT 15
				Platinum	NMT 10

Preparation of Diluent:

The diluent solution was assessed by transferring 20 ml of concentrated nitric acid (69%) and concentrated hydrochloric acid (35%) into a 1000 mL volumetric flask, previously rendered with 500 mL of purified water and the volume was adjusted up to the mark with purified water.

Preparation of Standard mix stock solution:

The required volume of standard concentration 1000 ppm of each element were pipetted out and was transferred into a 50 mL volumetric flask and the volume was made up to the level with diluent and mixed well.

Preparation of Standard linearity level solutions:

The required volume of standard was prepared and pipetted out and transferred individually into a separate five 10 mL volumetric flask and 0.2 ml sulfuric acid solution and 4 ml reverse Aquaregia was added the volume was increased up to the required volume with water and mixed well. The required concentrations were pipetted out respectively in parts per billion and labeled as calibration standard level -2 to 6.

Preparation of sample solution

The homogenized sample of about 0.2 g was exactly weighed and transferred into a clean and dried Microwave digestion 50 mL capacity sample vessel and 0.5 mL of concentrated sulphuric acid (98%) was added and the vessels were closed and kept inside Microwave digester following program condition.

Microwave Digestion Program

The vessels were cooled at room temperature after completion of pre-digestion. Then 9.0 ml of concentrated nitric acid and 1 mL concentrated hydrochloric acid was added, then the vessels were closed and kept again for pre digestion for 15 minutes on bench top, then the vessels were kept inside Microwave digester following program conditions.

The vessels were cooled after completion of digestion at room temperature and the sample solution was transferred into a 25 mL volumetric flask, the vessels were washed with a portion of 10 mL purified water and transferred to above volumetric flasks then the volume was adjusted to the mark with purified water and mixed well.

System suitability

A study was conducted to demonstrate the system precision, blank and calibration standard solutions were prepared as per the test method and aspirated into ICPMS system. Correlation coefficient of calibration curve should be ≥ 0.99 for each analyte. Concentration of each analyte in bracketing standard should not be vary by ± 20% of actual concentration.

Specificity

A study was conducted to demonstrate the blank, sample blank, calibration standard solutions and non-spiked test solution as per method of analysis which were prepared and aspirated into ICPMS system. Elements

response was evaluated and the interference of blank and sample blank in each element abundance was calculated. The average (five times aspiration) of each calibration blank CPS and sample blank CPS for each analyte should not be more than 5% of 100% level standard solution CPS.

Determination of LOD and LOQ

A study was conducted to demonstrate the limit of detection and limit of Quantitation level based on the Residual standard deviation method by aspirating six levels (5%, 10%, 25%, 50%, 75% and 100%) with respect to the target level. The LOD and LOQ for each analyte should not be more than 30% of the specification limit. The % RSD of class – 1, class – 2A & 2B elements response at LOQ level should be NMT 20%.

Method Precision

The method precision of test method was evaluated by analyzing six spiked test samples and aspirated into ICPMS system. The content of elemental impurities in sample was calculated. The % RSD of the content of each elemental impurities in six samples should be NMT 20%.

Linearity and Range

To demonstrate the linearity of test method, prepared the standard solutions of LOQ, 25%, 50%,100%, 200% and 300% of the targeted concentration and analyzed as per the method. Correlation coefficient for each analyte should not be less than 0.99.

Ruggedness (Intermediate Precision)

The intermediate precision of test method was evaluated by analyzing six spiked samples and aspirated into ICPMS system. The study was performed on different day and different analyst. The content of elemental impurities in sample was calculated. The % RSD of the content of each elemental impurities in six samples should be NMT 20%. The cumulative % RSD for residue of class – 1, class – 2A & 2Belements in twelve preparations (i.e. method and intermediate precision) for each analyte should not be more than 25%.

Accuracy (Recovery)

To demonstrate the accuracy of test method, recovery of element from spiked samples was evaluated. Samples were prepared by spiking the element class – 1, class – 2A & 2B with sample at different levels ranging from LOQ to 300 % of the target concentration of known standards. The sample solutions were prepared in triplicate at LOQ, 100%, 200% and 300% spiked levels and subtract the content from the unspiked sample. The mean % recovery for each analyte at each level should be 70 % to 130 %.

Robustness

The robustness of the analytical method was established by its reliability against deliberate changes in instrumental condition and sample preparation. The test sample was prepared and spiked at specification level and analyzed as per method of analysis by changing the following parameters, such as variation in stabilization time (± 10%), variation in sample diluent concentration (± 10%),

RESULTS AND DISCUSSION

System suitability

A study was performed to investigate the system precision, blank and calibration standard solutions. The samples were prepared as per the test method and aspirated into ICPMS system. The system suitability parameters were calculated and found to be within the prescribed percentage limits. The correlation coefficient of calibration curve for each analyte was found to be > 0.99. Concentration of each analyte in bracketing standard was within the acceptance criteria (± 20% of actual concentration) from the obtained data it was concluded that system was suitable. [19] The results are summarized in Table–3

