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Original Article

# QUANTITATIVE DETERMINATION OF PLATINUM AND PALLADIUM IN DONEPEZIL HYDROCHLORIDE USING INDUCTIVELY COUPLED PLASMA – OPTICAL EMISSION SPECTROSCOPY

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**ABSTRACT**

**Objective:** To develop a precise, accurate, sensitive and selective analytical method using inductively coupled plasma – optical emission spectroscopy (ICP-OES) for the determination of platinum and palladium in Donepezil hydrochloride raw material, a reversible acetyl cholinesterase inhibitor.

**Methods:** The method developed and validated uses dry ashing for the extraction of platinum and palladium from Donepezil hydrochloride. Ash thus obtained was leached into an acidic solution followed by analysis of platinum and palladium using ICP-OES at wavelength 306.471 nm and 340.458 nm respectively. The method was studied for the various validation parameters including precision, accuracy, linearity, etc. for both the elements.

**Results:** The method was found to be linear in the wide working range of 0.2 µg/ml to16 µg/ml with a correlation coefficient of 0.9998 for platinum and 0.1µg/ml to 8µg/ml with a correlation coefficient of 0.9999 for palladium. The recoveries of platinum and palladium from the spiked samples of Donepezil hydrochloride at three different spiking levels were found to be in the range of 86.87 – 98.59% for both platinum and palladium. The limit of detection was found as 0.1 µg/ml and 0.05 µg/ml for platinum and palladium respectively while the limit of quantitation was found to be 0.2 µg/ml and 0.1 µg/ml for platinum and palladium.

**Conclusion:** The results of the validation studies indicate that the proposed method can be used for the simultaneous determination of platinum and palladium in Donepezil hydrochloride to ensure the quality and purity of Donepezil hydrochloride as a raw material for formulating the pharmaceutical formulations.

**Keywords:** ICP-OES, Platinum, Palladium, Donepezil hydrochloride.

## INTRODUCTION

Donepezil hydrochloride (fig. 1, 5,6-dimethoxy-2-[[1-(phenyl methyl)-4-piperidinyl] methyl]-2,3-dihydro-1*H*-inden-1-one hydrochloride) [1] is an acetyl cholinesterase inhibitor that inhibits the acetyl cholinesterase enzyme from breaking down the acetylcholine, thereby increasing the level and duration of action of acetylcholine, a neurotransmitter acetyl cholinesterase enzyme from breaking down the acetylcholine, thereby increasing the level and duration of action of acetylcholine, a neurotransmitter [2]. It binds to acetyl cholinesterase via hydrogen bonding and is easily hydrolyzed in biological fluid, thus the duration of enzyme inhibition at the receptor level is very short, and hence therefore referred to as 'reversible'. It is used mainly for the treatment of Alzheimer's disease where it is used to increase cortical acetylcholine [2].

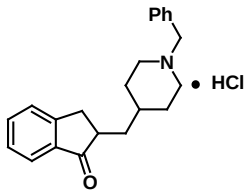


**Fig. 1: Structure of Donepezil hydrochloride**

During the synthesis of Donepezil hydrochloride, which involves several steps, platinum and palladium are commonly used as a catalytic agent in one of the steps [3]. Therefore, trace amount of platinum and palladium may remain in the final product, which is not desirable as residual impurities may cause adverse effects on the health. The intake of palladium causes fever, haemolysis, erythema, oedema and eye irritation. Although during the earlier days palladium hydroxide was used to treat obesity, however it was found to cause localized necrosis [4-5]. High intake of platinum results into respiratory allergies, bronchitis, asthma, rhinitis, conjunctivitis, contact dermatitis, irritation of eyes and nose with coughing [6-7].

It is therefore imminent that the platinum and palladium used as a catalyst during the manufacturing process are removed from the final product by adopting suitable purification processes. In order to ensure that the product is free from impurities of platinum and palladium, it is utmost essential that a validated method be used for determining the content of residual impurities of platinum and palladium. The method should be such that it does not suffer from any interference from the residual impurities of other metals used as catalysts. The present study was undertaken to develop and validate a highly sensitive and selective method using ICP-OES for simultaneous determination of platinum and palladium in Donepezil hydrochloride with better accuracy, precision, limit of detection and limit of quantification.

