British Journal of Pharmaceutical Research
15(4): 1-7, 2017; Article no.BJPR.32254
ISSN: 2231-2919, NLM ID: 101631759

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Development and Validation of UV-Spectrophotometric Method for Determination of Palladium Content in Rasagiline Mesylate

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Authors' contributions

This work was carried out in collaboration between all the authors. All authors designed the study. Author TS wrote the protocol, performed the analysis and wrote the first draft of the manuscript. Authors SH and AG managed the literature searches and analyses the results. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJPR/2017/32254
Editor(s):
(1) Othman Ghribi, Department of Pharmacology, Physiology & Therapeutics,University of North Dakota, USA.
Reviewers:
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Complete Peer review History: http://www.sciencedomain.org/review-history/18533

Original Research Article

Received 17th February 2017
Accepted 3rd April 2017
Published 6th April 2017

ABSTRACT

A simple, precise, linear, accurate and robust spectrophotometric method was developed for the estimation of palladium content in Rasagiline Mesylate. The proposed method is based on complex formation of palladium with α-nitroso-β-napthol in alkaline medium and extraction with toluene and estimation. The spectrum shows maximum absorption at 425 nm. The method is validated as per on International council for harmonization (ICH) guidelines. The absorbance-concentration plot is linear over the concentration range of 3.08 to15.38 ppm with limit of detection (LOD) of 0.06 ppm and limit of quantification (LOQ) of 0.17 ppm. The recovery of Palladium in Rasagiline Mesylate obtained was between 95 to 105 %. The proposed method can be applied for the determination of palladium content in Rasagiline Mesylate.

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Keywords: Spectrophotometer; palladium; development; validation; Rasagiline Mesylate.

1. INTRODUCTION

Rasagiline Mesylate is chemically known as (1R)-N-Prop-2-yn-1-ylindan-1 amine methane sulfonic acid salt (Fig. 1). Rasagiline is an irreversible monoamine oxidase inhibitor used in the treatment of Parkinson disease [1-2].

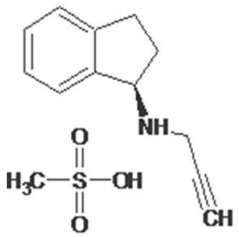

Fig. 1. Rasagiline mesylate molecule structure

Elemental impurities are traces of metals that can come from various sources such as equipment, container or catalyst used in the synthesis of drug substances. These metallic residue in drug substance have no therapeutic benefit and in some case can cause patient harm. Palladium on carbon is a catalyst use in the synthesis of Rasagiline Mesylate. According to Q3D guideline palladium comes under class 2 elements where these elements are toxic to a greater or lesser extent. Permissible daily exposure (PDE) for palladium is 100 µg/day and its oral limit comes out to be 10 ppm considering maximum daily dose of 10 g/day [3-4].

There are various special analytical techniques such as Inductive coupled plasma-Mass spectrometer (ICP-MS) [5], X-Ray Fluorescence (XRF) [6] and Atomic absorption spectroscopy (AAS) [7] used for the determination of metallic impurities in drug substances [5-6]. These instruments are not easily available in routine laboratory, hence there needs an alternative technique which can be used in routine analysis. Hence method was developed by taking advantage that palladium (II) can form colored complex with various reagents.

There are various analytical methods reported for determination of palladium by complexing with various reagents such as propericiazine [8], thioglycollic acid [9] thiocyanate-rodamine b [10], nicotinaldehyde-4-phenyl-3-thiosemicarbazone [11] and other reagents [12-16]. These methods have various drawbacks such as stability of complex, pH-buffer dependent, multiple extractions. The most stable and easy complex formation was achived with α-nitroso-β-napthol which can be measured on a spectrophotometer (Fig. 2). The literature survey reveals that presently there is no any published method for determination of Palladium content in Rasagiline Mesylate or bulk drug by spectrophotometry.