Table – 3 System suitability results of Elemental Impurities

System suitability parameter	Correlation coefficient of calibration curve	System suitability parameter	Correlation coefficient of calibration curve
Element Name	**Observed value**	**Element Name**	**Observed value**
Vanadium (V)	17	Cadmium (Cd)	3
Cobalt (Co)	2	Osmium (Os)	1
Nickel (Ni)	2	Iridium (Ir)	1
Arsenic (As)	0	Platinum (Pt)	1
Selenium (Se)	1	Gold (Au)	1
Ruthenium (Ru)	0	Mercury (Hg)	0
Rhodium (Rh)	0	Thallium (Tl)	0
Palladium (Pd)	1	Lead (Pb)	3
Silver (Ag)	11		

Specificity

A study was performed in order to demonstrate the blank, sample blank, calibration standard solutions, and unspiked test solutions which were prepared according to the method of analysis and aspirated into the ICPMS system. The response of the elements was evaluated and calculated, and the interference of the blank and sample blank in each element abundance was noted. The average (five times aspiration) of each calibration blank CPS and sample blank CPS for each analyte should not be more than 5% of 100% level standard solution CPS. From the observed data it was concluded that method was specific. [20] The results are summarized in Table – 4

Table – 4 Specificity results

Element name	% Interference of Blank (Difference from 100% level standard CPS)		Element name	% Interference of Blank (Difference from 100% level standard CPS)	
Vanadium (V)	1.4	1.5	Cadmium (Cd)	0.2	0.8
Cobalt (Co)	0.0	0.1	Osmium (Os)	0.7	0.4
Nickel (Ni)	0.2	0.9	Iridium (Ir)	0.3	0.1
Arsenic (As)	1.2	1.2	Platinum (Pt)	0.1	0.1
Selenium (Se)	0.2	0.2	Gold (Au)	2.2	0.9
Ruthenium (Ru)	0.0	0.0	Mercury (Hg)	0.5	0.2
Rhodium (Rh)	0.0	0.0	Thallium (Tl)	2.1	0.9
Palladium (Pd)	0.1	0.0	Lead (Pb)	1.0	4.3
Silver (Ag)	0.1	0.1			

Determination of LOD and LOQ

A study was carried out to demonstrate the limit of detection and limit of Quantitation level based on the relative standard deviation method by aspirating six levels (5%, 10%, 25%, 50%, 75% and 100%) with respect to the target level. The concentration of LOD and LOQ of the solution was derived by using the formula and the results are evaluated in Table – 5. Mass spectrum was evaluated for the limit of detection and limit of Quantitation level. The LOD level was confirmed by aspirating the solution in triplicate and the precision was determined at limit of Quantitation level by injecting six times a solution of spiked standard with the concentration at LOQ level and calculated the relative standard deviation of peak response. The LOQ for each analyte should not be more than 30 % of the specification limit. LOQ for each analyte was found to be below 30% of the specification limit. The response of LOD solution for each element was found to be consistent. From the LOQ data the % RSD of class – 1, class – 2A & 2B elements response at LOQ level was found to be within 20%. Based on the observed data, it was concluded that the LOD and LOQ value for each elemental impurities reported values were observed to be at lowest possible level. [21]

Table 5-Establishment of LOD and LOQ level of elemental impurity

Element name	Correlationcoefficient	Observed LOD in ppm	Observed LOQ in ppm
Vanadium (V)	0.99996	0.00093	0.00282
Cobalt (Co)	0.99998	0.00038	0.00116
Nickel (Ni)	0.99995	0.00222	0.00673
Arsenic (As)	0.99976	0.00037	0.00111
Selenium (Se)	0.99991	0.00227	0.00689
Ruthenium (Ru)	0.99998	0.00076	0.00230
Rhodium (Rh)	0.99999	0.00053	0.00161
Palladium (Pd)	0.99997	0.00085	0.00257
Silver (Ag)	0.99991	0.00226	0.00686
Cadmium (Cd)	0.99998	0.00004	0.00011
Osmium (Os)	0.99999	0.00054	0.00164
Iridium (Ir)	0.99997	0.00084	0.00255
Platinum (Pt)	0.99993	0.00135	0.00409
Gold (Au)	0.99932	0.00411	0.01245

Method Precision

The method precision of test method was evaluated by analyzing six spiked test samples and aspirated into ICPMS system. The content of elemental impurities in sample was calculated. The relative standard deviations of six sample preparation of each % elemental impurity were found to be within acceptance criteria. The % RSD of the content of each elemental impurities in six samples were found to be less than 20 %. From the obtained data it was concluded that method was precise. [22] The results are summarized in Table –6