A number of methods have been reported for the determination of platinum and palladium, most of them being colorimetric methods. The colorimetric reagents which are commonly used quantitative determination of palladium and platinum are such as p-Nitrosodimethylaniline [8-9], p-Nitrosodiphenylamine [10], Erichorme cyanine-R [11], Methyl thymol blue [12],α-furildioxime [13], 2-Nitroso-1-naphthol [14], stannous chloride [15], 5-(p-

dimethylaminobezalidine)-Rhodanine [16]. The colorimetric methods are not so sensitive and moreover suffer from a number of factors like pH, matrix, longer time required to extract from the matrix and stabilization of color intensity. The fluorimetric methods [17] are more sensitive than colorimetric methods, but are susceptible to interferences from certain chemical species and are sensitive to pH, temperature, etc. Therefore, fluorimetric methods are not widely used for the determination of platinum and palladium although AAS technique is widely used for the determination of low concentrations of platinum and palladium in a solution, but lacks simultaneous determination of elements and suffers from chemical interferences too. In case of atomic absorption, signal of platinum and palladium is depressed in the presence of most other noble metals and also due to the presence of acids, hence chemical modifiers like lanthanum chloride, EDTA etc. are required to eliminate these interferences. On the other hand, ICP-OES technique provides higher sensitivity, lower detection limits, and no chemical interferences. This technique is less time consuming and provides rapid simultaneous multi-element analysis of platinum and palladium.

The present study pertains to the development of an analytical method for simultaneous determination of platinum and palladium in Donepezil hydrochloride raw material and validation of method for various analytical parameters i. e. the accuracy, precision, sensitivity, linearity, specificity and selectivity.

## MATERIALS AND METHODS

### Reagents and chemicals

Samples of Donepezil hydrochloride raw material of different batches (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, A. R. grade nitric acid and hydrochloric acid were procured from Merck Specialties Chemical Limited. All the glassware used were Type "A" and Borosil make. Calibrated micropipette with range 100 µl – 1000 µl was used. Standard reference solutions of 1000 µg/ml platinum and palladium (traceable to NIST) were procured from Scharlau Chemie, Spain. Standard solution of yttrium with concentration of 10000 µg/ml was procured from Sigma-Aldrich Co., USA. Whatman filter paper no. 41 was used for filtration.

### Instrumentation

Varian (Australia) Vista MPX Inductively Coupled Plasma- Optical Emission Spectrometer (ICP-OES) equipped with argon saturation assembly, CCD detector and software 4.1.0 complying with 21 CFR 11 was used for data acquisition and processing. Electronic analytical balance: Afcoset 3200, Mettler toledo with readability 0.01 mg was used. A muffle furnace from Ambassador, with temperature 600 ± 5°C caliberation was used for ashing the sample for the purpose of preparation of solution.

### Methods

#### Preparation of yttrium solution (for suppressing non-spectral interferences)

1 ml of a standard solution of yttrium (10000 µg/ml) was pipetted into a 1000 ml volumetric flask and diluted to volume with HPLC grade water. This gave a solution with a concentration of 10 µg/ml. Yttrium solution was used for suppressing any non spectral interference [18]. This 10 µg/ml solution is aspirated simultaneous along with the sample and the standard solution while determination of platinum and palladium.

#### Preparation of calibration standard solutions of platinum and palladium

#### Preparation of multi-element stock solution of platinum and palladium (5 µg/ml) for ICP-OES

10 ml of standard reference solution of platinum (1000 µg/ml) and 5 ml of standard reference solution of palladium (1000 µg/ml) was pipetted into a 100 ml volumetric flask and diluted to volume with HPLC grade water. This gave a mixed solution of platinum and palladium with platinum concentration of 100 µg/ml and palladium concentration of 50 µg/ml (solution A). From solution A, 20 ml was further diluted to 100 ml to give a solution with platinum and palladium concentration of 20 µg/ml and 10 µg/ml respectively (solution B). This was then used as a multi-element stock solution for preparation of calibration standard solutions of platinum and palladium.