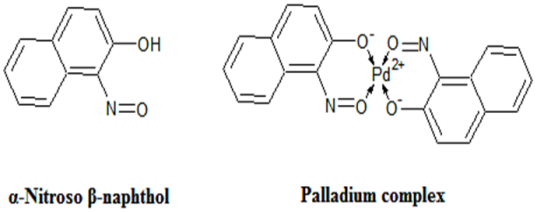

Fig. 2. Reagent and palladium complex structures

2. MATERIALS

2.1 Apparatus

Perkin Elmer, Lamda 35 Spectrophotometer with UV-Win Lab software was used for scanning and absorbance measurement. For weighing of materials, Sartorius analytical balance was used. Water was used as a solvent for method development and validation study was obtained from the Milli-Q system (Millipore, Germany).

2.2 Reagents and Chemicals

Concentrated Hydrochloric acid, Toluene, Ethanol and Sodium Hydroxide were purchased from Merck (India). Palladium chloride was purchased from Spectrochem while α-nitroso-β-napthol was purchased from SD fine chem. Rasagiline Mesylate (bulk drug) samples as a gift sample from Indoco research center, Navimumbai India.

3. METHODOLOGY

3.1 Preparation of Solutions

3.1.1 Preparation of α-Nitroso β-naphthol reagent (0.5% w/v)

Transferred 0.5 g of α-Nitroso β-naphthol into 100 mL volumetric flask, dissolved in 50 mL of ethanol and made up to volume with the same.

3.1.2 Preparation of sodium hydroxide solution (2.0% w/v)

Transferred 2.0 g of Sodium hydroxide into 100 mL volumetric flask, dissolved in 50 mL of water and made up to volume with the same.

3.1.3 Preparation of standard stock solution

Transferred 10.0 mg of palladium chloride into 100 mL volumetric flask, added 2.0 mL conc. Hydrochloric acid. Dissolved in 50 mL of water and made up to volume with the same.

3.1.4 Preparation of standard solution (10 ppm with respect to sample)

Transferred 2.0 mL of standard stock solution into 100 mL volumetric flask and made up to volume with water. Transferred 15 mL of this solution into 250 mL separating funnel. Added 0.5 mL of α-Nitroso β-naphthol reagent. Mixed well and allowed to stand for 15 mins. (complex formation took place). Added 15 mL of toluene and shake for 1 min. Allowed the layers to separate. Discarded the lower aqueous layer. Added 15 mL of 2% sodium hydroxide solution and shake well. Again allowed the layers to separate. Discarded the yellow aqueous layer containing excess reagent (perform the toluene layer extraction with sodium hydroxide solution twice). Measured the absorbance of the complex at 425 nm.

3.1.5 Preparation of sample solution

Transferred 2.4 g of Rasagiline Mesylate sample into 20 mL volumetric flask. Dissolved in 10 mL of water and made upto volume with the same. Transferred 15 mL of this solution into 250 mL separating funnel. Added 0.5 mL of α-Nitroso β-naphthol reagent. Mixed well and allowed to stand for 15 mins. (Complex formation took place). Added 15 mL of toluene and shake for 1 min. Allowed the layers to separate. Discarded the lower aqueous layer. Added 15 mL of sodium hydroxide solution and shake well. Again allowed the layers to separate. Discarded the yellow aqueous layer containing excess reagent (performed the toluene layer extraction with sodium hydroxide solution twice). Measured the absorbance of complex at 425 nm.

3.1.6 Preparation of sample solution (Spiked)

Transferred 2.4 g of Rasagiline Mesylate sample into 20 mL volumetric flask. Dissolved in 10 mL of water and made upto volume with the same. Transferred 15 mL of this solution into 250 mL separating funnel. Added 2.0 ml standard stock Solution and Added 0.5 mL of α-Nitroso β-naphthol reagent. Mixed well and allowed to stand for 15 mins (Complex formation took place). Added 15 mL of toluene and shake for 1 min. Allowed the layers to separate. Discarded the lower aqueous layer. Added 15 mL of sodium hydroxide solution and shaked well. Again allowed the layers to separate. Discarded the yellow aqueous layer containing excess reagent (performed the toluene layer extraction with sodium hydroxide solution twice).