Table – 6 Method Precision results

Element name	Recovered concentration in %							% RSD
	Met. Precision-1	Met. Precision-2	Met. Precision-3	Met. Precision-4	Met. Precision-5	Met. Precision-6	Average	
Vanadium	107.7	105.7	109.4	108.2	107.3	105.1	107.2	1.5
Cobalt	94.8	92.7	95.7	94.5	94.4	92.1	94.0	1.4
Nickel	94.4	93.0	95.6	94.6	94.4	92.3	94.1	1.3
Arsenic	94.5	89.3	93.1	94.2	92.3	93.2	92.8	2.0
Selenium	92.7	93.3	98.8	96.3	93.2	91.7	94.3	2.8
Ruthenium	94.1	92.9	95.4	94.4	94.5	92.5	94.0	1.1
Rhodium	94.9	93.1	96.1	95.1	95.0	92.9	94.5	1.3
Palladium	94.1	92.4	94.3	93.8	94.9	93.2	93.8	0.9
Silver	85.8	84.1	88	86.6	87.9	84.9	86.2	1.8
Cadmium	97.0	92.5	94.4	94.5	93.7	91.6	94.0	2.0
Osmium	94.2	95.6	98.6	97.9	98.4	96.6	96.9	1.8
Iridium	97.3	96.0	99.8	98.2	98.8	97.0	97.9	1.4
Platinum	95.9	94.9	97.6	96.6	97.4	94.8	96.2	1.3
Gold	91.1	92.6	100.5	96.4	101.7	98.8	96.9	4.4
Mercury	95.6	94.8	98.4	97.3	97.5	95.7	96.6	1.4
Thallium	91.6	93.1	100.3	95.8	100.9	98.5	96.7	4.0
Lead	94.3	93.0	95.7	94.9	94.6	93.0	94.3	1.1

Linearity and Range

The linearity of test method was demonstrated by preparing the standard solutions of LOQ, 25%, 50%, 100%, 200% and 300% of the targeted concentration and analyzed as per the method. The correlation coefficient was observed to be within the acceptance limit. The Correlation coefficient for each analyte was found to be >0.99. The residual sum of square, the intercept and the slope of the regression line were reported. Based on the linearity, precision and accuracy data, the range of the test method was from LOQ to 300 % of the target concentration was observed to be within the range. From the obtained values, it was concluded that method was found to be linear. [23] The results are summarized in Table –7

Table – 7 Linearity and Range results

Element name	Correlation coefficient	Squared correlation Coefficient (r^2) for linearity levels	% Variation of bracketing standard solution	
			Before linearity levels	After linearity levels
Vanadium	0.99809	0.994	10	4
Cobalt	0.99996	0.999	0	4
Nickel	0.99992	0.999	1	5
Arsenic	0.99989	0.999	5	8
Selenium	0.99993	0.999	2	3
Ruthenium	0.99997	0.999	0	6
Rhodium	0.99992	0.999	3	1
Palladium	0.99997	0.999	1	5
Silver	0.99894	0.997	3	1
Cadmium	0.99989	0.999	4	2

Element name	Correlation coefficient	Squared correlation Coefficient (r^2) for linearity levels	% Variation of bracketing standard solution	
			Before linearity levels	After linearity levels
Osmium	0.99993	0.999	2	9
Iridium	0.99995	0.999	4	0
Platinum	0.99996	0.999	4	0
Gold	0.99999	1.000	1	12
Mercury	0.99957	0.998	3	2
Thallium	0.99903	0.997	2	11
Lead	0.99994	0.999	3	2

Ruggedness

The intermediate precision of test method was evaluated by analyzing six spiked samples and aspirated into ICPMS system. The study was performed on different day and different analyst. The content of elemental impurities in the sample was calculated. The relative standard deviations of six sample preparation of each % elemental impurity were found to be within acceptance criteria. The % RSD of the content of each elemental impurities in six samples were found to be below 20 %. The cumulative % RSD for residue of class – 1, class – 2A & 2B elements (i.e. method and intermediate precision) for each analyte was found to be less than 25 %. From the obtained data it was concluded that the method was precise and rugged. [24] The results are summarized in Table 8.

Table –8 Ruggedness results

Element name	Recovered concentration in %							% RSD
	Int. Precision-1	Int. Precision-2	Int. Precision-3	Int. Precision-4	Int. Precision-5	Int. Precision-6	Average	
Vanadium	116.7	117.7	117.2	115.7	118.6	115.8	117.0	1.0
Cobalt	102.0	102.4	102.1	101.4	103.3	101.5	102.1	0.7
Nickel	100.8	101.5	101.2	100.8	102.6	101.0	101.3	0.7
Arsenic	98.1	102.8	98.0	101.0	103.2	99.1	100.4	2.3
Selenium	101.0	101.5	98.8	101.8	101.8	101.3	101.0	1.1
Ruthenium	101.2	101.6	101.1	100.9	102.8	100.9	101.4	0.7
Rhodium	101.3	102.1	101.2	101.4	102.5	101.8	101.7	0.5
Palladium	100.7	100.1	101.1	98.7	102.4	102.0	100.8	1.3
Silver	89.4	89.7	91.1	90.0	95.2	91.7	91.2	2.4
Cadmium	103.5	98.9	100.5	99.1	102.8	102.3	101.2	1.9
Osmium	98.3	101.3	100.4	100.7	103.7	101.6	101.0	1.7
Iridium	101.6	102.5	103.0	102.1	104.4	103.2	102.8	1.0
Platinum	100.1	101.4	101.2	100.5	102.9	101.0	101.2	1.0
Gold	92.0	95.9	101.3	95.7	105.4	103.7	99.0	5.3
Mercury	98.7	101.6	101.8	100.2	102.7	99.9	100.8	1.5
Thallium	94.6	98.4	102.4	97.4	106.7	103.9	100.6	4.5
Lead	98.5	99.6	98.6	98.3	100.0	98.7	99.0	0.7