#### Preparation of multi-element calibration solutions of platinum and palladium for ICP-OES

From the solution B, aliquots of 0.125 ml, 0.25 ml, 0.50 ml, 1.25 ml, 2.50 ml, 5.00 ml, 7.50 ml, 10.0 ml and 20.0 ml were pipetted into six different volumetric flasks of 25 ml. 2.5 ml of aqua regia was added into each flask and the solutions were diluted to mark using HPLC grade water. This gave a series of multi-element calibration solutions having the concentrations of platinum and palladium as given in table 1. Five replicate injections were made for each of the calibration solution.

**Table 1: Calibration solutions of platinum and palladium**

| | Volume of aliquot pipetted from solution B, ml | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **0.125** | **0.25** | **0.50** | **1.25** | **2.50** | **5.00** | **7.50** | **10.0** | **20.0** |
| Conc. of Pt, µg/ml | 0.10 | 0.20 | 0.40 | 1.00 | 2.00 | 4.00 | 6.00 | 8.0 | 16.00 |
| Conc. of Pd, µg/ml | 0.05 | 0.10 | 0.20 | 0.40 | 1.00 | 2.00 | 3.00 | 4.00 | 8.00 |

### Sample preparation

About 10.00 ± 0.1 gram sample of Donepezil hydrochloride was weighed accurately in a silica crucible and 2 ml of distilled water was added to moist the sample. The crucible was then heated on a hot plate to dryness followed by ashing at 600 ± 5°C in a muffle furnace for 4 hours to remove all the organic material. The contents were cooled and the ash residue was leached in 1 ml aqua regia. The crucible was then heated on a hot plate gently (slow heat) to dissolve the ash residue completely, and the contents were transferred to a 10 ml volumetric flask and made to volume using HPLC grade water. The above procedure is similarly followed for preparation other samples (sample B, C, D and E). The solution was then aspirated into ICP-OES.

### Preparation of reagent blank

1 ml of HPLC grade water was taken in silica crucible and heated on a hot plate to dryness and kept in a muffle furnace at 600 ± 5°C for 4 hours. After cooling, the contents were leached using 1 ml aqua regia and transferred to 10 ml volumetric flask and made up to volume with HPLC grade water. The solution was then aspirated into ICP-OES.

### ICP-OES operating conditions

Inductively coupled plasma-optical emission spectrometry (ICP-OES) with radial torch equipped with argon saturation assembly was used for the simultaneous determination of platinum and palladium in Donepezil 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 1.25 kW. The vertical height of the plasma was fixed at 4 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 analyses of 5 sec was maintained throughout the studies for ICP-OES. All the observations of emission were recorded

at 306.471 nm and 340.458 nm for platinum and palladium respectively, which corresponds to the most sensitive emission wavelength and no spectral interferences of platinum or palladium respectively. The instrument was calibrated for various parameters before the studies.

## RESULTS AND DISCUSSION

### Analytical method development

### Sample preparation

One of the challenges of method development is the efficient extraction of platinum and palladium from Donepezil hydrochloride. For this purpose, generally, the sample digestion technique using acids is recommended. During the initial method development work, it was observed that when the sample was digested with acids, complete extraction of platinum and palladium was not obtained and the process was time consuming. Thus the method used here for the extraction of platinum and palladium for ICP-OES was dry ashing of the drug. No ashing agent was used during the ashing procedure, since platinum and palladium are not volatile at the ashing temperature of 600 ± 5°C.

### Optimization of concentration of yttrium solution

To get the maximum intensity of platinum and palladium and to compensate for the effects of intensity and fluctuations (noise) due to the sample matrix, concentration of yttrium solution was optimized. Donepezil hydrochloride sample solution was spiked with different concentration of standard solutions of platinum and palladium and each spiked sample was aspirated into ICP-OES along with a standard solution of yttrium. Different concentration of yttrium solution were used for optimization of methods for determination of platinum and palladium. The maximum recovery of platinum and palladium was observed at concentrations of 10 µg/ml of yttrium solution. Throughout the study yttrium was aspirated into the spray chamber through the third channel of peristaltic pump. The results of this study are presented in table 2.