3.1.7 Preparation of blank solution

Taken 15 mL of water into a 250 mL separating funnel. Added 0.5 mL of α-Nitroso β-naphthol reagent. Mixed well and allowed to stand for 15 mins. Added 15 mL of toluene and shake for 1 min. Allowed the layers to separate. Discarded the lower aqueous layer.Added 15 mL of sodium hydroxide solution and shake well. Again allowed the layers to separate. Discarded the yellow aqueous layer containing excess reagent (perform the toluene layer extraction with sodium hydroxide solution twice). Measured the absorbance of complex at 425 nm.

3.2 Selection of Wavelength

A complex of palladium with α-Nitroso β-naphthol is yellow in colour therefore spectra was taken in UV-visible range from 300 to 800 nm. For this cuvette was rinsed and filled with blank solution and scanned, similarly scanned standard solution of 10 ppm. The absorption spectrum shows maxima (λmax) at 425 nm (Fig. 3). Therefore, for measurements, wavelength 425 nm was selected.

3.3 Measurements

For measurement of absorbance, 425 nm wavelength was selected and instrument made auto zero and measured the absorbance of blank solution, standard solution and sample solutions. Palladium content in the sample is found out using the following formula given below.

3.4 Calculations

Palladium content (ppm w.r.t. sample) = (At/As) x (Ws/Wt) x F.

A_t is absorbance of the test sample solution, As is absorbance of standard solution, Ws is the Weight of Palladium chloride for standard (mg),

Wt is the weight of test sample taken in sample solution (g) and F is 2.4 (factor).

4. RESULTS AND DISCUSSION

The developed method was subjected to analytical method validation, which was conducted according to the International council for harmonization (ICH) guidelines [17-22]. The parameter with which analytical method is validated are specificity, limit of detection, limit of quantitation, linearity, accuracy, precision, robustness and solution stability.

4.1 Specificity

The ability of the method to measure the required analyte in presence of matrix and other components is specificity. In this, blank, standard, test and spiked test sample solutions prepared in section 3.1 were scanned from 300 to 800 nm wavelength and observed for any interference at working wavelength 425 nm. No interference was observed at 425 nm from blank and test sample solutions. Spectra of standard and spiked test sample solutions were matching (Fig. 3).

4.2 Linearity, Limit of Detection and Limit of Quantiation

Linearity study was performed with six different concentration solutions of palladium ranging from 3 to 15 ppm (3.08, 5.13, 8.20, 10.25, 12.30 and 15.38 ppm). Absorbance of each solution was measured in triplicate and calculated the average absorbance. Plotted the linearity curve of absorbance of linearity solution against concentration (Fig. 4) and reported the Slope, Intercept, % y intercept and the regression coefficient for line in Table 1. LOD is the lowest detectable concentration of the analyte by the method while LOQ is the minimum quantifiable concentration. LOD and LOQ were calculated from linearity data by using standard deviation of response and slope, and reported in Table 1.

$$LOD = 3.3 \times \sigma/S \quad (1)$$

$$LOQ = 10 \times \sigma/S \quad (2)$$

Where σ = the standard deviation of the response; S= the slope of the regression line.

