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Research Article

QUANTITATIVE DETERMINATION OF BORON CONTENT IN TAMSULOSIN HYDROCHLORIDE USING INDUCTIVELY COUPLED PLASMA - OPTICAL EMISSION SPECTROSCOPY

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ABSTRACT

A precise, accurate, sensitive and selective analytical method using Inductively Coupled Plasma- Optical Emission Spectroscopy (ICP-OES) has been developed and validated for the determination of trace levels of boron, present as an impurity in Tamsulosin hydrochloride, an alpha blocker drug. Boron was suitably extracted from Tamsulosin hydrochloride and brought into the solution using ashing technique followed by quantitative determination by ICP-OES.

The limit of detection of the validated method was found as 15 µg/l and the limit of quantitation was calculated as 25 µg/l. The method was found to be linear in the wide working range of 25 µg/l to 800 µg/l with correlation coefficient of 0.99978. The recoveries of boron from the spiked samples of Tamsulosin hydrochloride were found in the acceptable range of 90 to 98 % at three different spiking levels. The method can routinely be used for the quantitative determination of boron to ensure the quality of Tamsulosin hydrochloride

Keywords: ICP-OES, Boron, Tamsulosin hydrochloride, Method development

INTRODUCTION

Tamsulosin hydrochloride, 5-[(2R) -2- [[2- (2-Ethoxyphenoxy) ethyl] amino] propyl] -2- methoxy benzene sulfonamide hydrochloride[1,2,3], is an alpha blocker drug . It is used for the treatment of urinary problems caused by an enlarged prostate. Its intake relaxes the muscles of the prostate and bladder, which helps free flow of urine[2, 3].

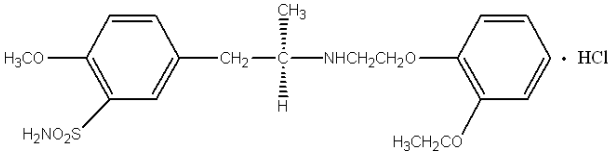

Fig. 1: Structure of Tamsulosin Hydrochloride

During the synthesis of Tamsulosin hydrochloride, which involves several steps, sodium borohydride-iodine or sodium borohydride sulfate is used as a reducing agent in one of the steps[2, 3]. As a result, trace amount of boron may remain in the final product, which is not desirable as residual impurities may cause adverse effects on health. It is therefore imminent that the boron used as catalyst during the manufacturing process is removed from the final product by adopting suitable purification processes. In order to ensure that the product is free from impurities of boron, it is utmost essential that the validated method is used for determining the content of residual impurities. The method should be such that it does not suffer from any interferences from the residual impurities of other metals used as catalysts (such as nickel, palladium and rhodium[2,3]). The present study was undertaken to develop and validate an analytical method to detect boron at low concentration levels; well below acceptable limits.

A number of methods have been reported for the determination of boron, most of them being colorimetric methods[4,5,7]. For the quantitative determination of boron by colorimetry, a number of reagents are available such as curcumin[4,5,7], carminic acid[4,5,7] or carmine[4,5,7], quinalizarin[4,5,7] , azomethine-H[4,5] etc. The colorimetric methods are not so sensitive and moreover suffer due to the interference form other metallic impurities as well as from the components of matrix[10]. The fluorimetric methods are more sensitive than colorimetric methods but are susceptible to interferences from certain chemical species and are also sensitive to pH and the temperature[7,8]. Therefore, fluorimetric methods are not widely used for the determination of boron. The Flame –Atomic absorption technique (Flame-AAS) has unsatisfying detection limits for boron[4-6, 8]. Similarly, other analytical techniques for the determination of boron are time consuming and not so sensitive and precise[8].

But the use of Inductively Coupled Plasma – Optical Emission Spectroscopy (ICP-OES), provides higher sensitivity, lower detection limits, less chemical interferences and is less time consuming as compared to all the above mentioned techniques.

The present paper describes the determination of residues of boron in Tamsulosin hydrochloride by ICP-OES using radial torch, which can easily be adopted by any analytical laboratory. The method was validated for various parameters in accordance with International Conference on Harmonization (ICH) and Eurachem guidelines. Method was also optimized for sample preparation using ashing procedure whereby calcium hydroxide was added to trap boron.

MATERIALS AND METHODS

Chemicals and reagents

Samples of Tamsulosin hydrochloride raw material (five in number coded as A, B, C, D and E) were procured from M/S Ranbaxy Research Laboratories. HPLC grade water used throughout the experimental analysis was procured from s.d.fine-chem limited. Calcium hydroxide and Hydrochloric Acid, AR grade were procured from Merck Specialties Chemical Limited. All the glassware used was Type "A" and Borosil make. Calibrated micropipette with range 100 µl – 1000 µl was used. Standard reference solutions of 1000 µg/ml boron, nickel, platinum and palladium (traceable to NIST) were procured from Scharlau Chemie, Spain. Whatman filter paper no. 41 was used.

