

ATOMIC ABSORPTION SPECTROPHOTOMETER – A VERSATILE TOOL FOR THE ESTIMATION OF NICKEL CONTENT IN DRONEDARONE

VASAVI DEVI DASARI^{1*}, SWARNALATHA DUGASANI² VENKATASUBBA REDDY GOPIREDDY³

¹ JNTUA, Ananthapuramu, Andhra Pradesh, India. ²Department of Pharmaceutical Sciences, Annamacharya College of Pharmacy, Rajampeta, Andhra Pradesh, India. ³Department of Chemistry, Jawaharlal Nehru Technological University Anantapur College of Engineering, Pulivendula, Andhra Pradesh, India. Email: dvas.reddy@gmail.com

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ABSTRACT

Objective: The present investigation is to develop a validated analytical method for the determination of nickel content in dronedarone hydrochloride bulk drug by atomic absorption spectrophotometer (AAS).

Methods: Samples were analyzed after a preparation of sample solution by dissolving in suitable diluents of nitric acid and perchloric acid. In the present method, AAS with 0.2 nm slit width, nickel hollow cathode lamp with a wavelength of 232 nm has been employed.

Results: The system suitability parameters were performed to assess the system performance. The limit of detection and limit of quantification (LOQ) were found to be 0.051 ppm and 0.15 ppm, respectively. The percentage recovery at LOQ, 50%, 100%, and 150% levels of nickel in dronedarone was found to be 95.55, 109.33, 96, and 97.55, respectively.

Conclusion: With the developed method, the nickel content in dronedarone bulk sample was found to be 3.0 ppm.

Keywords: Dronedarone, Nickel, Atomic absorption spectrophotometer, Validation.

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INTRODUCTION

Dronedarone is a Class III antiarrhythmic drug recently approved by the US Food and Drug Administration in 2009 for the treatment of non-permanent atrial fibrillation and atrial flutter [1]. The chemical name is N-[2-butyl-3[4-[3-(dibutylamino) propoxy]benzoyl]-1-benzofuran-5-yl] methanesulfonamide hydrochloride according to IUPAC. Its molecular formulae are $C_{31}H_{44}N_2O_5S.HCl$ with a molecular weight of 593.22 g/mol [2]. Chemically, it is a benzofuran derivative containing heterocyclic compound which is a structural analog of amiodarone. DRO reduces the toxic effects in amiodarone by replacing the iodine group with a methanesulfonyl group [3]. Due to reduced lipophilicity, it has lower toxicity and superior pharmacokinetic characteristics than the amiodarone belonging to the same Class III antiarrhythmic drug [4]. DRO is crystalline in nature with a melting point of 149–153°C [5], with white to practically white, non-hygroscopic fine powder. It is a new active substance, and there is no official pharmacopoeial procedure available [6]. Literature overviews confess that drug was estimated by different analytical strategies such as spectrophotometric [7], high-performance liquid chromatography [8-17], and liquid chromatography mass spectrometry [18,19] in bulk drugs and formulation of dronedarone. From the review, it was found that there were no reported methods for the estimation of elemental impurity, i.e., nickel in dronedarone. Impurity profiling of pharmaceutical products was an extensive scope of concern. Rigid modulations are leaving behind for their effective use. Regarding the various regulatory guidelines, impurities are majorly organic or inorganic in nature (USP, ICH). To a great extent, we know about organic impurities, during the time inorganic impurities are procuring importance at recent times. The inorganic impurities, i.e., metal contamination, enter the standard reference materials and intermediates through crude materials, impetuses, reagents, solvents, and different supplies utilized for blend and for synthesis, This metal ions invaded possess the capability to decompose the materials of interest, which may sometimes prompt to potential noxious impacts, further to self-toxicity. Hence, it is necessary to monitor metal ion

contents in the standard reference material of drugs [20,21]. Various analytical strategies were utilized for the determination of inorganic metal impurities including titration, ion-exchange chromatography, capillary electrophoresis, and spectroscopic techniques such as flame photometry, fluorimetry, atomic absorption spectroscopy, and inductively coupled plasma. The titration strategies are not exact, whereas ion-exchange chromatography and capillary electrophoresis stabilization is a time-taking procedure and sensitivities are low when contrasted with atomic absorption spectrophotometer (AAS). For the above reasons, AAS has become a tool of choice for estimating metals. The present study was to carry out method development and validated using atomic absorption spectrophotometry to determine nickel content in dronedarone.

EXPERIMENTAL

Chemicals and reagents

Nickel standard from Merck, nitric acid and perchloric acid from SDFCL chemicals, Milli-Q water, and API as a gift sample were used in the study.

