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Development and validation of a simple and rapid ICP-OES method for quantification of elemental impurities in voriconazole drug substance

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Abstract

Background: The aim of the present study was to develop and validate an inductively coupled plasma optical emission spectroscopic (ICP–OES) method for quantification of elemental impurities, i.e., Lead, Palladium, and Zinc, in voriconazole drug substance, and this method was employed for the regular sample analysis of Lead, Palladium, and Zinc in voriconazole drug substance for pharmaceutical use. The method has been validated using RF power of 1150 W, auxiliary gas of 0.5 L/min, and nebulizer flow of 0.4 L/min and plasma view at axial mode for Lead and Palladium and radial mode for Zinc. The wavelength was monitored for Lead, Palladium, and Zinc at 220.3 nm, 340.4 nm, and 213.8 nm respectively.

Results: The method is selective and is capable of detecting desired elemental impurities with regulatory acceptance limits in the presence of other elements. The validation experiments involve the demonstration of system suitability, specificity, LOD and LOQ, linearity, precision, and accuracy experiments. The linearity results obtained > 0.9990 for all three impurities.

Conclusion: The proposed method is simple, sensitive quality control tool for the simultaneous quantitative determination of Lead, Palladium, and Zinc at low levels in voriconazole drug substance.

Keywords: Inductively coupled plasma optical emission spectroscopy, Pharmaceutical analysis, Elemental impurities, Voriconazole and method validation

Background

Voriconazole is a second-generation triazole antifungal agent used to treat serious fungal infections. Chemically, voriconazole is ($\alpha R, \beta S$)- α -(2,4-difluorophenyl)-5-fluoro- β -methyl- α -(1*H*-1,2,4-triazol-1-ylmethyl)-4-pyrimidineethanol (OR) (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1*H*-1,2,4-triazol-1-yl) butan-2-OL with a molecular formula of $C_{16}H_{14}F_3N_5O$ and a molecular weight of

349.3 [1]. Voriconazole was first synthesized by Pfizer in the brand name of Vfend® which has broad-spectrum activity against pathogenic yeasts, including *Aspergillus*, *Cryptococcus*, and *Candida* species and ineffective against *Rhizopus*, *Zygomycosis* reduced activity [2, 3]. Pharmaceutically, voriconazole formulations are available in both oral and intravenous administration. The similar drug of Fluconazole structurally modified to develop the Voriconazole [4]. In the literature, a few analytical methods have been reported for the quantitative estimation of voriconazole in pharmaceutical dosage form and in biological fluids [5–8], electrophoresis and chromatographic separation of voriconazole stereoisomers [9], determination

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of voriconazole impurities by HPLC [10], and determination of voriconazole in formulation by HPLC [11]. Quantitative determination of voriconazole in rat and beagle dog plasma reported [12]. In voriconazole, synthetic process Lead, Palladium, and Zinc-related complex molecules are used as catalytic agents. During the synthesis of drug substances, elemental impurities may arise from several sources and may be catalysts that were added intentionally in synthesis or may be present as impurities. These elemental impurities do not provide any therapeutic benefit to the patient, and levels in the drugs should be controlled within acceptable limits. Depending upon their permitted daily exposures, lower levels have to be considered for elemental risk [13]. The intake of palladium causes fever, hemolysis, erythema, edema, and eye irritation [14]. Lead causes depression, loss of appetite, intermittent abdominal pain, nausea, diarrhea, constipation, muscle pain, and problems with sleep [15]. Zinc causes nausea, vomiting, loss of appetite, stomach cramps, diarrhea, and headaches [16]. Hence, residual elemental impurities controls are required in voriconazole drug substance for regulatory requirements. Several colorimetric and spectrometric methods for determination of Lead [17–19], Palladium [20–23], and Zinc [24–28] was reported. In view of this, we have developed and validated the inductively coupled plasma optical emission spectroscopy (ICP-OES) method and presented in this research paper. To the best of our knowledge, no method for the determination of Palladium, Lead, and Zinc by ICP-OES was reported in voriconazole drug substance. The developed method was validated according to International Conference on Harmonization (ICH) (Q2A) guidelines [29]. The chemical structure of voriconazole is shown in Fig. 1.

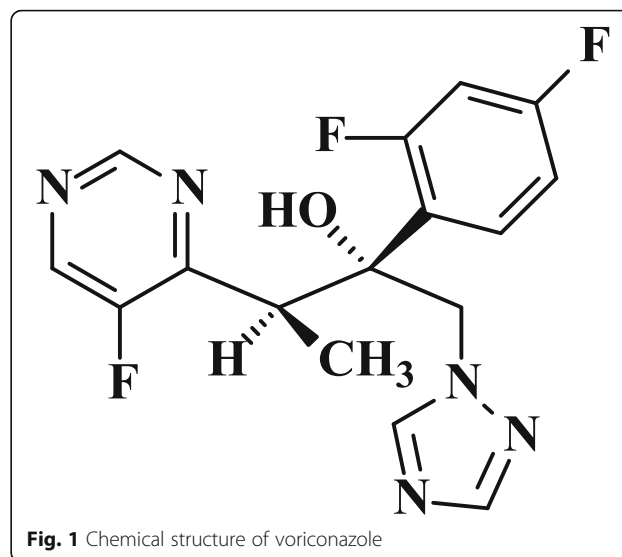
Methods

Chemicals and reagents

Sulfuric acid, hydrochloric acid, and hydrogen peroxide purchased were from Merck chemicals limited. ICP standards, Lead, Zinc, and Palladium each 1000 mg/L and multi-element standard solution IV (1000 mg/L) were purchased from Sigma-Aldrich. Voriconazole working standard was gifted from APL Research Centre-II (a division of Aurobindo Pharma Limited) and Milli Q-water produced from Milli pore water system. Borosil type glassware and calibrated 100–1000 μ l pipettes were used.