**Table 2: Optimization of concentration of standard yttrium solution.**

| Conc. of yttrium (µg/ml) | Spiked conc. of Pt (µg/ml) (n=3) | Spiked conc. of Pd (µg/ml) (n=3) | % Recovery | |
|---|---|---|---|---|
| | | | Pt | Pd |
| **0** | 0.2 | 0.2 | 65 | 67 |
| | 2.0 | 2.0 | 64 | 67 |
| | 8.0 | 8.0 | 62 | 65 |
| **5** | 0.2 | 0.2 | 74 | 77 |
| | 2.0 | 2.0 | 74 | 76 |
| | 8.0 | 8.0 | 71 | 75 |
| **10** | 0.2 | 0.2 | 96 | 97 |
| | 2.0 | 2.0 | 96 | 98 |
| | 8.0 | 8.0 | 97 | 96 |
| **12** | 0.2 | 0.2 | 95 | 95 |
| | 2.0 | 2.0 | 97 | 98 |
| | 8.0 | 8.0 | 98 | 96 |

From the results of table 2, it is evident that yttrium solution with concentration 10 µg/ml was sufficient enough to obtain more than 95% recovery of both platinum and palladium when determined simultaneously at concentration ranges between 0.2 µg/ml to 8.0 µg/ml.

### Analytical data

For the simultaneous quantitative determination of platinum and palladium using ICP-OES, conditions were optimized as detailed above, so as to get the maximum signal intensity with 10 µg/ml concentration of standard yttrium solution aspirated through 3rd channel of peristaltic pump. For platinum and palladium content in both i. e. samples of Donepezil hydrochloride and the reagent blank was determined against a seven point calibration curve plotted for the standard solutions of platinum and palladium ranging from 0.2 µg/ml to 16.0µg/ml and 0.1µg/ml to 8.0µg/ml vs their emission intensity respectively for ICP-OES (fig. 2). Results for platinum and palladium content by ICP-OES in five samples (A, B, C, D and E) of Donepezil hydrochloride are given in table 3.

### Method performance characteristics

The method was validated for various parameters for the simultaneous quantification of platinum and palladium as per the guidelines of the International Conference on Harmonization (ICH) [19].

### Linearity

Seven point calibration curve was plotted for the standard solutions of both platinum and palladium vs emission intensity (c/s) in the concentration range from 0.2 µg/ml to 16 µg/ml for platinum and 0.1 µg/ml to 8 µg/ml for palladium. Each of the calibaration solution was measured five times and the average of the five readings for each of the calibarion solution was used for plotting the calibration curve (Table 4).

Platinum showed a correlation coefficient of 0.9998, whereas palladium showed a correlation coefficient of 0.9999 thus indicating a very good linear response between an increase in concentration of platinum \ palladium and the emission intensity.

The correlation coefficient ($R^2$) of both platinum and palladium were greater than ≥ 0.9995, which shows that the method is linear in the range from 0.2 µg/ml to 16 µg/ml and 0.1 µg/ml to 8 µg/ml for platinum and palladium respectively.

**Table 3: Platinum and palladium content in samples of Donepezil hydrochloride (Results are the mean of the five replicate determinations for each of the 5 batches)**

| Parameters | Sample code | | | | |
|---|---|---|---|---|---|
| | A | B | C | D | E |
| Weight of Donepezil HCl taken (g) | 10.00±0.1 | 10.00±0.1 | 10.00±0.1 | 10.00±0.1 | 10.00±0.1 |
| Dilution factor, ml | 10 | 10 | 10 | 10 | 10 |
| Conc. of platinum in reagent blank (µg/ml) | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Platinum content in sample of Donepezil HCl (µg/g ±% RSD) | 0.456±2.29% | 0.459±2.16% | 0.501±2.32% | 0.519±2.48% | 0.546±2.16% |
| Conc. of palladium in reagent blank (µg/ml) | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Palladium content in sample of Donepezil HCl (µg/g ±%RSD) | 0.261±3.65% | 0.247±2.39% | 0.264±2.85% | 0.253±3.14% | 0.265±2.7% |