Instrumentation and operating conditions

AAS of model AA-6300 (Shimadzu) equipped with fully integrated atomizers of Shimadzu make was used for the analysis. The system was regulated from an interfaced PC running Wizard software. Atomic absorption measurements were carried out at 232 nm analysis wavelength, using nickel hollow cathode lamp, lamp current - 7 mA, slit width - 0.2 mm, burner height - 7 mm, oxidant flow - 15 L/min, acetylene flow - 1.6 L/min, lamp mode - BGC-D2, pre-spray time - 5.0 s, integration time - 5 s, and recommended flame - air acetylene.

Preparation of solutions

Preparation of nickel standard stock solution (solution A)

The 10 mL of 1000 mg/L concentrated nickel standard solution is taken into a 100 mL volumetric flask and dilute up to mark with Milli-Q

water which contains 100 mg/L of nickel. Prepare 5 mg/L of nickel by transferring 5 mL of above solution into a 100 mL volumetric flask and make up to volume with Milli-Q water.

Preparation of blank solution

Take 10 mL of concentrated nitric acid and 10 mL of perchloric acid to a 100 mL beaker. Heat on a hot plate until the volume is reduced to about 6 mL to 7 mL and white fumes are evolved. Cool the solution and transfer to 10 mL volumetric flask and dilute up to mark with Milli-Q water.

Preparation of sample solution

Weighed accurately 1.0023 g of sample and transfer into 100 mL beaker. To this add 10 mL of concentrated nitric acid and 10 mL of perchloric acid. Heat on hot plate until the volume is reduced to about 6 mL to 7 mL and white fumes are evolved. Cool the solution and transfer to 10 mL of clean and dry volumetric flask and dilute up to mark with Milli-Q water.

Preparation of LOQ standard solution

The limit of quantification (LOQ) standard solutions were prepared by taking 0.77 ml of the above solution A to a 25 ml volumetric flask and dilute up to volume with Milli-Q water which contains 0.154 ppm of nickel. This solution has been used for the determination of precision at LOQ level.

ESTABLISHMENT OF THE METHOD

Selection of wavelength

The wavelength for the selected metal is taken as a default by the AAS instrument. The wavelength which is used in the determination of metal is given in Fig. 1. The prepared sample was aspirated in the Shimadzu AA-6300, AAS instrument. Here, a light shaft from a nickel hollow cathode lamp is gone through the sample which is atomized in a flame into a monochromator and onto a detector that estimates the amount of absorbed light.

Validation of the established method

The validation of the systematic method for quantitative assurance of nickel was performed as per the USP guidelines by evaluating linearity, specificity, detection limit, quantitation limit, accuracy, precision at LOQ level, and method precision. The goal of analytical estimation is to get steady, solid, and exact information. Approved analytical strategies assume a noteworthy job in accomplishing this objective. The outcomes from strategy approval can be utilized to pass judgment on the quality, unwavering quality, and consistency of logical outcomes, which is an indispensable piece of any great analytical practice.

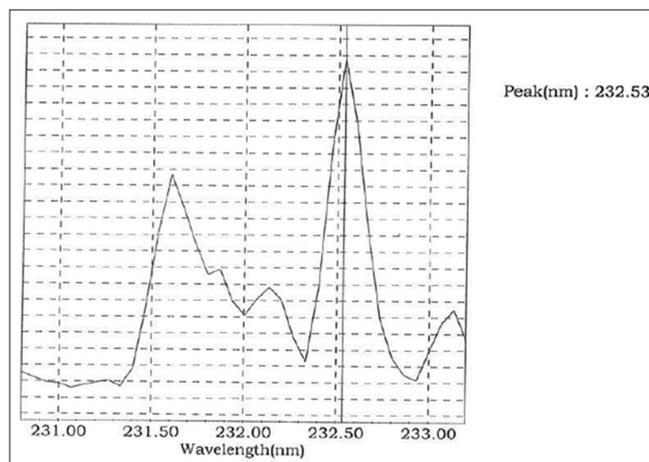


Fig. 1: Wavelength selection

System suitability

To guarantee the execution of the framework, the system suitability is measured, which is an essential piece of analytical systems. The system suitability test was carried out to validate whether nickel content can be identified by injecting system suitability solution. The standard working solution with a concentration of 0.5 mg/L, 1 mg/L, 1.5 mg/L, 2 mg/L, and 2.5 mg/L was prepared using solution A and aspirated into the flame of AAS.