Equipment

An inductively coupled plasma system equipped with optical emission spectrophotometer make Thermo Fisher Scientific with data handling system controlled with iTEVA software used for method development and validation.



Preparation of solutions

Lead and Palladium standard stock solution (Pb: 5 ppm and Pd: 10 ppm)

Fifty microliters of Lead ICP standard solution (1000 mg/L) and 100 μ l of Palladium ICP standard solution (1000 mg/L) was transferred into a 10 ml clean dry volumetric flask, mixed, and made up to volume with Milli-Q Water.

Preparation of calibration standard-1 (Lead: 0.015 ppm, Palladium: 0.03 ppm, and Zinc: 3.9 ppm)

Seventy-five microliters of Lead and Palladium standard stock solution and 97.5 μ l of Zinc ICP standards (1000 mg/L) pipette into a 25 ml clean dry volumetric flask, containing 15 ml of water, 2.5 ml of Hydrogen peroxide solution, 1.0 ml of Hydrochloric acid, and slowly 0.5 ml of sulfuric acid was added. The solution was and diluted to the mark with Milli-Q water.

Calibration standard-2 (Lead: 0.03 ppm, Palladium: 0.06 ppm, and Zinc: 7.8 ppm)

One hundred fifty microliters of Lead and Palladium standard stock solution and 195 μ l of Zinc ICP standards (1000 mg/L) were mixed into a 25 ml clean dry

Table 1 Specificity experiments

Elemental impurity	Mean value of element (μ g/g)		% Difference
	Controlled sample	Spiked sample	
Lead	0.55	0.55	0.0
Palladium	0.91	0.84	8.0
Zinc	128.0	125.9	1.7

Table 2 LOD and LOQ prediction

LOD and LOQ prediction						
S. No	Lead		Palladium		Zinc	
	Conc (ppm)	Counts/S	Conc (ppm)	Counts/S	Conc (ppm)	Counts/S
1	0.00501	16.435	0.01001	84.239	1.0000	232.94
2	0.01001	31.430	0.02002	203.890	2.0000	453.07
3	0.01502	46.324	0.03003	287.300	3.9000	872.50
4	0.02002	69.326	0.04004	393.450	5.9200	1349.10
5	0.03003	99.411	0.06006	575.420	7.8000	1747.00
6	0.04505	151.640	0.09009	881.090	11.7200	2665.10
7	0.06006	206.010	0.12012	1180.900	15.6000	3583.00
STEYX	2.269403105		8.707586102		18.37286651	
Conc (ppm)	LOD	LOQ	LOD	LOQ	LOD	LOQ
	0.005	0.015	0.010	0.030	0.300	1.000
LOD (ppm) w.r.st test conc	0.08		0.20		5.00	
LOQ (ppm) w.r.st Test conc	0.25		0.50		16.70	

volumetric flask, containing 15 ml of water, 2.5 ml of hydrogen peroxide solution, 1.0 ml of hydrochloric acid, and slowly 0.5 ml of sulfuric acid was added. The solution was mixed and diluted to the mark with Milli-Q water.

Calibration standard-3 (Lead: 0.06 ppm, Palladium: 0.12 ppm, and Zinc: 15.6 ppm)

Three hundred microliters of Lead and Palladium standard stock solution and 390 µl of Zinc ICP standards (1000 mg/L) were mixed into a 25 ml clean, dry volumetric flask, containing 15 ml of water, 2.5 ml of hydrogen peroxide solution, 1.0 ml of hydrochloric acid, and slowly 0.5 ml of sulfuric acid was added. The solution was mixed and diluted to the mark with Milli-Q water.

Table 3 LOD and LOQ experiments of Lead

LOD and LOQ of Lead		
S. No	LOD (ppm)	LOQ (ppm)
1	0.0045	0.0140
2	0.0042	0.0132
3	0.0045	0.0144
4	0.0043	0.0143
5	0.0042	0.0132
6	0.0040	0.0135
Mean	0.0043	0.0138
%RSD	4.7	3.6
con., (ppm)	0.005	0.015
conc., (ppm) w.r.t test concentration	0.08	0.25

Blank solution

Transferring 5.0 ml of hydrogen peroxide solution into a 50 ml clean dry volumetric flask, containing 30 ml of water, add 2.0 ml of hydrochloric acid and slowly 1.0 ml of sulfuric acid was added. The solution was mixed and diluted to the mark with Milli-Q water.