**Table 4: Emission intensity of platinum (Pt) and palladium (Pd) standard solutions at different concentration levels (Results are the mean of the five replicate determinations for each of standard preparation)**

| Standard solution | Emission intensity | | | | | % RSD |
|---|---|---|---|---|---|---|
| Concentration (µg/ml) | Replicate 1 | Replicate 2 | Replicate 3 | Replicate 4 | Replicate 5 | |
| Pt 0.2 | 99.1 | 95.81 | 94.92 | 90.11 | 89.31 | 4.365 |
| 0.4 | 186.56 | 180.67 | 171.82 | 172.9 | 177.98 | 3.378 |
| 1 | 465.35 | 489.12 | 475.16 | 469.8 | 490.32 | 2.364 |
| 2 | 912.36 | 934.16 | 967.11 | 949.19 | 924.15 | 2.284 |
| 4 | 1801.15 | 1794.12 | 1786.12 | 1846.19 | 1883.71 | 2.277 |
| 6 | 2703.52 | 2649.16 | 2546.46 | 2605.75 | 2608.19 | 2.218 |
| 8 | 3548.23 | 3417.12 | 3579.19 | 3512.62 | 3502.91 | 1.738 |
| 16 | 6986.35 | 6813.12 | 6824.1 | 6801.26 | 6910.17 | 1.155 |
| Pd 0.1 | 89.15 | 93.21 | 81.48 | 79.62 | 78.91 | 7.525 |
| 0.2 | 175.31 | 161.49 | 155.23 | 161.31 | 181.31 | 6.528 |
| 0.4 | 347.36 | 323.47 | 356.92 | 341.85 | 377.91 | 5.727 |
| 1 | 852.32 | 822.19 | 829.68 | 872.32 | 878.12 | 2.924 |
| 2 | 1698.12 | 1654.92 | 1667.43 | 1614.6 | 1701.3 | 2.128 |
| 3 | 2550.45 | 2514.89 | 2516.9 | 2593.8 | 2501.6 | 1.468 |
| 4 | 3396.25 | 3319.2 | 3299.1 | 3275.1 | 3358.12 | 1.444 |
| 8 | 6715.65 | 6701.19 | 6692.9 | 6701.4 | 6724.8 | 0.190 |

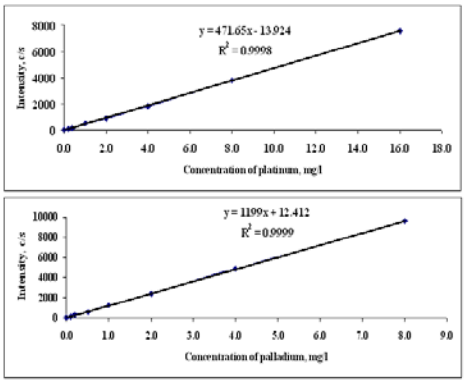


**Fig. 2: Calibration curve for concentration of platinum (Pt) and palladium (Pd) (µg/l) vs emission intensity (c/s) by ICP-OES**