Saturated solution of calcium hydroxide

Saturated solution of calcium hydroxide was prepared by dissolving an excess amount of calcium hydroxide in warm HPLC grade water till the point where no further dissolution of calcium hydroxide occurs even on warming the solution. The excess calcium hydroxide was filtered prior to use.

Instrumentation

Varian (Australia) Vista MPX Inductively Coupled Plasma- Optical Emission Spectrometer (ICP-OES) equipped with argon saturation assembly, CCD detector and 21 CFR 11 version 4.1.0 software for data acquisition and processing was used. Muffle furnace:

Ambassador with least count 1 °C was used. Electronic analytical balance: Afcoset 3200, Mettler toddler with readability 0.01 mg was used.

Preparation of calibration standards of boron

Preparation of stock solution of boron (5 µg/ml)

5 ml of standard reference solution of boron (1000µg/ml) was pipetted into a 100 ml volumetric flask and diluted to volume with HPLC grade water. This gave a solution with concentration of 50 µg/ml (solution A). From solution A, 10 ml was further diluted to 100 ml to give a solution with boron concentration of 5 µg/ml (solution B). This was then used as a stock solution for preparation of calibration standard solutions of boron.

Preparation of calibration solutions of boron

From the solution B, aliquots of 0.125 ml, 0.25 ml, 0.50 ml, 1.00 ml, 2.00 ml and 4.00 ml were pipetted into six different volumetric flasks of 25 ml and diluted to mark using HPLC grade water. This gave a series of standard calibration solutions having concentration of 25 µg/l, 50 µg/l, 100 µg/l, 200 µg/l, 400 µg/l and 800 µg/l respectively.

Sample treatment

About 4.00 ± 0.01 gram sample of Tamsulosin hydrochloride was weighed accurately in a silica crucible, and 10 ml of saturated solution of calcium hydroxide was added. The crucible was then heated on a hot plate to dryness and the mixture was ashed at 550 ± 25°C in a muffle furnace for 4 hours. The contents were cooled and leached in 2 ml hydrochloric acid and transferred to a 25 ml volumetric flask and made to volume using HPLC grade water. All sample preparation required for studies of various validation parameters was done as per the above procedure.

Preparation of reagent blank

10 ml of saturated solution of calcium hydroxide was taken in silica crucible and heated on a hot plate to dryness and ashed at 550 ± 25°C in a muffle furnace for 4 hours. After cooling, the contents were leached using 2 ml hydrochloric acid and transferred to 25 ml volumetric flask and made to volume using HPLC grade water. Five replicates of reagent blank were prepared.

ICP-OES conditions

Inductively coupled plasma-optical emission spectrometery (ICP-OES) with radial torch equipped with argon saturation assembly was used for the determination of boron in Tamsulosin hydrochloride. High purity (99.99%) argon was used as plasma, auxiliary and nebulizer gas. The gas flows were kept at 15.0 l/minute for plasma, 1.50 l/ minute for auxiliary and 0.56 l/ minute for nebulizer. Radio frequency (R.F.) power of the plasma generator was 1.20 kW. Vertical height of the plasma was fixed at 7 mm. Sample uptake time of 30.0 sec, delay time of 5 sec, rinse time of 5 sec, initial stabilization time of 5 sec and time between replicate analysis of 5 sec was maintained throughout the studies for ICP-OES. All the observations of emission were recorded at 249.772nm, which corresponds to the most sensitive emission wavelength of boron. The instrument was calibrated for various parameters before the studies.

RESULTS AND DISCUSSION

Analytical method development

Sample digestion

One of the challenges of method development was the efficient extraction of boron from Tamsulosin hydrochloride. For this purpose, generally, the digestion using acids is recommended. During the initial development work, it was noted that the acids used for this purpose were contaminated with impurities of boron to the extent beyond the residual impurity of boron in the drug. The method used here for this purpose therefore, was ashing of the drug in the presence of calcium hydroxide. The use of calcium hydroxide prevents volatilization of boron since calcium hydroxide helps in formation of calcium boride[4, 5], which is a highly stable compound as per the reaction:

$$2Ca(OH)_2 + 12\ B \longrightarrow 2\ CaB_6 + 2H_2O$$

Optimization of requirement of saturated solution of calcium hydroxide

For the purpose of complete extraction of boron, the studies for optimization of the requirements of calcium hydroxide for the purpose were conducted. Tamsulosin hydrochloride was spiked with different concentration of standard solution of boron and each spiked sample was ashed in the presence of varying amount of calcium hydroxide. The results of the study are presented in Table 1.

