Determination of Palladium Content in Nebivolol HCl Bulk Drug by ICP-OES

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The aim of the present work is to develop a validated analytical method for the determination of palladium content in nebivolol HCl bulk drug by inductive coupled plasma-optical emission spectroscopy (ICP-OES). Samples were analyzed after a preparation of sample solution by dissolving in suitable diluents of nitric acid along with hydrogen peroxide. In the present method, RF power of 1500 watts, plasma flow of 15 L/min, nebulizer flow of 0.7 L/min and plasma view at axial mode were used. The wavelength was monitored at 340.46 nm. This allowed a rapid determination of amount of palladium metal present in nebivolol bulk drug. The developed method was validated according to ICH guidelines. Calibration curve for palladium determination were conducted in the range of 10-100 µg/mL. The correlation coefficient for palladium was found to be 0.999970 which indicates good linearity. Recovery rates for palladium were in the range of 86.66-102.66. Limit of detection (LOD) and limit of quantification (LOQ) present in the sample was found to be 3 µg/mL and 10 µg/mL, respectively. The method developed and validated was selective, sensitive, rapid and capable of detecting palladium in the presence of other elements in bulk drugs.

Keywords: Nebivolol HCl, Inductive coupled plasma-optical emission spectroscopy, Metal analysis.

INTRODUCTION

Nebivolol is a β1 receptor blocker with nitric oxide poten-tiating vasodilator effect used in treatment of hypertension and in Europe, also for left ventricular failure [1]. It is highly cardio selective under certain circumstances. β-Blockers help patients with cardiovascular disease by blocking β receptors, while many of the side-effects of these medications are caused by their block-ade of β2 receptors [2]. Nebivolol is unique as a β-blocker. Unlike carvedilol, it has a nitric oxide potentiating vasodilator effect [3,4]. Along with labetalol, celiprolol and carvedilol, it is one of four β-blockers to cause dilation of blood vessels in addition to effects on heart [5]. However, recent studies question the clinical relevance of this property to Nebivolol's efficacy [6,7].

Various analytical techniques were employed for the determination of inorganic metal impurities include titration, ion-exchange chromatography, capillary electrophoresis and spectroscopic techniques like flame photometry, flourimetry, atomic absorption spectroscopy and inductive coupled plasma. Among the above mentioned techniques, inductive coupled plasma is a versatile tool for detection and quantification of elements in accurate manner and it works on the basis of atomic spectrometry. Inductive coupled plasma also further include 2 types which are ICP-optical emission spectroscopy and ICP-mass spectroscopy. Most specifically, ICP-OES is emission spectrometric technique that exploits the fact that excited atoms emit energy at a given wavelength as the electrons return to their ground state from excited state. A given element emits energy at specific wavelengths peculiar to its chemical nature. The intensity of the energy emitted at that wavelength is proportional to the amount of that element in the analyzed sample. When compared with the other techniques ICP-OES has an additional advantage in terms of detection limits (where it can detect to a concentration range of ppm or ppb) and a rapid analysis. In ICP-OES, sample experiences temperature estimated to be in the vicinity of 10,000 K. These results in atomization and excitation of even most refractory elements with high efficiency so that detection limits for these elements with ICP-OES can be well over and order of magnitude better than the corresponding values of other techniques [8].

The titration methods are not accurate whereas ion exchange chromatography and capillary electrophoresis stabilization is a time taking process and sensitivies are low when compared to ICP-OES. For the above reasons, ICP-OES has become a tool of choice for estimating metals. Literatures revealed that few methods like determination of metals in food samples like vinegar [9], environmental samples (soil and drinking water) [10-16], potato chips [17], honey [18] eliphos tablets [19] and escitalopram oxalate bulk drug [20] are reported.

This paper describes the methodology and validation procedure by ICP-OES for determination of metals in nebivolol bulk drug and the method was validated according to ICH (Q2R1) guidelines.

EXPERIMENTAL

Nitric acid (analytical grade) from Merck, India, MilliQ water and palladium metal standard of certified reference material were used. The nebivolol HCl was obtained as a gift sample from Varun Herbals, India. The method development and validation was performed by using ICP-OES and 3 % nitric acid is used as diluent.

ICP-OES conditions: The RF power used was 1300 W, plasma flow was 13 L/min, auxiliary gas flow was kept at 0.2 L/min, nebulizer flow was kept at 0.7 L/min, and pump rate was kept at 1 mL/min. Palladium was monitored at wavelength 340.458 nm. Plasma view was in axial view. Three replicates were performed.

Preparation of sample: The sample preparation was done by using Microwave digester. Weighed 200 mg of sample and added 5 mL of nitric acid and 2 mL of H_2O_2 dropwise, after completion of digestion cool the vessel and transferred it into 20 mL volumetric flask and made up to volume with diluent.