**Precision**

Precision studies of the method were carried out for both intra-day and inter-day repeatability and reproducibility using six replicates each of i) combined standard solution A, B and C of platinum and palladium at three different concentrations. Standard solution A was prepared with concentration of platinum 0.2 µg/ml and palladium 0.4 µg/ml, standard solution B was prepared with concentration of platinum: 2.0 µg/ml and palladium 4.0 µg/ml and standard solution C was prepared with concentration of platinum 4.0 µg/ml, Pd 8.0 µg/ml ii) using three different digested samples (A, B and C) of Donepezil hydrochloride. Data for the precision studies are given in table 5. In the combined standard solutions A, platinum at concentration level of 0.2 µg/ml showed a %RSD of 2.026% on the first day, 1.373% on the second day and 1.223% on the third day while palladium at concentration level of 0.4 µg/ml, a % RSD of 1.040% on the first day, 0.842% on the second day and 1.286% on the third day was observed. In the combined standard solution B, platinum showed a % RSD of 0.129% on the first day, 2.208% on the second day and 0.128% on the third day for platinum while for palladium a % RSD of 1.098% on the first day, 0.098 % on the second day and 0.204% was observed on the third day. Similarly, a combined standard solution C, platinum at concentration level of 4.0 µg/ml showed a % RSD of 0.068% on the first day, 0.075% on the second day and 0.077% on the third day for platinum and 0.761% RSD on the first day, 0.306% RSD on the second day and 0.471% RSD on the third day observed for palladium. For the sample 'A', containing platinum and palladium, a % RSD of 2.043% on the first day, 0.974% on the second day and 2.485% on the third day was observed for platinum while for palladium a % RSD of 2.532% on the first day, 2.531% on the second day and 1.591% was observed on the third day. For the sample 'B', a % RSD of 1.648% on the first day, 1.377% on the second day and 1.214% on the third day was obtained for platinum while for palladium, a % RSD of 2.082% on the first day, 2.518% on the second day and 1.327% was observed on the third day. For the sample 'C', a % RSD of 1.449% on the first day, 2.417% on the second day and 1.265% on the third day was obtained for platinum while for palladium, a % RSD of 1.975% on the first day, 2.409% on the second day and 1.445% was observed on the third day

The studies were also carried out for determination of Inter-day precision of quantitative estimation of platinum and palladium incombined standard solutionSs (standard solution A,B and C) containing platinum and palladium, and three digested sample solutions of Donepezil hydrochloride (sample A, B and C). The combined standard solution A containing platinum and palladium, showed a % RSD of 0.448% for platinum and 0.511% for palladium; the combined standard solution B showed a % RSD of 0.800% and 0.094% for platinum and palladium respectively and for combined standard solution C % RSD of 0.025% and 0.332% of platinum and palladium respectively was obtained.

Inter-day precision in case of digested sample 'A', % RSD was found to be 1.015% of platinum and 1.797% for palladium; in the case of sample 'B', a % RSD for platinum was 0.434% and 1.558% for palladium and in the case of sample 'C', the % RSD for platinum was 0.533% and 0.575% for palladium was obtained. All these values indicate that the method has a good repeatability and reproducibility both inter-day as well as intra-day. The acceptance criteria for % RSD of intra-day precision and inter-day precision is that % RSD should not be more than 10%.

**Accuracy**

For accuracy (recovery) studies standard solutions of known concentrations of platinum and palladium were spiked in three different samples of Donepezil hydrochloride (marked as B, C and D) at three different concentration levels of 0.2 µg/ml, 4.0 µg/ml and 8.0 µg/ml for platinum and 0.1 µg/ml, 2.0 µg/ml and 4.0 µg/ml for palladium. The samples were thoroughly homogenized. The spiked samples were digested as per the procedure described under sample preparation. The platinum and palladium content in the 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 theoretical concentration level of the spiked solutions with that of the observed values of the concentration of platinum and palladium. Recoveries ranging between 89.30- 97.64% of platinum and 85.44-98.45 % for palladium were obtained in the three spiked samples with different concentrations of platinum and palladium which is well within the acceptable criteria at trace concentration levels. Data for the accuracy studies of platinum and palladium is given in table 6. Acceptance criteria for recovery study is 80-120%.

**Table 5: Precision Studies for Intra-day and Inter-day for determination of platinum and palladium in three combined standard solutions of platinum and palladium and three samples of Donepezil hydrochloride**