Sample solution

Accurately weighed and transferred about 0.6 g of sample in to 10 ml clean dry volumetric flask, 1.0 ml of hydrogen peroxide solution, 0.4 ml of hydrochloric acid was added, and sonicate to dissolve. Then, 0.2 ml of sulfuric acid was slowly added, mixed well, and make up to volume with Milli-Q water. (To obtain the clear solutions, centrifuge the sample solutions at 6000 rpm for 10

Table 4 LOD and LOQ experiments of Palladium

LOD and LOQ of Palladium		
S. No	LOD(ppm)	LOQ(ppm)
1	0.0105	0.0302
2	0.0101	0.0301
3	0.0109	0.0296
4	0.0113	0.0297
5	0.0108	0.0299
6	0.0111	0.0301
Mean	0.0108	0.0299
%RSD	3.7	0.7
con., (ppm)	0.01	0.03
conc., (ppm) w.r.t test concentration	0.2	0.5

Table 5 LOD and LOQ experiments of Zinc

LOD and LOQ of Zinc		
S. No	LOD (ppm)	LOQ (ppm)
1	0.3092	1.0000
2	0.3036	0.9992
3	0.3008	1.0060
4	0.3011	0.9972
5	0.3093	1.0080
6	0.3063	1.0030
Mean	0.3051	1.0022
%RSD	1.2	0.4
con., (ppm)	0.3	1.0
conc., (ppm) w.r.t test concentration	5.0	16.7

min and the same solutions are used for sample analysis).

Method development and optimization of conditions

The principal goal of our research study is to develop an accurate and precise ICP-OES method to quantify Lead, Palladium, and Zinc present in voriconazole drug substance. During the development of the method, Lead, Palladium, and Zinc standard solution of known concentration was monitored for different emission lines 217.0 nm, 220.3 nm, 216.4 nm, and 283.3 nm for Lead; 340.4 nm, 363.4 nm, and 324.2 nm for Palladium; and 206.2 nm, 213.8 nm, and 202.5 nm for Zinc respectively by aspirating the solution. The responses of Lead, Palladium, and Zinc are very prominent at 220.3 nm, 340.4 nm, and 213.8 nm respectively when applied the target power of RF 1150W. No possible inferences were observed at this emission lines and good baseline was observed than other wavelengths. During the method development, above said wavelengths were optimized to get better sensitivity. Axial view was used for Lead and Palladium and radial view for Zinc. Instrumental settings are given below.

Source settings

Nebulizer pump	Flush pump rate(rpm):	100
	Analysis pump rate(rpm):	50
	Pump relaxation time:	5 s
	Pump tubing type :	Tygon orange/white
RF power:	1150 W	
Auxiliary gas:	0.5 L/min	
Nebulizer gas flow:	0.40 L/min	
Wavelength	220.3 nm for Lead	
	340.4 nm for Palladium	
	213.8 nm for Zinc	

Table 6 Summary of LOD and LOQ experiments results

Elemental impurity	% RSD		LOD (µg/g)	LOQ (µg/g)
	LOD	LOQ		
Lead	4.7	3.6	0.08	0.25
Palladium	3.7	0.7	0.2	0.5
Zinc	1.2	0.4	5.0	16.7

Results

Method validation

Specificity

To demonstrate specificity of test sample (control sample) and test sample spiked with multi elements, including Lead, Palladium, and Zinc standard (spiked sample) in triplicate were aspirated as per ICP-OES test methodology and determine the Lead, Palladium, and Zinc contents. Acceptance criteria is % difference between mean of each content in control sample and spiked sample should be not more than 10.0% as per method validation protocol. The specificity results are tabulated below (Table 1).

LOD and LOQ

Limit of detection (LOD) was obtained by aspirating a linear series of Lead 0.005 to 0.06 ppm, Palladium 0.01 to 0.12 ppm, and Zinc 1.0 to 15.6 ppm standard solutions were prepared in seven concentration ranges

Table 7 Linearity experiment results

S. No	Conc (ppm)	Counts/S	Statistical analysis	
Results for Lead				
1	0.0150	55.73	Slope	3833
2	0.0224	83.63	Intercept	-2
3	0.0300	113.39	STEYX	2
4	0.0450	167.83	Correlation co-efficient	0.9995
5	0.0600	229.23		
Results for Palladium				
1	0.0300	245.30	Slope	7546
2	0.0448	356.00	Intercept	13
3	0.0601	455.33	STEYX	10
4	0.0901	685.07	Correlation co-efficient	0.9990
5	0.1201	927.37		
Results for Zinc				
1	1.0000	24.675	Slope	24
2	3.9000	94.506	Intercept	0
3	7.8000	190.24	STEYX	3
4	11.7200	278.93	Correlation co-efficient	0.9997
5	15.6000	379.17		