Table 1: Optimization of saturated solution of calcium hydroxide

Volume of saturated solution of $Ca(OH)_2$, ml	**5**			**8**			**10**			**12**		
Spiked concentration of boron, µg/l (n=3)	25	200	800	25	200	800	25	200	800	25	200	800
% Recovery	60	55	52	75	73	73	92	94	97	91	94	95

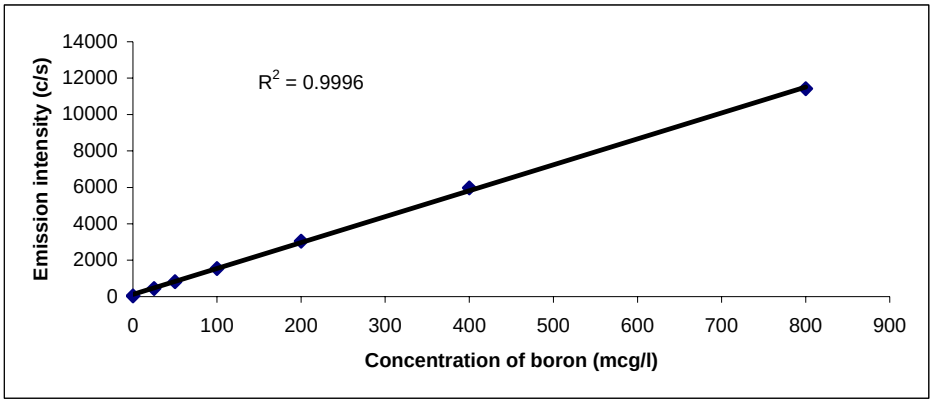

Fig. 2: Calibration curve for concentration of boron (µg/l) vs emission intensity (c/s)

Table 2: Boron content in samples of Tamsulosin hydrochloride (Results are the mean of the five replicates)

Sample code	Observations					
	Concentration of boron in reagent blank, µg/l	Total concentration of boron in the sample solution, µg/l	Concentration of boron in the sample solution due to Tamsulosin HCl, µg/l	Weight of Tamsulosin HCl taken, g	Dilution factor	Boron content in the sample of Tamsulosin HCl, ppb
A	62.79	78.54	15.75	4.00	25	98.44
B	62.79	82.13	19.34	4.00	25	120.88
C	62.79	84.73	21.94	4.00	25	137.13
D	62.79	81.97	19.18	4.00	25	119.875
E	62.79	83.69	20.90	4.00	25	130.625

From the results, it become evident that 10 ml of saturated solution of calcium hydroxide was sufficient enough for more than 90 % recovery of boron at concentration levels between 25 µg/l to 800 µg/l. While studying the effect of different concentration of calcium on the intensity of boron signal, no significant signal decrease was observed for boron.

Analytical data

For the quantitative determination of boron using ICP-OES, conditions were optimized as detailed above so as to get the maximum signal intensity. Boron content in both i.e. sample of Tamsulosin hydrochloride and the reagent blank was determined against a six point calibration curve plotted for the standard solutions of boron ranging from 25 µg/l to 800 µg/l vs their emission intensity (Figure 2). Results for boron content in five samples of Tamsulosin hydrochloride are given in Table 2.

Method performance characteristics

The method was validated for various parameters as per the International Conference on Harmonization (ICH) and the Eurachem guidelines.

Linearity

A six point calibration curve (Figure 2) for the standard solutions of boron ranging from 25 µg/l to 800 µg/l vs emission intensity (c/s) was found to be linear and showed a correlation coefficient of 0.99978.

Precision

Precision studies of the method were carried out for both intra-day and inter-day repeatability and reproducibility using replicates of standard solutions of boron at three different concentrations (25µg/l, 200µg/l and 400µg/l) and using digested samples of Tamsulosin hydrochloride spiked with standard solutions of boron at three different concentrations (25µg/l, 200µg/l and 400µg/l). Data for the precision studies are given in Table 3. Precision (% RSD) of 4.9% and 4.4% at 25 µg/l; 4.3% and 3.1% at 200 µg/l and 3.2% and 2.5% at 400 µg/l was obtained for analysis on the same day or intra-day for the standard solutions of boron and the spiked solutions respectively.

Precision for the inter-day analysis for three subsequent days was found to be 5.0% and 4.8% at 25 µg/l; 4.2% and 3.6% at 200 µg/l and 3.6% and 2.4% at 400 µg/l for the standard solutions of boron and the spiked solutions respectively. Precision obtained for both inter-day & intra-day was well within the acceptable limits.

Accuracy

For accuracy (recovery) studies standard solutions of boron were spiked in three sample of Tamsulosin hydrochloride (marked as A, B and C) at the levels of 25µg/l, 50µg/l and 100µg/l. The spiked samples were digested as the procedure described above.