| Solutions Type | Intra-day precision | | | | | | Inter-day precision | |
|---|---|---|---|---|---|---|---|---|
| | Day I (µg/ml) (n=6) | | Day II (µg/ml) (n=6) | | Day III (µg/ml) (n=6) | | | |
| | Pt | Pd | Pt | Pd | Pt | Pd | Pt | Pd |
| Standard A | 0.213 | 0.401 | 0.206 | 0.406 | 0.204 | 0.413 | | |
| i) Pt: 0.2 µg/ml | 0.209 | 0.403 | 0.204 | 0.414 | 0.201 | 0.406 | | |
| ii) Pd: 0.4 µg/ml | 0.206 | 0.406 | 0.203 | 0.413 | 0.206 | 0.402 | 0.206 | 0.405 |
| | 0.204 | 0.401 | 0.209 | 0.409 | 0.208 | 0.414 | 0.204 | 0.409 |
| | 0.205 | 0.409 | 0.203 | 0.406 | 0.206 | 0.402 | 0.205 | 0.408 |
| | 0.201 | 0.411 | 0.201 | 0.408 | 0.203 | 0.409 | | |
| Mean | 0.206 | 0.405 | 0.204 | 0.409 | 0.205 | 0.408 | 0.205 | 0.407 |
| SD | 0.004 | 0.004 | 0.003 | 0.003 | 0.003 | 0.005 | 0.001 | 0.002 |
| % RSD | 2.026 | 1.040 | 1.373 | 0.842 | 1.223 | 1.286 | 0.448 | 0.511 |
| | 2.012 | 4.022 | 2.016 | 4.016 | 2.013 | 4.014 | | |
| Standard B | 2.014 | 3.991 | 2.101 | 4.017 | 2.018 | 4.018 | | |
| i) Pt: 2.0 µg/ml | 2.019 | 3.982 | 2.101 | 4.02 | 2.019 | 4.017 | 2.015 | 4.015 |
| ii) Pd: 4.0 µg/ml | 2.017 | 3.996 | 2.001 | 4.009 | 2.017 | 4.001 | 2.044 | 4.016 |
| | 2.013 | 3.999 | 2.017 | 4.013 | 2.014 | 4.003 | 2.017 | 4.009 |
| | 2.015 | 4.101 | 2.026 | 4.018 | 2.019 | 4.001 | | |
| Mean | 2.015 | 4.015 | 2.044 | 4.016 | 2.017 | 4.009 | 2.025 | 4.013 |
| SD | 0.003 | 0.044 | 0.045 | 0.004 | 0.003 | 0.008 | 0.016 | 0.004 |
| %RSD | 0.129 | 1.098 | 2.208 | 0.098 | 0.128 | 0.204 | 0.800 | 0.094 |
| | 4.012 | 7.912 | 4.011 | 7.96 | 4.011 | 7.992 | | |
| Standard C | 4.019 | 7.991 | 4.018 | 7.948 | 4.018 | 7.972 | | |
| i) Pt: 4.0 µg/ml | 4.013 | 8.102 | 4.017 | 7.992 | 4.019 | 7.914 | 4.015 | 8.005 |
| ii) Pd: 8.0 µg/ml | 4.015 | 7.996 | 4.019 | 8.001 | 4.016 | 7.931 | 4.017 | 7.977 |
| | 4.016 | 8.014 | 4.016 | 8.004 | 4.019 | 7.992 | 4.016 | 7.952 |
| | 4.012 | 8.016 | 4.019 | 7.959 | 4.015 | 7.913 | | |
| Mean | 4.015 | 8.005 | 4.017 | 7.977 | 4.016 | 7.952 | 4.016 | 7.978 |
| SD | 0.003 | 0.061 | 0.003 | 0.024 | 0.003 | 0.037 | 0.001 | 0.027 |
| % RSD | 0.068 | 0.761 | 0.075 | 0.306 | 0.077 | 0.471 | 0.025 | 0.332 |
| | 0.466 | 0.261 | 0.455 | 0.256 | 0.449 | 0.261 | | |
| Sample A | 0.483 | 0.249 | 0.469 | 0.263 | 0.459 | 0.253 | | |
| i) Pt: µg/g | 0.466 | 0.245 | 0.461 | 0.249 | 0.462 | 0.261 | 0.471 | 0.25 |
| ii) Pd: µg/g | 0.459 | 0.251 | 0.463 | 0.262 | 0.459 | 0.254 | 0.462 | 0.259 |
| | 0.482 | 0.248 | 0.463 | 0.258 | 0.483 | 0.252 | 0.464 | 0.256 |
| | 0.469 | 0.243 | 0.463 | 0.268 | 0.469 | 0.254 | | |
| Mean | 0.471 | 0.250 | 0.462 | 0.259 | 0.464 | 0.256 | 0.466 | 0.255 |
| SD | 0.010 | 0.006 | 0.005 | 0.007 | 0.012 | 0.004 | 0.005 | 0.005 |
| % RSD | 2.043 | 2.532 | 0.974 | 2.531 | 2.485 | 1.591 | 1.015 | 1.797 |
| | 0.462 | 0.261 | 0.468 | 0.251 | 0.463 | 0.269 | | |
| Sample B | 0.457 | 0.252 | 0.459 | 0.268 | 0.468 | 0.261 | | |
| i) Pt: µg/g | 0.461 | 0.261 | 0.455 | 0.264 | 0.453 | 0.264 | 0.459 | 0.255 |
| ii) Pd: µg/g | 0.446 | 0.249 | 0.461 | 0.253 | 0.465 | 0.259 | 0.461 | 0.26 |
| | 0.469 | 0.258 | 0.468 | 0.259 | 0.468 | 0.261 | 0.463 | 0.263 |
| | 0.459 | 0.251 | 0.453 | 0.262 | 0.461 | 0.263 | | |
| Mean | 0.459 | 0.255 | 0.461 | 0.260 | 0.463 | 0.263 | 0.461 | 0.259 |
| SD | 0.008 | 0.005 | 0.006 | 0.007 | 0.006 | 0.003 | 0.002 | 0.004 |
| % RSD | 1.648 | 2.082 | 1.377 | 2.518 | 1.214 | 1.327 | 0.434 | 1.558 |
| | 0.484 | 0.269 | 0.467 | 0.261 | 0.473 | 0.261 | | |
| Sample C | 0.471 | 0.274 | 0.462 | 0.268 | 0.479 | 0.269 | | |
| i) Pt: µg/g | 0.477 | 0.266 | 0.482 | 0.272 | 0.471 | 0.259 | 0.475 | 0.266 |
| ii) Pd: µg/g | 0.469 | 0.261 | 0.489 | 0.276 | 0.469 | 0.267 | 0.472 | 0.267 |
| | 0.481 | 0.262 | 0.468 | 0.259 | 0.468 | 0.263 | 0.47 | 0.264 |
| | 0.467 | 0.261 | 0.461 | 0.268 | 0.461 | 0.266 | | |
| Mean | 0.475 | 0.266 | 0.472 | 0.267 | 0.470 | 0.264 | 0.472 | 0.266 |
| SD | 0.007 | 0.005 | 0.011 | 0.006 | 0.006 | 0.004 | 0.003 | 0.002 |
| % RSD | 1.449 | 1.975 | 2.417 | 2.409 | 1.265 | 1.445 | 0.533 | 0.575 |