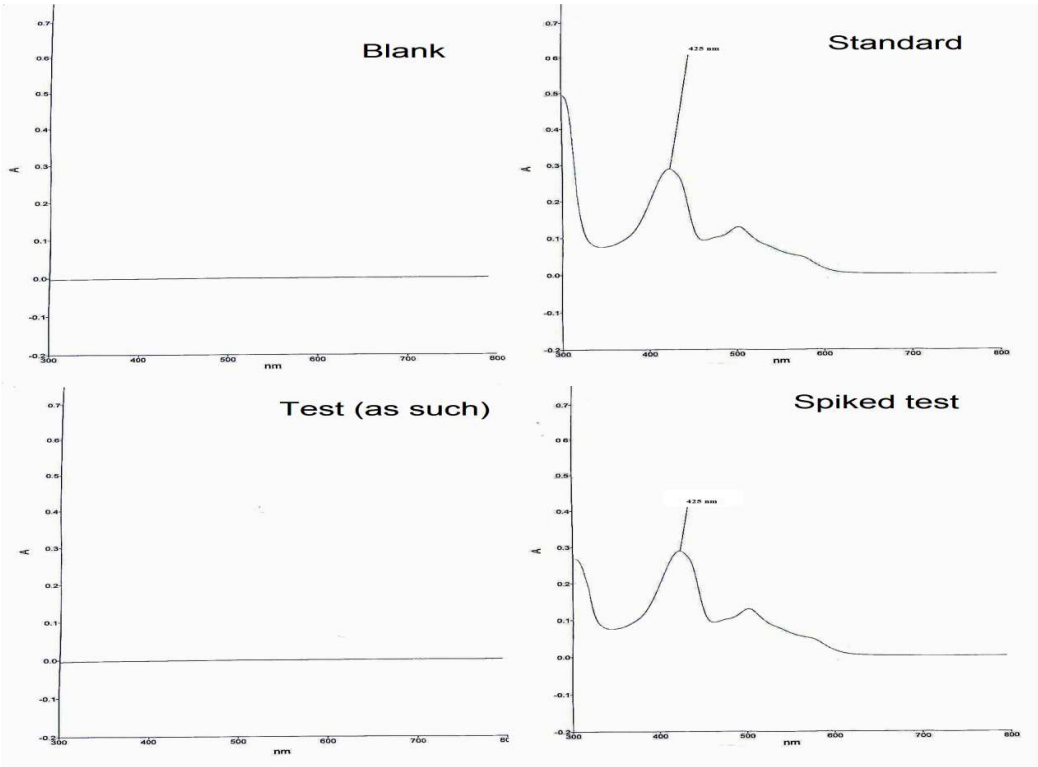

Fig. 3. UV-visible spectra of blank, standard, test & spiked test solutions

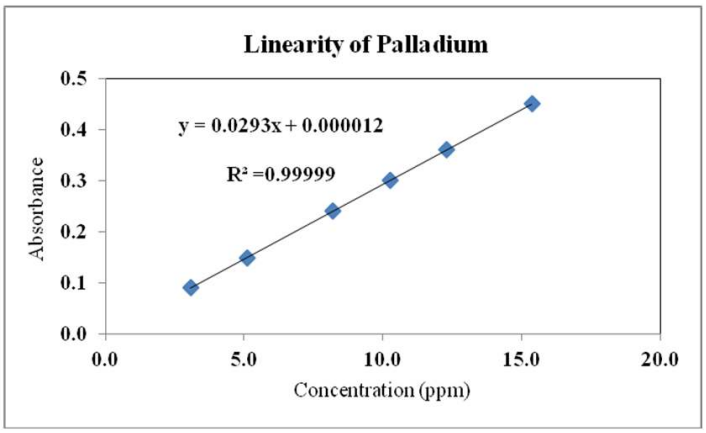

Fig. 4. Linearity plot for palladium

Table 1. Linearity, LOD and LOQ for palladium in rasagiline mesylate

Parameter	Result
Slope	0.0293
Intercept	0.000012
Standard error ($S_{y/x}$)	0.000506
% y intercept	0.004
Regression coefficient (r^2)	0.99999
Range (ppm)	3.08 to 15.38
Limit of detection	0.06 ppm
Limit of quantitation	0.17 ppm

4.3 Accuracy

Accuracy of method was established by performing the recovery studies were palladium was spiked in the test sample at four different concentration levels i.e. 3, 5, 10 and 15 ppm. Each level was prepared in triplicate. Palladium content for each accuracy sample was calculated. To calculate the recovery for palladium, the ratio is taken of the observed palladium content in accuracy solution and theortical spike palladium content and reported in percentage. Average recovery for each level is calculated for palladium, which was obtained between 95% and 105% (Table 2).