Linearity graph of Lead

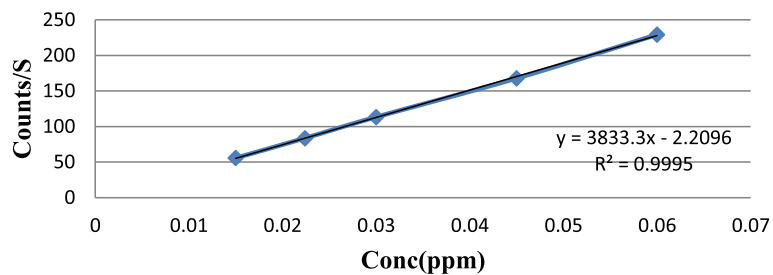


Fig. 2 Linearity graph of Lead

Linearity graph of Palladium

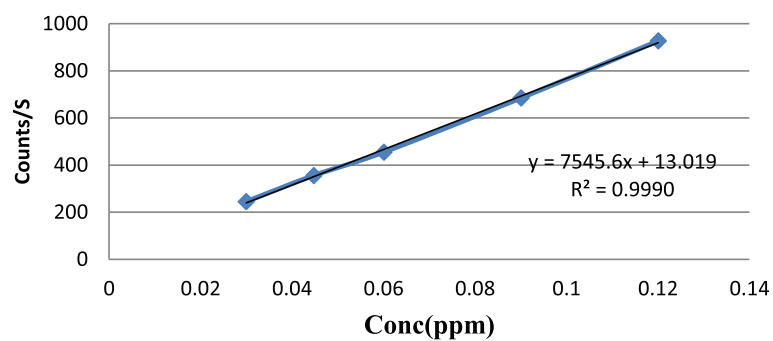


Fig. 3 Linearity graph of Palladium

Linearity graph of Zinc

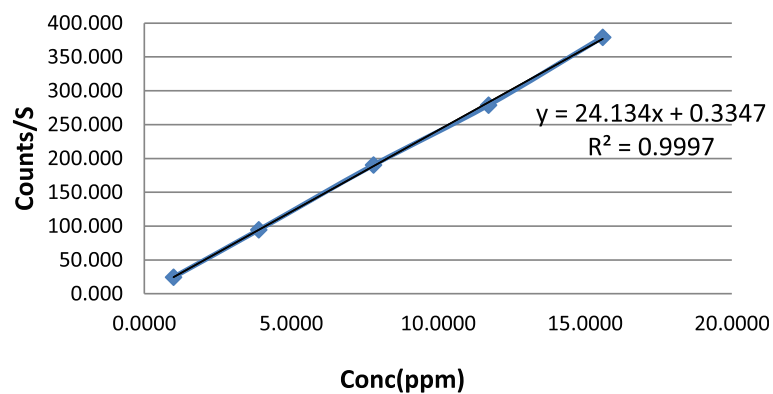


Fig. 4 Linearity graph of Zinc

Table 8 Accuracy results for Lead, Palladium, and Zinc

Concentration/sample ID	Mean % recovery (triplicate injections each)	%RSD
Results for Lead		
LOQ level sample	102.8	0.3
50% level sample	108.0	0.0
100% level sample	110.0	1.8
150% level sample	112.0	1.2
Results for Palladium		
LOQ level sample	85.3	1.4
50% level sample	85.3	1.4
100% level sample	91.3	7.0
150% level sample	87.6	6.2
Results for Zinc		
LOQ level sample	102.8	0.3
50% level sample	100.9	3.2
100% level sample	98.6	1.6
150% level sample	96.3	0.2

Table 9 System precision results of Lead, Palladium, and Zinc

Results of system precision			
Repetitions	Lead (mg/mL)	Palladium (mg/mL)	Zinc (mg/mL)
1	0.0140	0.0302	1.0000
2	0.0132	0.0301	0.9992
3	0.0144	0.0296	1.0060
4	0.0143	0.0297	0.9972
5	0.0132	0.0299	1.0080
6	0.0135	0.0301	1.0030
%RSD	3.6	0.7	0.4

Table 10 Method precision and ruggedness results

Results for method precision and ruggedness						
Sample preparations	Method precision Lead (µg/g)	Ruggedness	Method precision Palladium (µg/g)	Ruggedness	Method precision Zinc (µg/g)	Ruggedness
1	0.29	0.29	0.47	0.51	18.92	16.50
2	0.30	0.30	0.50	0.51	18.62	16.69
3	0.31	0.29	0.48	0.48	18.40	16.37
4	0.29	0.30	0.47	0.50	17.74	16.16
5	0.29	0.32	0.47	0.49	17.70	16.56
6	0.29	0.30	0.46	0.47	17.67	16.43
%RSD	2.8	3.7	2.9	3.3	3.0	1.1
Overall % RSD	3.2		3.6		5.7	