Accuracy/ Recovery

To demonstrate the accuracy of test method, recovery of element from spiked samples was evaluated. Samples were prepared by spiking the element class – 1, class – 2A & 2B with sample at different levels ranging from LOQ to 300 % of the target concentration of known standards. The sample solutions were prepared in triplicate at LOQ, 100 %, 200 % and 300 % spiked levels and subtract the content from the unspiked sample. The mean % recovery for each analyte at each level was found to be within 70 % to 130 %. From the above data, it was concluded that method was accurate. [25] The results are summarized in Table – 9

Table –9 Accuracy/ Recovery results

Name of the elements	LOQ level Recovered conc. in ppm			100%level Recovered conc. in ppm		
	1	2	3	1	2	3
Vanadium (V)	0.0033	0.0033	0.0033	0.0887	0.0887	0.0884
Cobalt (Co)	0.0012	0.0012	0.0012	0.0382	0.0386	0.0381
Nickel (Ni)	0.0067	0.0068	0.0069	0.1531	0.1545	0.1519
Arsenic (As)	0.0011	0.0011	0.0011	0.0113	0.0112	0.0114
Selenium (Se)	0.0064	0.0067	0.0067	0.1157	0.1147	0.1163
Ruthenium (Ru)	0.0022	0.0022	0.0021	0.0762	0.0762	0.0759
Rhodium (Rh)	0.0015	0.0015	0.0015	0.0772	0.0771	0.0764
Palladium (Pd)	0.0023	0.0023	0.0023	0.0755	0.0754	0.0746
Silver (Ag)	0.0067	0.0069	0.0069	0.1086	0.1031	0.1109
Cadmium (Cd)	0.0001	0.0001	0.0001	0.0038	0.0038	0.0040
Osmium (Os)	0.0016	0.0015	0.0014	0.0744	0.0742	0.0747
Iridium (Ir)	0.0026	0.0025	0.0024	0.0773	0.0779	0.0768
Platinum (Pt)	0.0038	0.0038	0.0037	0.0772	0.0768	0.0763
Gold (Au)	0.0112	0.0111	0.0115	0.0680	0.0696	0.0749
Mercury (Hg)	0.0007	0.0007	0.0007	0.0233	0.0231	0.0230
Thallium (Tl)	0.0008	0.0007	0.0007	0.0056	0.0055	0.0060
Lead (Pb)	0.0002	0.0002	0.0002	0.0039	0.0040	0.0040

Robustness

Effect of variation in Stabilization time

The robustness of the analytical method was established by its reliability against deliberate changes in instrumental condition and sample preparation. The test sample was prepared and spiked at specification level and analyzed as per method of analysis by changing the following, variation in stabilization time (± 10%). The system suitability parameters were evaluated by calculating the % RSD of the content of each elemental impurity in the sample as per the variant test method. The % RSD of the content of each elemental impurities in duplicate spiked samples were found to be below 20 %. From the data presented, it was observed that method was robust and precise. [26] The results are summarized in Table – 10

Table – 10 Robustness results

Robustness – Actual condition							
Element name	**Correlation coefficient**	**Robust-1 % recovered conc.**	**Robust-2 % recovered conc.**	**Average**	**% RSD**	**% Variation of Bkt. std solution recovery before sample**	**% Variation of Bkt. std solution recovery after sample**
Vanadium	0.9929	114.8	116.9	115.9	1.3	14	15
Cobalt	0.9998	100.3	102.5	101.4	1.5	0	1
Nickel	0.9998	100.6	101.6	101.1	0.7	2	0
Arsenic	0.9998	96.9	100.4	98.7	2.5	1	1
Selenium	0.9995	100.5	103.6	102.1	2.1	4	0
Ruthenium	0.9999	101.1	101.6	101.4	0.3	1	0
Rhodium	0.9998	101.3	101.8	101.6	0.3	1	0
Palladium	0.9999	100.9	101.0	101.0	0.1	1	2
Silver	0.9998	89.4	90.3	89.9	0.7	12	14
Cadmium	0.9998	102.6	100.6	101.6	1.4	0	3
Osmium	0.9999	98.6	102.1	100.4	2.5	1	0
Iridium	0.9998	102.8	103.8	103.3	0.7	2	3
Platinum	0.9998	101.2	101.8	101.5	0.4	0	1
Gold	0.9997	94.0	99.3	96.7	3.9	0	0
Mercury	0.9999	100.8	102.5	101.7	1.2	1	0
Thallium	0.9984	96.0	101.0	98.5	3.6	2	3
Lead	0.9996	101.0	100.7	100.9	0.2	3	2

Method variation details

The method variations were performed by taking the actual condition, the stabilization time was 50 seconds, the lower variation limit was found to be (-10%) 45 sec and the Higher variation (+10%) was observed at 55 seconds. The calibration data of elements are summarized in Table 11 Fig 2, 3 & 4.