Specificity

Specificity is the capacity to evaluate the analyte in the test with presents of startling different components which meddle the consequences of analyte in test. One hundred percent nickel standard solution is prepared by taking 5 mL of solution A into a 25 mL volumetric flask and make up to volume with Milli-Q water. The obtained solution with a concentration of 1 mg/L of nickel solution is used as 100% standard solution. The blank and sample solutions which are prepared have been aspirated into the flame of AAS.

Linearity

Linearity is assessed through graphical portrayal of the deliberate absorbance and concentration of the solution. The calibration plot was constructed with blank samples and five different concentrations from 0.5 mg/L to 2.5 mg/L. From the linear solutions, correlation coefficient, Y-intercept, slope was calculated.

The execution of an instrument or an analytical technique is evaluated by determining detection limit and quantitation limit.

Detection limit

The detection limit is the most reduced measure of analyte in a sample that can be distinguished, yet not really quantitated, under the expressed experimental conditions. In this manner, limit tests only substantiate that the measure of analyte is above or underneath a specific level. As far as possible, it is normally expressed as the concentration of analyte (% or ppb) in the sample.

Quantitation limit

It is the most reduced measure of analyte in a sample that can be resolved with adequate precision and accuracy under the expressed experimental conditions. As far as possible, it is expressed as the concentration of analyte (e.g., % or ppb) which can be quantitatively measured in the sample.

Precision at LOQ level

The prepared LOQ sample was taken and used in the precision studies. Precision was reported as percentage relative standard deviation (% RSD) by aspirating the nickel standard for 6 times. The results were presented in a table, which are within the range of acceptance criteria (% RSD \leq 5).

Accuracy

Accuracy is the closeness of the test outcomes gotten by the technique to the genuine esteem value which was obtained by spiking 50%, 100%, and 150% of dronedarone working standard concentrations in triplicates, and accuracy/recovery was shown in % RSD and its percentage recovery should be in between 80% and 120%.

Method precision

The analytical procedure should be surveyed by estimating the concentrations of six autonomously prepared sample solutions at 100% of the assay test concentration.

Batch analysis

Weigh precisely 1.0033 g of sample and transfer into 100 ml of beaker. Add 10 ml of concentrated nitric acid and 10 ml of perchloric acid. Heat on hot plate until the volume is reduced to about 6 ml to 7 ml and white fumes are evolved. Cool the solution and transfer to 10 ml of clean and dry volumetric flask and dilute up to mark with Milli-Q water.

DISCUSSION OF THE RESULTS

Using the above sophisticated AAS method, samples were analyzed using the wavelength 232.53 nm which was default selected by the AAS (Fig. 1). The nickel content in the given dronedarone hydrochloride was found to be 3.0 ppm. The developed technique was approved according to USP rules, and the linearity was within the scope of 0.5 mg/L to 2.5mg/L and is shown in Fig. 2 and Table 1.

The detection limit and LOQ values were established from linearity and were found to be 0.050698 ppm and 0.15363 ppm, respectively. The % RSD for absorbance of nickel standard solution (LOQ solution) six replicates was found to be 6.237. The method was specific, and the absorbance obtained with the blank solution was below the absorbance obtained for 100% standard solution and is shown in Table 2. The

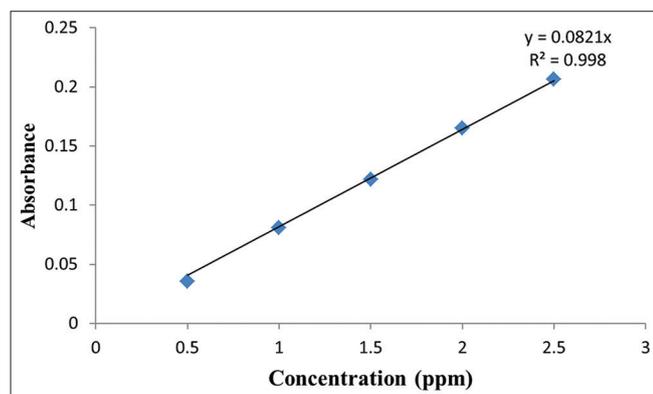


Fig. 2: Calibration graph

repeatability of the method was determined by injection of six preparations, and the % RSD was found to be 1.52608. The percentage recovery was determined at LOQ, 50%, 100%, and 150% levels, and their percentage recovery and % RSD are represented in Table 2. The percentage recovery by performing accuracy was within the acceptable limit and is represented in the table.