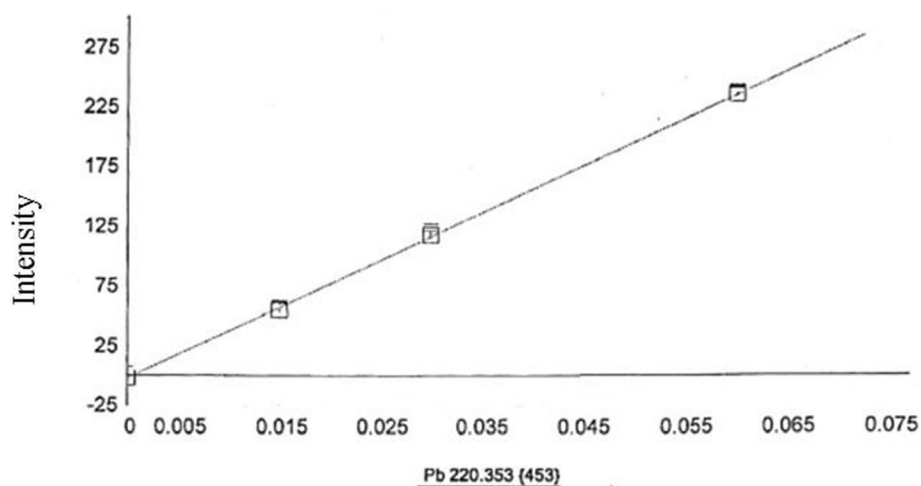


Fig. 5 Method precision representation of Lead

respectively. From the linearity data, slope and residual sum of squares (STEYX) obtained from above LOD and limit of quantitation (LOQ) values were predicted. And acceptance criteria is %RSD is not more than 33.0 for LOD and 10.0 for LOQ. LOD was calculated as 0.08 ppm for Lead, 0.2 ppm for palladium, and 5.0 ppm for Zinc. LOQ was obtained as 0.25 ppm for Lead, 0.5 ppm for palladium, and 16.7 ppm for Zinc. % RSD for 6 replicates obtained for LOQ was 3.6%, 0.7%, and 0.4% for Lead, Palladium, and Zinc respectively. Summarized results are shown in Tables 2, 3, 4, 5, and 6.

Linearity

Analytical method linearity is defined as the ability for showing the response of the analyte is proportional to the analyte concentration within a given range. The peak response obtained from the

ICP-OES was plotted against corresponding concentrations to obtain the calibration graph. The results of the linearity study gave linear relationship over the concentration range of 50% to 200% for Lead and Palladium, and of 12.8% to 200% for Zinc of specification level. From the regression analysis, the coefficient of determination R^2 was 0.9990 for all three analytes, indicating a linear relationship between the concentration of analyte and response under the peak. Linearity results for three analytes are shown in Table 7 and linearity graphs shown in Figs. 2, 3, and 4.

Accuracy (recovery)

Accuracy expresses the familiarity of conformity between the value obtained and the value which is accepted either as a predictable true value or an accepted reference value. The accuracy of the method is

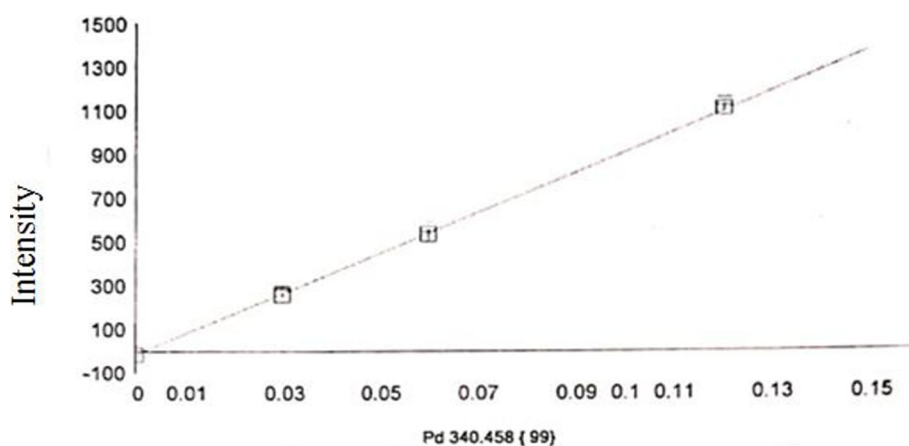


Fig. 6 Method precision representation of Palladium

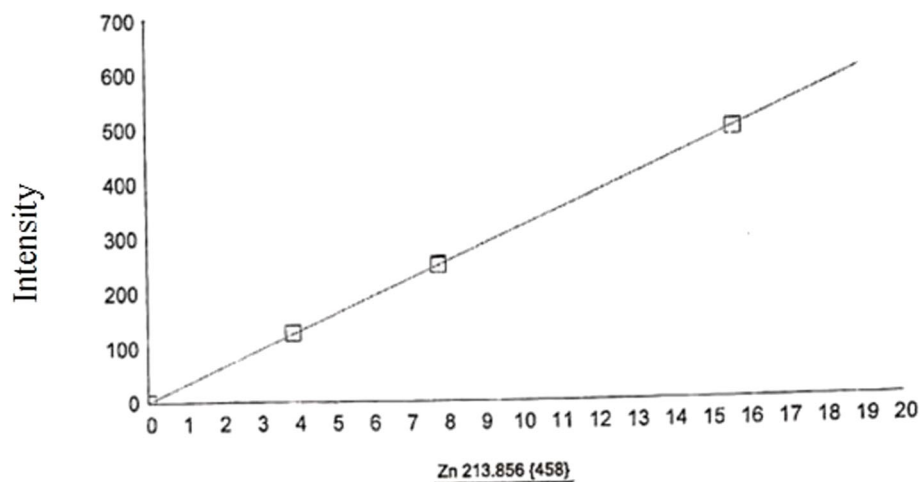


Fig. 7 Method precision representation of Zinc

determined by recovery studied for Lead, Palladium, and Zinc. The sample solutions were prepared in triplicate by spiking Lead, Palladium, and Zinc at LOQ level, 50%, 100%, and 150% of specification and analyzed individually as per test method. The percentage recovery of added Lead, Palladium, and Zinc and the % RSD were calculated for each replicate samples. Acceptance criteria is recovery should be between 70.0 and 150.0%. Accuracy results tabulated below (Table 8).