Table 11 Calibration data of Elements

Calibration of Elements								
Vanadium	**Cobalt**	**Nickel**	**Arsenic**	**Selenium**	**Ruthenium**	**Rhodium**	**Palladium**	**Silver**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
22.112	9.672	39.127	2.88	28.127	19.186	19.618	18.8	26.5
45.981	20.241	81.228	5.816	60.488	40.215	41.24	39.729	60.937
91.276	40.172	160.111	11.707	119.185	79.843	80.782	79.059	118.794
115.582	60.372	240.324	18.048	181.045	120.05	120.364	120.554	179.271
155.917	79.616	319.503	24.171	239.736	160.089	159.074	160.273	241.353
	Cadmium	**Osmium**	**Iridium**	**Platinum**	**Gold**	**Mercury**	**Thallium**	**Lead**
	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	0.986	18.556	19.481	19.227	16.98	5.891	1.381	0.96
	2.004	39.449	41.187	40.741	39.022	12.258	3.173	2.028
	3.996	79.24	80.068	80.384	78.231	23.92	6.387	4.013
	6.046	119.859	119.863	120.251	121.768	35.963	9.941	6.005
	7.968	160.804	159.837	159.531	160.18	48.017	13.107	7.988

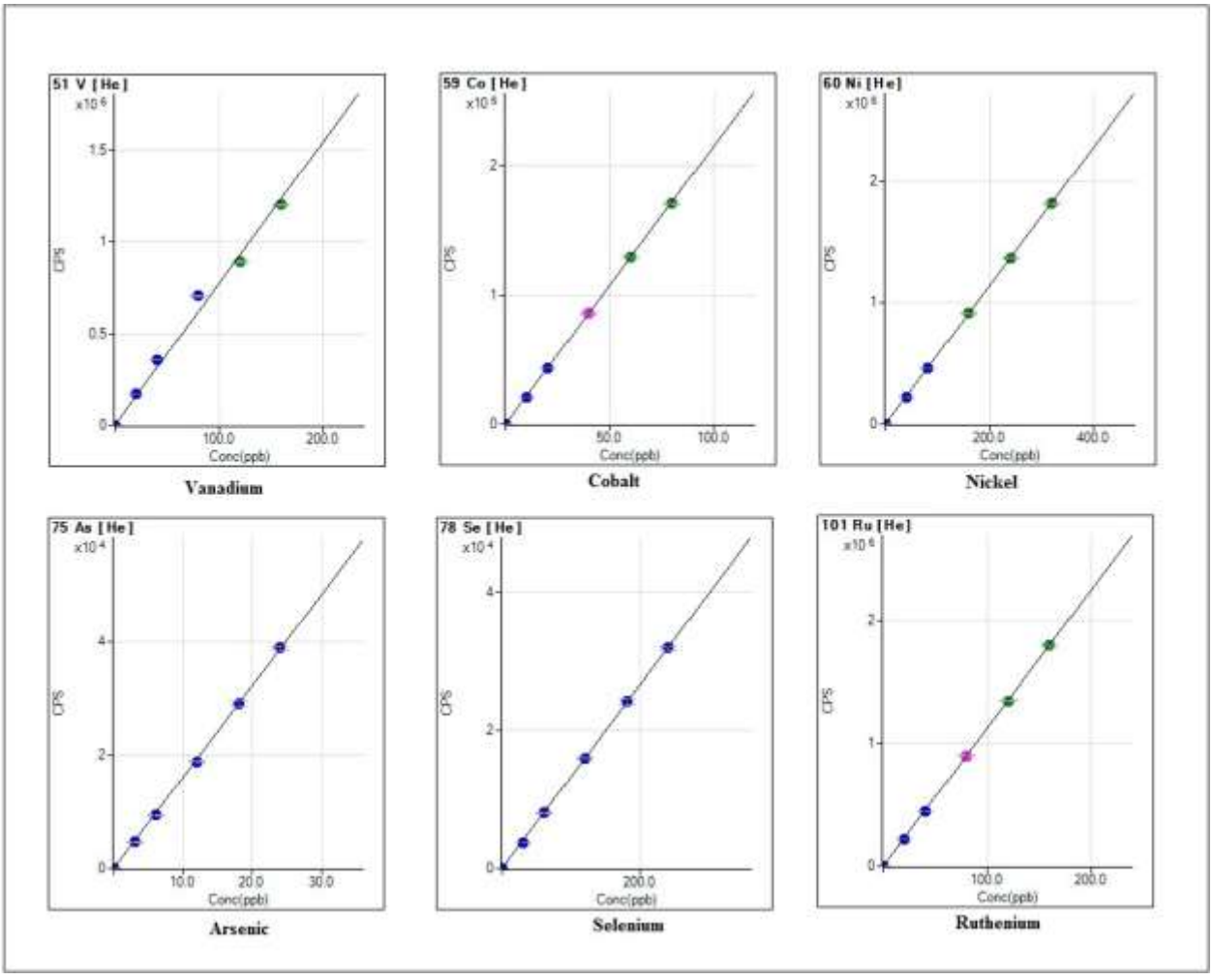

Fig 2 Calibration data for V, Co, Ni, As, Se and Ru

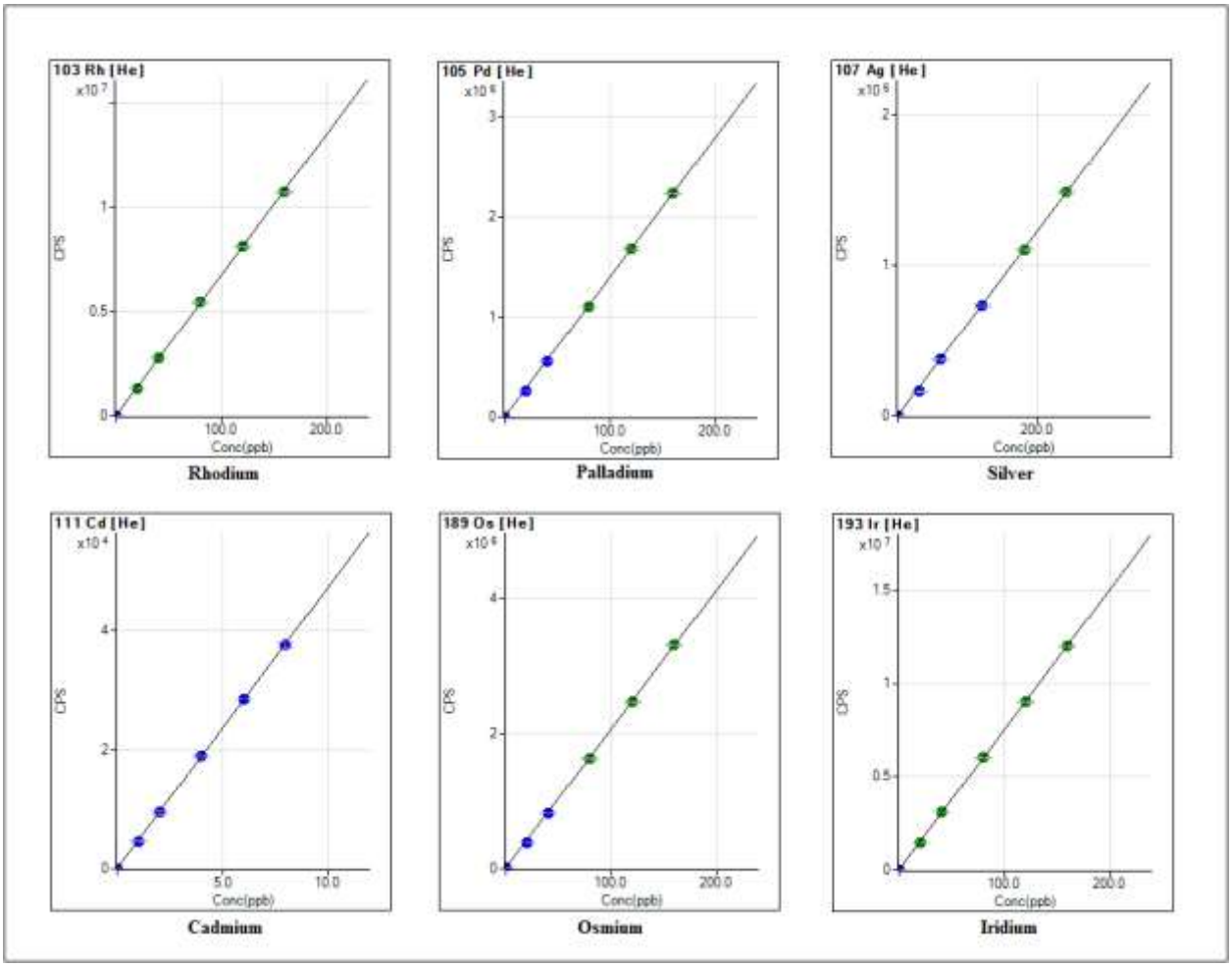

Fig 3 Calibration data for Rh, Pd, Ag, Cd, Os, Ir

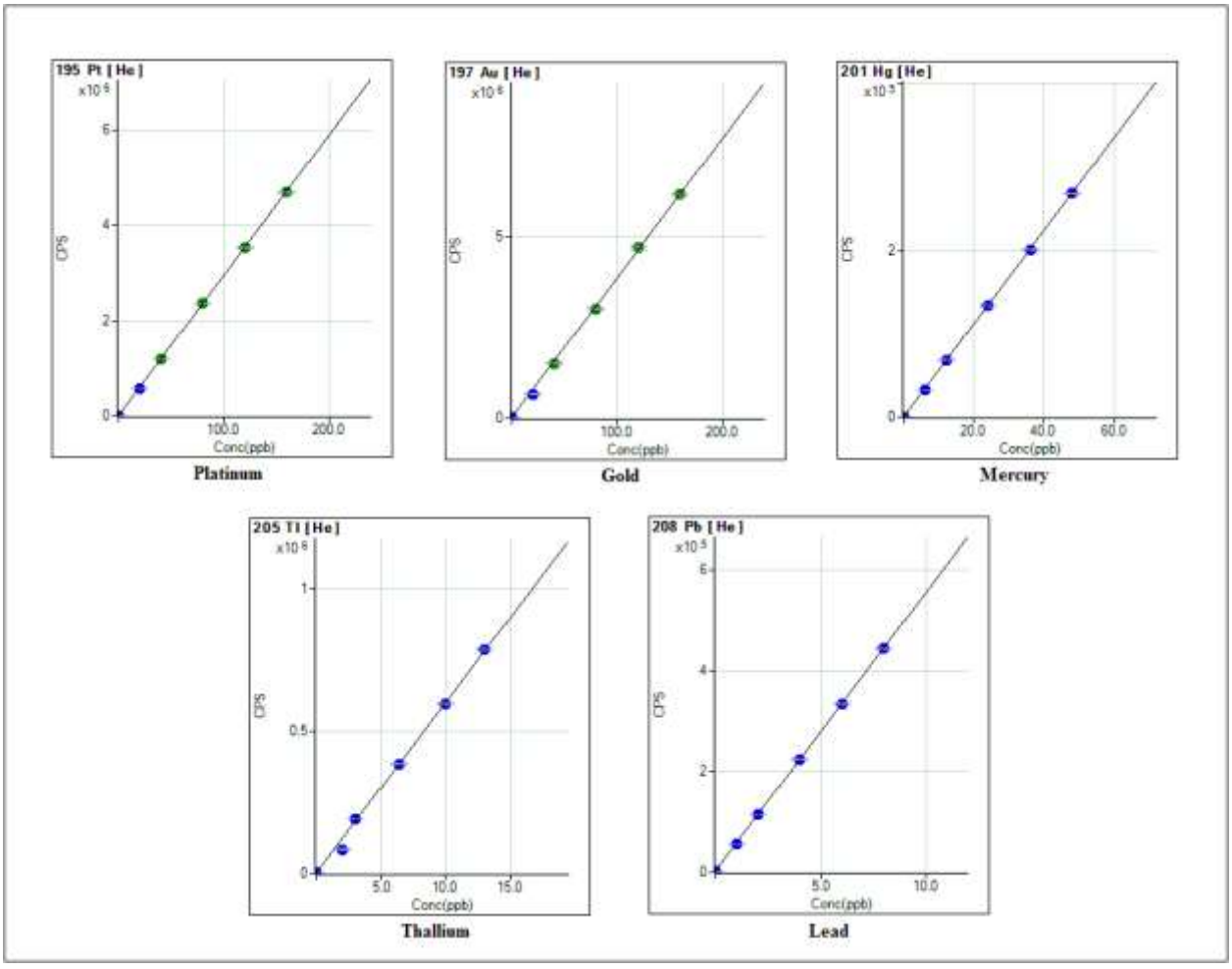

Fig 4 Calibration data for Pt, Au, Hg, TI, Pb

DISCUSSION

The present research work focused on simple and rugged ICP-MS method development and validation of 17 elemental impurities, i.e., Class 1 impurities Cd, Pb, As, Hg, Class 2A Co, V, Ni and Class 2B T1, Se, Ag, Au, Pd, Ir, Os, Rh, Ru, and Pt in propafenone hydrochloride drug substance. For the analysis of propafenone hydrochloride, drug substance sample digestion was done using nitric acid and sulfuric acid. Among the elemental impurities detected in propafenone hydrochloride drug substance samples, elemental impurities in class 