CONCLUSIONS

The state-of-the-art describes the development and validation of a method for the examination of nickel in dronedarone using flame atomic absorption spectroscopy. The allowed nickel content is up to 20 ppm as per USP-NF 40. The sample which is analyzed using the method developed is 3.0 ppm, so the nickel content in the taken sample is unacceptable range. Hence, the method can be successfully used for the quantification of nickel in dronedarone drug substance. The validation results are displayed and sorted out in tables with the end goal to give a simple overview of the method execution. The validation information demonstrates that the present developed technique has met all acceptance criteria.

AUTHOR'S CONTRIBUTIONS

Concept - Vasavi; Design - Subba Reddy, Vasavi, Swarnalatha; Supervision - Subba Reddy, Swarnalatha; Materials - Vasavi; Data Collection and/or Processing - Vasavi; Analysis and/or Interpretation - Vasavi, Subba Reddy, Swarnalatha; Literature Search - Vasavi, Subba Reddy, Swarnalatha; Writing - Vasavi; Critical Reviews - Vasavi, Subbareddy, Swarnalatha.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

Table 1: Calibration curve

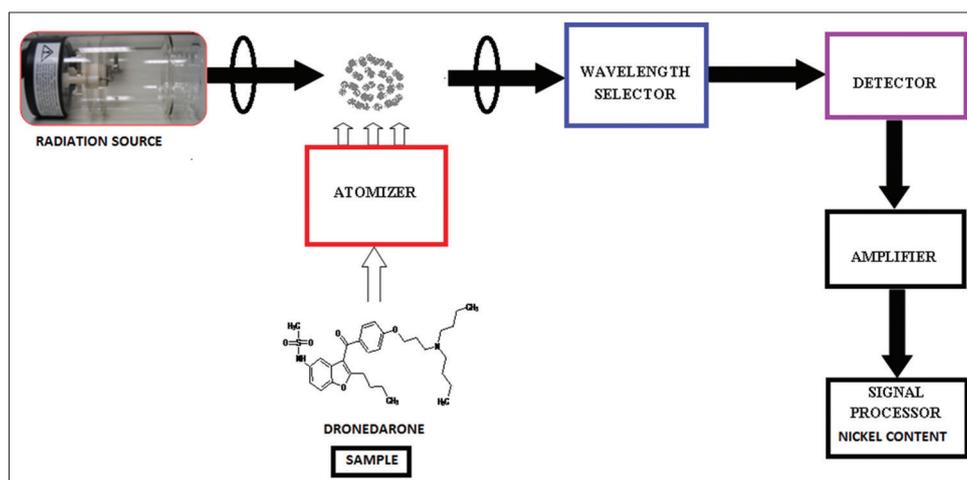
S.No.	Concentration (PPM)	Absorbance	Correlation coefficient
1	Standard 1 (0.5 mg/L)	0.0355	0.998
2	Standard 2 (1.0 mg/L)	0.0811	
3	Standard 3 (1.5 mg/L)	0.1221	
4	Standard 4 (2.0 mg/L)	0.1651	
5	Standard 5 (2.5 mg/L)	0.2066	

Table 2: Summary report

Summary report				
S.No.	Parameter	Acceptance criteria	Observation	Result
1	System suitability	Correlation coefficient should be NLT 0.99	0.996	Pass
2	Specificity	Any absorbance obtained with the blank solution should be ≤5% of the absorbance obtained for 100% standard solution	Meeting the acceptance criteria	Pass
3	Linearity	Correlation coefficient should be NLT 0.99	0.998	Pass
4	LOD and LOQ precision at LOQ	LOD and LOQ values established from linearity	LOD - 0.05 ppm and LOQ - 0.15 ppm	Pass
		The percentage RSD for absorbance of Nickel standard solution (LOQ solution) six replicates should be NMT 15.0	6.237%	Pass
5	Accuracy/recovery	The percentage recovery at each level should be in between 80%–120% and for LOQ level should be in between 70%–130%	At LOQ - 95.55%	Pass
		The percentage RSD at each Level 3 preparation should be NMT 5.0	At 50% - 109.33%	Pass
			At 100% - 96.00%	
			At 150% - 97.55%	
			At LOQ - 4.03%	
			At 50% - 4.22%	
			At 100% - 1.04%	
			At 150% - 0.3965%	
6	Method precision	The percentage RSD for nickel content six preparations should be NMT 15.0	1.526	Pass
7	Batch analysis	Obtained results are reported	3.0 ppm	Pass
		The Nickel content should be NMT 20 ppm		

LOD: Limit of detection, LOQ: Limit of quantification, NLT: Not less than, NMT: Not more than, RSD: Relative standard deviation

GRAPHICAL ABSTRACT



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