Precision (ruggedness)

The closeness of agreement between a series of measurements obtained from multiple sampling of the same homogeneous sample under given conditions. The precision was checked both for system and method. System precision was demonstrated by aspirating standard solution of Lead, Palladium, and Zinc at LOQ level and measured six times. The requirement of

acceptance criteria is %RSD should not be more than 10.0. The results were within the acceptable criteria. The experimental system precision results are shown in Table 9.

Method precision

Method precision was determined by preparing six sample solutions individually using single batch of voriconazole drug substance spiked with Lead, Palladium, and Zinc at LOQ level and aspirated into ICP-OES as per methodology. Ruggedness was obtained by six sample solutions were prepared individually using single batch of voriconazole (used for method precision) spiked with Lead, Palladium, and Zinc at LOQ level and aspirated into ICP-OES as per methodology and determined Lead, Palladium, and Zinc contents using different analyst on different day. Acceptance criteria is % RSD should not be more than 10.0% for method precision, ruggedness, and overall. Results were given in

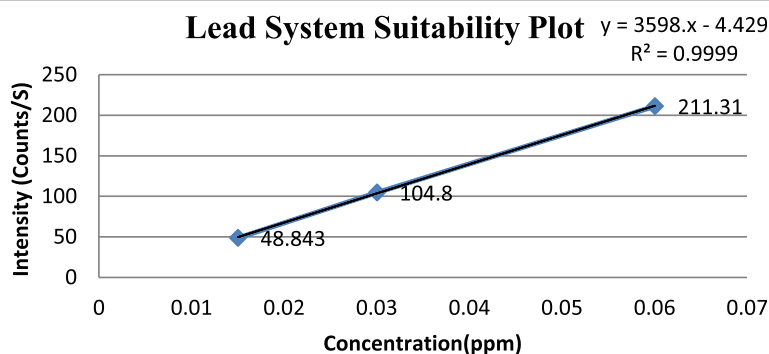


Fig. 8 System suitability plot of Lead

Table 11 System suitability results of Lead

S. No	Concentration (ppm)	Counts/S	Statistical analysis	
1	0.01502	48.843	Slope	3599
2	0.03003	104.8	Intercept	-4
3	0.06006	211.31	STEYX	1
Correlation co-efficient				0.9999

Table 10. Method precision spectra were shown in Figs. 5, 6, 7, and 8.

System suitability

A series of standard solutions of Lead, Palladium, and Zinc were prepared in the concentrations in the range for Lead (0.015 ppm, 0.03 ppm, and 0.06 ppm), Palladium (0.03 ppm, 0.06 ppm, and 0.12 ppm), and Zinc (3.9 ppm, 7.8 ppm, and 15.6 ppm) and aspirated to ICP-OES system as per methodology. From the linear solutions, correlation coefficient, Y-intercept, slope, and residual sum of squares (STEYX) were calculated, and thus the linear relationship of concentration vs Counts/S was verified over the range specified. Correlation coefficient results were 0.9999 for Lead, 0.9998 for Palladium, and 0.9999 for Zinc, respectively against acceptance criteria not less than 0.99. Results were given in Tables 10, 11, and 12. Method precision spectra are shown in Figs. 9 and 10.

Discussion

The research work focused on simple and rugged ICP-OES method development and validation [30–34] of three elemental impurities, i.e., Pb, Pd, and Zn, in voriconazole drug substance simultaneously. For the analysis of voriconazole, drug substance sample digestion was done using 2.5 ml of hydrogen peroxide solution, 1.0 ml of hydrochloric acid, and slowly 0.5 ml of sulfuric acid. Among the three elemental impurities determined in voriconazole drug substance samples, one elemental impurity is class 1 (Pb), one impurity is class 2B (Pd), and one impurity is class 4 (Zn) according to the elemental impurities classification based on toxicity from ICH guidelines [13]. Till date, no ICP-OES method reported

for the simultaneous determination of above three elemental impurities in any drug substance. So effort was through to develop simple, rapid ICP-OES method, and it was validated with LOD and LOQ 0.08 µg/g, 0.2 µg/g, 5 µg/g, and 0.25 µg/g, 0.5 µg/g, 16.7 µg/g for Pb, Pd, and Zn respectively. Linearity obtained was 0.9995, 0.9990, and 0.9997 for Pb, Pd, and Zn respectively. The average recovery found was 110% for Pb, 87.4% for Pd, and 98.6% for Zn. Determined concentrations of these analytes in drug substance samples were lower than the limits established by the chapter 232 [34]. In true sense, the daily maximum dose for voriconazole is 200 mg and thus the risk is very little; therefore, the limits established considering this maximum daily dose are even elevated (Table 13).