1, impurities in class 2A & 2B, according to the elemental impurities' classification based on toxicity from ICH guidelines. Till date, no ICP-MS method was reported for the concurrent quantification of elemental impurities in propafenone hydrochloride drug substance. So, an attempt was made to develop simple, rapid ICP-MS method, and it was validated with precision, specificity, linearity, ruggedness, robustness, accuracy,

LOD and LOQ consecutively. Linearity obtained was with the acceptable prescribed limits respectively. The average recovery value was observed to be within the permissible limits. Estimated concentrations of these elements in drug substance samples were lower than the limits established by the chapter 232. [7]

For System suitability the correlation coefficient of calibration curve for each analyte was found to be > 0.99. Concentration of each analyte in bracketing standard was within the acceptance criteria (± 20% of actual concentration) from the obtained data it was concluded that system was suitable. The specificity studies demonstrated that the average (five times aspiration) of each calibration blank CPS and sample blank CPS for each analyte should not be more than 5% of 100% level standard solution CPS. From the observed data it was concluded that method was specific. The Limit of Quantification LOQ for each analyte should not be more than 30 % of the specification limit. LOQ for each analyte was found to be below 30% of the specification limit. The response of LOD solution for each element was found to be consistent. From the LOQ data the % RSD of class – 1, class – 2A & 2B elements response at LOQ level was found to be within 20%. Based on the observed data, it was concluded that the LOD and LOQ value for each elemental impurities