Table 2. Recovery of palladium

Accuracy level	% recovery of palladium
Accuracy level-1 (3 ppm)	103.7
Accuracy level-2 (5 ppm)	99.1
Accuracy level-3 (10 ppm)	97.7
Accuracy level-4 (15 ppm)	98.9

4.4 Precision

For system precision, six standard solutions were prepared from standard stock solution and measured the absorbance. Calculated relative standard deviation (RSD). The palladium content of six spiked test sample solution was determined on the same day to check the repeatability (intra-day precision) whereas to check the intermediate precision the same procedure was repeated for six times on different days (inter-day precision). The % RSD obtained was less than 2.0 % for the individual intra-day and inter-day precision and also for cumulative of both. The precision is reported in % RSD in Table 3.

Table 3. Precision for palladium

Parameter	% RSD
System precision (Standard solution)	0.00
Repetability (Intra-day)	1.32
Intermediate precision (Inter-day)	1.59
Cumulative (Intra-day and Inter-day)	1.41

4.5 Robustness

For robustness, three deliberate changes were made with respect to wavelength of measurement, time of complex formation and quantity of reagent added (Table 4). Each change consists of one upper set and one lower set. For each set, three preparations were done by spiking the palladium in the test sample at limit level and analysed. Relative standard deviation for spiked palladium content was observed, which was less than 2.0 % (Table 4). Also robustness result is compared with repetability result and cumulative RDS is reported which was also less than 2.0%.

Table 4. Robustness parameter changes

Changes	Value	Sample ID	% RSD	
			Individual	Cumulative
Change in wavelength by ±1 nm	424 nm	Robustness-1	0.92	1.15
	426 nm	Robustness-2	0.74	1.14
Change in complex formation time by ±5 min	10 min	Robustness-3	0.73	1.19
	20 min	Robustness-4	0.95	1.16
Change in reagent quantity by ±0.1 ml	0.4 ml	Robustness-5	1.09	1.38
	0.6 ml	Robustness-6	1.14	1.19

4.6 Solution Stability

Test solution stability was established by spiking the test sample with palladium at limit level and analysing the same solution after every one hour's time interval for six hours against freshly prepared standard solution. Relative standard deviation for the palladium content of the spiked test sample was determined which was found out to be less than 2.0%, thus solution stability was established up to 6 hours.

4.7 Validation Summary

The percentage recovery obtained for palladium was in the range of 95% to 105% which is within ICH acceptance criteria 80-120%. Precision parameter shows the relative Standard deviation (RSD) values 0.00% for system precision, 1.32% for repetability and 1.59% for intermediate precision (1.41% cumulative) at 100% concentration level which is within the ICH acceptance criteria of RSD ≤ 5%. Linearity was observed in the concentration range of 3.08 – 15.38 ppm (30 & to 150%) with r^2 values of 0.99999 and %y intercept 0.04 showing a good correlation between the response and analyte concentration with standard error 0.000506, slope 0.0293 and intercept 0.000012.The calculated LOD for palladium was 0.06 ppm and the calculated LOQ was 0.17 ppm. The spectra of blank and test sample shows no interference at working wavelength 425 nm indicates that there is no interference from reagents and sample. The method is robust as in robustness parameter deliberate changes were made for which individual and cumulative RSD values for each set were less than 2.0%. Solution stability was established up to 6 hours.

5. CONCLUSIONS

This spectrophotometric developed method can be successfully applied for quantitative trace level determination of palladium in Rasagiline Mesylate crude or pure bulk drug sample. Developed method is simple, fast and sensitive as compared to sophisticated and costly instrument methods such by AAS and ICP, hence can be used for routine analysis in quality control department. The method is validated and found out to be linear, accurate, precise, robust, specific and stable. Acceptable data for all method validation parameters tested and found out to be satisfactory.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENT

The authors wish to thank the management of Indoco Remedies Ltd. for supporting this work. The authors wish to acknowledge the process research department for providing the samples for this research.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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