Conclusion

ICP-OES method was developed and validated according to current ICH and FDA guidelines to quantify Lead, Palladium, and Zinc in voriconazole drug substance. The proposed ICP-OES method has been evaluated over the linearity, precision, accuracy, and specificity and proved convenient and effective for the quality control of voriconazole drug substance. Thus, the present study demonstrates that ICP-OES has the advantages over other conventional analytical methods for the determination of Lead, Palladium, and Zinc because of sensitivity, i.e., the lower limit of detection, for Lead, Palladium, and Zinc in voriconazole drug substance. Therefore, the method can easily be adopted for routine quantitative analysis of Lead, Palladium, and Zinc present as residual impurities in voriconazole drug substance.

Table 12 System suitability results of Palladium

S. No	Concentration (ppm)	Counts/S	Statistical analysis	
1	0.03003	304.97	Slope	9584
2	0.06006	587.93	Intercept	4
3	0.12012	1190.1	STEYX	10
Correlation Co-efficient				0.9998

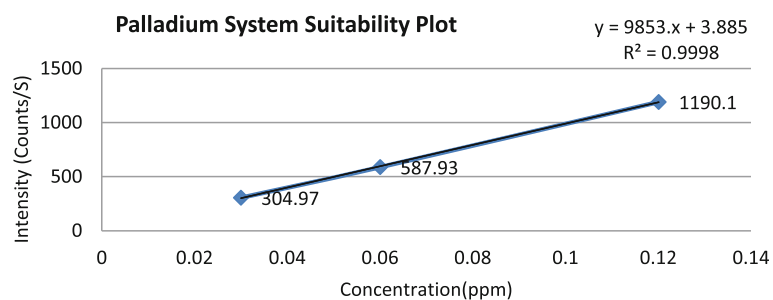


Fig. 9 System suitability plot of Palladium

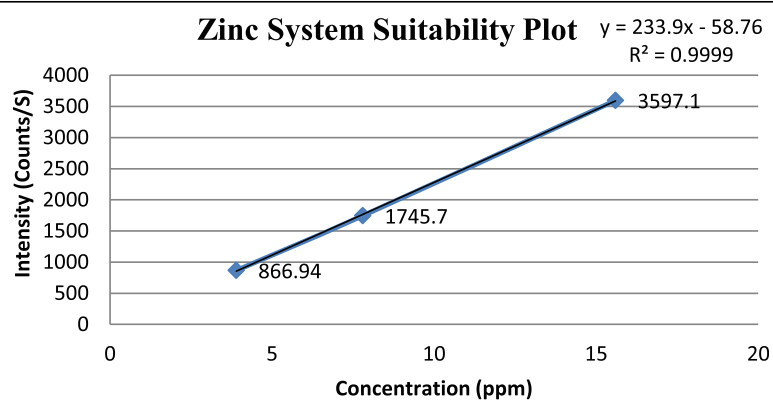


Fig. 10 System suitability plot of Zinc

Table 13 System suitability results of Zinc

S. No	Concentration(ppm)	Counts/S	Statistical analysis	
1	3.9	866.94	Slope	234
2	7.8	1745.7	Intercept	-59
3	15.6	3597.1	STEYX	25
Correlation co-efficient				0.9999

Abbreviations

LOD: Limit of detection; LOQ: Limit of quantitation; ICP-OES: Inductively coupled plasma optical emission spectroscopy; ICH: International Conference on Harmonization; FDA: Food and drug administration; R^2 : coefficient of determination

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Authors' contributions

MK performed the research work of the drug substance of Interest and TS as corresponding author executed the work. MK and JK prepared the manuscript and all authors (MK, TS, JK, CS, KS, KP) read the manuscript and approved.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

No competing interests to declare.