reported values were observed to be at lowest possible level. For method precision the % RSD of the content of each elemental impurities in six samples were found to be less than 20 %. From the obtained data it was concluded that method was precise. The Correlation coefficient for each analyte was found to be >0.99. the residual sum of square, the intercept and the slope of the regression line were reported. Based on the linearity, precision and accuracy data, the range of the test method was from LOQ to 300 % of the target concentration was observed to be within the range. From the observed values, it was concluded that method was found to be linear. For method and intermediate precision % RSD of the content of each elemental impurities in six samples were found to be below 20 %. The cumulative % RSD for residue of class – 1, class – 2A & 2B elements (i.e. method and intermediate precision) for each analyte was found to be less than 25 %. From the observed data it was concluded that the method was precise and rugged. The mean % recovery for each analyte at each level was found to be within 70 % to 130 %. From the above data, it was concluded that method was accurate. For robustness the % RSD of the content of each elemental impurities in duplicate spiked samples were found to be below 20 %. From the data presented, it was observed that method was robust and precise. All the validation parameters such as system suitability, specificity, linearity, precision, LOD and LOQ, Accuracy and robustness compiled with the acceptance limits according to USP and ICH guidelines. In true sense, the daily maximum dose for propafenone hydrochloride and thus the risk is very little; therefore, the limits established considering this maximum daily dose may be elevated. [27-2]