The boron content in reagent blank and the spiked sample solutions was determined against the standard calibration curve. Percent recovery was evaluated on the basis of the comparison of the actual concentration level of the spiked solutions with that of the observed values of the concentration of boron. Recoveries of more than 90% were obtained for all the three spiked samples at each spiked level, which is well within the acceptable criteria at trace concentration levels. Data for the accuracy studies are given in Table 4.

Table 3: Intra-day and Inter-day precision studies

Solution type	Boron concentration in solution, µg/l	Intra-day precision (n=6) mean observed concentration, µg/l	% RSD	Inter-day precision (n=6) mean observed concentration, µg/l	% RSD
Standard solution of Boron	25	24.7	4.9	24.5	5.0
	200	195.6	4.3	196.2	4.2
	400	393.4	3.2	394.7	3.6
Tamsulosin HCl spiked with standard solutions of boron	25	24.5	4.4	24.6	4.8
	200	194.3	3.1	193.6	3.6
	400	391.5	2.5	390.2	2.4

Table 4: Recovery studies for determination of boron in Tamsulosin hydrochloride

Sample code	Original concentration of boron in sample solution, µg/l	Spiked concentration, µg/l	Total concentration, µg/l	Mean observed concentration, µg/l (n=3)	% Recovery	% RSD
A	15.75	25	40.75	38.47	90.88	5.0
		50	65.75	62.73	93.96	4.9
		100	115.75	110.53	94.78	3.2
B	19.34	25	44.34	42.18	91.36	4.8
		50	69.34	65.52	92.36	4.7
		100	119.34	113.47	94.13	3.1
C	21.94	25	46.94	44.98	92.16	4.9
		50	71.94	67.33	90.78	4.7
		100	121.94	115.61	93.67	2.9

Specificity

The method was evaluated for specificity towards determination of boron in presence of other interferences (such as nickel, palladium and rhodium), which may also be present as impurities in the sample matrix at different concentration levels. Data for the specificity studies are given in Table 5.

In order to determine the specificity of the method, three boron solutions were prepared at concentration levels of 25μg/l, 100 μg/l and 800 μg/l the concentration of boron was measured using calibration curve. Boron solutions with different concentrations were then subsequently spiked with nickel (1000 μg/l), palladium (1000 μg/l) and rhodium (1000 μg/l) and the concentration of the boron was determined after addition of each of these interfering elements. It was found that impurities of nickel, palladium and rhodium even if present at high concentrations of 1000 μg/l did not interfere with the determination of boron present at extremely low concentration (the lowest concentration being 25 μg/l) and the recoveries of boron obtained in all the cases were between 98.3 to 102 %, thus, indicating that the method is specific to the determination of trace amount of boron in the presence of nickel, palladium and rhodium.

Table 5: Specificity of Boron in presence of Nickel, Palladium and Rhodium

Solution composition, μg/l B: Boron; Ni: Nickel; Pd: Palladium; Rh: Rhodium	Mean observed Boron content, μg/l (n=3)	% RSD	% Recovery
B:25	25.16	4.48	100.6
B:25+Ni:1000	24.70	0.23	98.8
B:25+Ni:1000+Pd:1000	24.57	1.95	98.3
B:25+Ni:1000+Pd:1000+Rh:1000	25.28	0.77	101.1
B:100	101.10	0.01	101.1
B:100+Ni:1000	100.99	0.07	101
B:100+Ni:1000+Pd:1000	98.70	0.48	98.7
B:100+Ni:1000+Pd:1000+Rh:1000	102.00	0.79	102.0
B:800	786.11	0.21	98.3
B:800+Ni:1000	806.36	0.04	100.8
B:800+Ni:1000+Pd:1000	811.42	0.77	101.4
B:800+Ni:1000+Pd:1000+Rh:1000	788.19	0.86	98.5

Limit of detection (LOD) and Limit of quantification (LOQ)

Limit of detection (LOD) was determined on the basis of signal to noise ratio (S:N) of 3:1 and was calculated as 15 μg/l. Limit of quantification (LOQ) was obtained as 25 μg/l evaluated on the basis of minimum concentration for which a reproducible signal was obtained with % RSD less than 5 for five replicates.

CONCLUSION

The experimental data demonstrates that the proposed analytical method is precise, accurate, sensitive and selective for the quantitative determination of boron in raw material of Tamsulosin hydrochloride using Inductively coupled plasma – optical emission spectroscopy (ICP-OES). The method provides wide linearity, specificity without interference from endogenous impurities like nickel, palladium and rhodium. The developed analytical method also provides excellent recovery at various concentration levels. In addition to all these features, one of the important advantages of the developed method is the simplicity and fast sample preparation procedure. Therefore, the method can be easily adopted for routine quantitative analysis of boron, present as residual impurity in quality of raw materials of Tamsulosin hydrochloride

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