Preparation of standard: Preparation of palladium stock standard solution (10 µg/mL), palladium standard (certified reference material) with 1000 ppm was obtained and labeled as reference standard. Further suitable aliquots were prepared from the standard stock solutions with the concentrations of 10, 30, 50, 70 and 100 µg/mL.

RESULTS AND DISCUSSION

The main objective of the study was to develop a suitable ICP-OES method to quantify palladium content present in nebivolol HCl. During the method development, palladium standard prepared of any working concentration was monitored at different possible emission lines of 338.57, 340.46 and 345.85 nm by aspirating the solution. Among these emission lines at applied target RF power of 1500 W the response for palladium was evaluated. The response of palladium was prominent at 340.46 nm. Moreover, the baseline was to be good at above stated wavelengths compared to other emission lines of elements. The possible inferences were not observed at this emission lines. The method was optimized at these wavelengths during method development. To get better sensitivity plasma view mode was selected as axial. As this mode is much larger than that viewed by normal radial or normal size on ICP resulting higher intensity for elements.

Specificity: Prepared the sample one spiked sample (sample spiked with 100% standard solution) as per the method and analyzed. The obtained results are reported in Table-1. An

TABLE-1
SPECIFICITY

Element	Palladium
Element content in controlled sample (ppm)	–
Element spiked amount (ppm)	0.05
Recovery amount (ppm)	0.049
Recovery (%)	98

acceptance criterion for specificity as per USP is no interference is observed with test sample.

Linearity: Linearity was evaluated by preparing a linear series of standard solutions of palladium in the concentrations range from LOQ level to 150 % level of specification level. From the linear solutions, correlation co-efficient, Y intercept, slope were calculated and thus the linear relationship of concentration *versus* counts was verified over the range specified. The correlation coefficient for palladium was found to be 0.999970 which indicates good linearity. The results are reported in Table-2.

TABLE-2
LINEARITY

Statistical analysis	Observation
Slope	125.5
Y-intercept	42.78
Correlation coefficient	0.999970

Limit of detection (LOD) and Limit of quantification (LOQ): Linear series of palladium standard solutions was prepared in the concentration range from 0.01 ppm to 0.1 ppm and a calibration curve is developed and calculate the corelation coefficient. The LOD and LOQ were calculated and the LOD and LOQ levels are found to be as LOD = 3 ppb and LOQ= 10 ppb.

Precision: The precision of method was checked by analyzing six individual preparations of sample as per the test method and prepared six individual spike samples (at 100% level). The % RSD was found to be within the specification (% RSD should not be more than 5 %). The system precision was checked by analyzing six replicates of palladium standard solution (100 % level). The concentration of element for each replication was calculated by using the calibration standards (Tables 3 and 4).

Accuracy: Sample solutions were spiked with palladium at LOQ level, 100 % level and 200 % level with respect to sample concentration. Each spiked solution was prepared in triplicate and aspirated. The recovery of palladium was calculated against the standard working concentration (Table-5).

Ruggedness: The recovery levels tested in (Analyst-1) were again carried out in Analyst-2 using same instrument. The recovery values were found to be comparable.

TABLE-3
SYSTEM PRECISION VALUES

Sample	Repetitions						Results	
	1	2	3	4	5	6		
Palladium 0.05 ppm	0.050 ppm	0.050 ppm	0.050 ppm	0.049 ppm	0.048 ppm	0.051 ppm	Mean	0.050
							SD	0.0009
							RSD (%)	1.74

	TABLE-4 METHOD PRECISION VALUES								
Sample	Repetitions						Results		
	1	2	3	4	5	6			
Palladium ppm	0.051 ppm	0.051 ppm	0.050 ppm	0.051 ppm	0.051 ppm	0.050 ppm	Mean SD RSD (%)		0.0505 0.0005 0.990099

TABLE-5
ACCURACY OF PALLADIUM

Spike level (%)	Amount added (ppm)	Amount recovered (ppm)	Recovery (%)	Mean recovery (%)
LOQ level Sample	0.01	0.090	90	86.66
	0.01	0.090	90	
	0.01	0.080	80	
100	0.05	0.051	102	102.66
	0.05	0.052	104	
	0.05	0.051	102	
200	0.10	0.097	97	97.00
	0.10	0.097	97	
	0.10	0.097	97	

Sample analysis: The previously prepared sample was aspirated in the instrument, the concentration of palladium was found to be 1 ppm.

Conclusion

A validated and accurate ICP-OES method has been developed to estimate palladium content in nebivolol drug. The method is selective and is capable to quantitate Palladium in the presence of other trace elements. The method has been validated in terms of specificity, precision, linearity, accuracy and limit of detection and quantification. The validated method can be used to estimate elements not only in nebivolol but also in other drug substances.

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