CONCLUSION

A novel ICP-MS method was developed and validated according to current ICH and FDA guidelines to quantify 17 elemental impurities, class 1, Class 2A and 2B in propafenone hydrochloride. The proposed ICP-MS method has been evaluated to be precise, specific, linear, rugged, robust and accurate and proved convenient and effective for the quality control of propafenone hydrochloride. Thus, the present study demonstrates that ICP-MS has advantages over other conventional analytical methods for the determination of elemental impurities because of sensitivity, i.e., the lower limit of detection, for 17 elemental impurities in propafenone hydrochloride drug substance. Therefore, the method can easily be adopted for routine quantitative analysis of elemental impurities present as residual impurities in propafenone hydrochloride drug substance.

ABBREVIATIONS

ICP-MS: Inductively coupled plasma – Mass spectroscopy; RSD: Relative Standard Deviation; LOD:

Limit of Detection; LOQ: Limit of Quantitation; mL: Milliliter; ppm: Parts per million; ppb: Parts per billion; W: Watts; V: Volts; L/min: Liter/minute; rps: rotations per second; cps: Counts per second; mg: milligram; min: minutes; Hrs: Hours; °C: degree Celsius; µL: microliter; Sec: seconds; mm: millimeter; Std: Standard, USP: United States Pharmacopeia; ICH: International Council for Harmonization; NMT: Not more than; RSD: Relative Standard Deviation; FDA: Food and Drug Administration; HPLC: High Performance Liquid Chromatography; LC-MS: Liquid Chromatography Mass Spectrometry; UFLC-Ultra Fast Liquid Chromatography; PDE: Permitted daily exposure.

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تطوير واعتماد أسلوب بسيط وحساس لنظام ICP-MS لقياس الشوائب الأساسية في مادة هيدروكلوريد البروبافينون

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ملخص

الشوائب الأساسية هي مواد موجودة في المنتجات الدوائية، أو المخارج، أو التركيبات الدوائية. وقد تتكون بوجود محفزات وملوثات بيئية. يمكن اكتشاف الشوائب الأساسية عن طريق طريقة متطورة مثل القياس الطيفي للكتلة البلازمية المقترن بالحث (.(ICP-MSيعد ICP-MS طريقة متقدمة للكشف عن الشوائب الأساسية في المواد الدوائية. في هذه الدراسة تم إستخدام دواء بروبافينون هيدروكلوريد، وهو دواء مضاد لاضطراب النظم تابع للفئة 1 ج يستخدم لمنع عدم انتظام ضربات القلب فوق البطيني والبطين.تهدف هذه الدراسة إلى تطوير واعتماد طريقة التنظير الطيفي للكتلة البلازمية المقترنة بالتحريض لاكتشاف الملوثات الأساسية، أي الفئة 1 والأقراص المضغوطة والبطاقة الأساسية والشوائب من الفئة 2 ألف والزئبق والكيميائية والخامسة وشوائب الفئة 2 باء مثل الشوائب من الفئة 2 ألف، T1، Se، Ag، Au، Pd، Ir، Os، Rh، Ru، و .PTتم الكشف عن 17 شوائب أساسية في هيدروكلوريد البروبافينون، واستخدمت هذه الطريقة في التحليل المنتظم لعينة من 17 شوائب أساسية في هيدروكلوريد البروبافينون للاستخدام الصيدلاني. وحددت شروط الصك باستخدام قوة الترددات اللاسلكية البالغة 1550 واط، والغاز الإضافي 0.5 لتر/دقيقة، وتدفق الرذاذ البالغ 1.01 لتر/دقيقة للضغط على مضخة الرذاذ يبلغ 0.10 آر بي، ودرجة حرارة غرفة الرذاذ تبلغ درجتين مئويتين، وكانت الحالة هي هو، وكان معدل التدفق 4.3 ملليلتر/دقيقة، وكان معدل التمييز في الطاقة 3.0 فولت. وتتسم التقنية بحساسية وقد تحدد الشوائب الأساسية المستصوبة ضمن الحدود التنظيمية المسموح بها عند وجود عناصر إضافية. وقد تبين أن نهج ICP-MS المقترح دقيق ودقيق وخطي وصلد وقوي وملائم لمراقبة جودة مادة بروبافينون هيدروكلوريد الدواء. وكانت نتائج الخطية لكل شوائب 0،9990. وقد تم التحقق من صحة هذه الأساليب وفقا لمتطلبات USP والمبادئ التوجيهية للمجلس الدولي لتنسيق تكنولوجيا المعلومات والاتصالات. والنهج المقترح هو أداة ممتازة لمراقبة الجودة للتقييم الكمي المتزامن، والكشف عن الملوثات الأساسية عند مستويات منخفضة في هيدروكلوريد مادة العقاقير البروبافينون.

الكلمات الدالة: الشوائب الأساسية، ICP-MS، هيدروكلوريد البروبافينون، التحقق.

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