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References

1. Zhou L, Glickman RD, Chen N, Sponsel WE, Graybill JR, Lam KW (2002) Determination of voriconazole in aqueous humor by liquid chromatography–electrospray ionization–mass spectrometry. *J Chromatogr B* 776:213–220
2. Ray, S. J.; Richardson, K. (1994) U.S. Patent 5278175
3. Butters, M., Pettman, A. J. Harrison, J. A. (1997) WO9706160.
4. De Sarro A, La Camera E, Fera MT (2008) New and investigational triazole agents for the treatment of invasive fungal infections. *J Chemother* 20(6): 661–671
5. Purkins L, Wood N, Gharamani P, Greenhalgh K, Allen MJ, Kleinermans D (2002) A review of determination of voriconazole in human serum. *Antimicrob. Agents Chemother.* 46:2546–2550
6. Zhou L, Glickman RD, Chen N, Sponsel WE, Graybill JR, Lam KW (2002) A review of determination of voriconazole in human serum. *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.* 213:776–778
7. Keevil BG, Newman S, Lockhart S, Howard SJ, Moore CB, Denning DW (2004) A review of determination of voriconazole in human serum. *Ther. Drug. Monit.* 26:650–655
8. Perea S, Pennick G, Modak A, Fothergill A, Sutton D, Sheehan D, Rinaldi M (2000) Comparison of high-performance liquid chromatographic and microbiological methods for determination of voriconazole levels in plasma. *Antimicrob Agents Chemother.* 44:1209–1213
9. Owens PK, Fell AF, Coleman MW, Berridge JC (2002) Separation of the voriconazole stereoisomers by capillary electrophoresis and liquid chromatography. *Enantiomer* 4:79–90
10. Ferretti, R., Gallinella, B., La Torre, F. and Zanitti, L. (1998). A review on determination of voriconazole impurities by HPLC. *Chromatographia* 47: 11–12.
11. Srinubabu G, Raju CAI, Sarath N, Kumar PK, Rao JVLNS (2007) Development and validation of a HPLC method for the determination of voriconazole in pharmaceutical formulation using an experimental design. *Talanta* 71(3): 1424–1429
12. Cheng S, Qiu F, Huang J, He J (2007) Development and validation of a simple and rapid HPLC method for the quantitative determination of voriconazole in rat and beagle dog plasma. *Journal of Chromatographic Science* 45(7):409–414
13. International conference on harmonization of technical requirements for registration of pharmaceuticals for human use, guideline for elemental impurities, Q3D Step 4 (December 16, 2014).
14. Kielhorn, J., Melber, C., Keller, D., & Mangelsdorf, I. (2002). Palladium—a review of exposure and effects to human health. *International journal of hygiene and environmental health*, 205(6), 417–432. <https://doi.org/https://doi.org/10.1078/1438-4639-00180>
15. U.S. Department of Health and Human Services (2007) Toxicological profile for Lead (update). <http://www.atsdr.cdc.gov/toxprofiles/tp13.pdf> (PDF 4901KB, 582 pages) [Public Health Service Agency for Toxic Substances and Disease Registry. <https://doi.org/10.15620/cdc.95222>
16. Fosmire GJ (1990) Zinc toxicity. *Am. J. Clin. Nutr.* 51(2):225–227
17. Saavedra R, Soto C, Gómez R, Muñoz A (2013) Determination of lead(II) by thermal lens spectroscopy (TLS) using 2-(2'-thiazolylazo)-p-cresol (TAC) as chromophore reagent. *Microchemical Journal* 110:308–313
18. Hauser, P. C. (2017). Analytical methods for the determination of lead in the environment. *Lead – Its Effects on Environment and Health*.
19. Zhai Q, Li J, Zhang JP (2013) Spectrophotometric Determination of Lead in Tea Leaf Sample with Dibromo-p-chloro-arsenazo. *Asian J Chemistry* 25(1): 538–540
20. Tokalioglu S, Oymak T, Kartal S (2004) Determination of palladium in various samples by atomic absorption spectrometry after preconcentration with dimethylglyoxime on silica gel. *Anal. Chim. Acta* 511:255–260
21. Mori I, Kawakatsu T, Fujita Y, Matsuo M (1999) Selective spectrophotometric determination of palladium(II) with 2(5-nitro-2-pyridylazo)-5-(N-propyl-N-3-sulfo-propylamino)phenol(5-NO(2).PAPS) and tartaric acid with 5-NO(2).PAPS-niobium(V) complex. *Talanta* 48:1039–1044
22. Shokrollahi A, Ramdar K (2017) Determination of trace amounts of palladium by solution scanometric method. *J Taibah Univ Sci* 11(5):782–787
23. Rajput, M.; Jain, V. K.; Hamid, H.; Aggarwal, M.; Khandal, R. K. (2014) Quantitative determination of platinum and palladium in donepezil hydrochloride using inductively coupled plasma–optical emission spectroscopy. *Int J Pharm PharmSci*, 7, 323–329.
24. Säbel CE, Shepherd JL, Siemann S (2009) A direct spectrophotometric method for the simultaneous determination of zinc and cobalt in metalloproteins using 4-(2-pyridylazo)resorcinol. *Analytical Biochemistry* 391(1):74–76
25. Säbel CE, Neureuther JM, Siemann S (2010) A spectro photometric method for the determination of zinc, copper, and cobalt ions in metalloproteins using Zincon. *Analytical Biochemistry* 397(2):218–226
26. Cherian L, Gupta VK (1991) A new spectrophotometric method for the determination of zinc in milk and standard samples. *Water Air Soil Pollut* 57:505–512
27. Moneeb MS (2006) Polarographic chemometric determination of zinc and nickel in aqueous samples. *Talanta* 70(5):1035–1043
28. Mamatha Veeramachaneni, Kumar Raja Jayavarapu (2013) Development and validation of new ICP-OES Analytical Technique to quantify the contents of Copper, Magnesium & Zinc in "Escitalopram Oxalate, *J Adv Pharm Edu Res* vol 3(4),516–523.
29. ICH (2005) Validation of analytical procedures: methodology (Q2R1). International Conference on Harmonization, Food and Drug Administration
30. United States Pharmacopeia (2008) Ad hoc advisory panel on inorganic impurities and heavy metals and USP staff—stimuli to the revision process: general chapter on inorganic impurities: heavy metals
31. The United States Pharmacopeia Convention (2013), The United States pharmacopeia, Chapter 232: Elemental Impurities – Limits
32. European Pharmacopoeia, Chapter 5.20. Metal catalysts or metal residues. European Directorate for the Quality of Medicines. 2012.

33. The United States Pharmacopeia Convention (2013) The United States Pharmacopeia, Chapter 233: elemental impurities—procedures, revision bulletin, Official February 1, 2013.
34. The United States Pharmacopeia Convention (2017) The United States Pharmacopeia, Chapter 232: Elemental Impurities - Limits, USP 40 – NF 35, First Supplement, Official December 1, 2017.

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