**Specificity**

The method was evaluated for specificity with respect to the determination of platinum and palladium in the presence of each other and also when present as impurities at trace levels in the bulk matrix of Donepezil hydrochloride. In order to determine the specificity of the method, three solutions each of platinum and palladium were prepared separately at a concentration of 0.2 µg/ml, 2.0 µg/ml and 8.0 µg/ml (a total of six solutions). The concentration of platinum and palladium were measured using a calibration curve. Eight solutions consisting of varied concentrations of platinum and palladium were prepared. Sample solution 'B' is spiked with varying concentration of platinum and palladium.

The solution composition of different standards and sample preparation with varying concentrations of platinum and palladium are given in table 7. The concentration of platinum and palladium were measured using the standard calibration curve. It was found that the quantification of impurities of platinum and palladium even if present at low concentration of 0.2 µg/ml or high concentrations of 8.0 µg/ml does not suffer from any kind of interferences either from each other or due to the bulk of the matrix. Recoveries of platinum and palladium obtained in all the cases were found to be in the range of 94.23 to 100.9 %, thus, indicating that the method is specific to the simultaneous determination of trace amount of platinum and palladium in the presence each other or present in the bulk of the sample.

**Table 6: Recovery studies for determination of platinum and palladium in three spiked samples of Donepezil hydrochloride (B, C and D) spiked with different conc. of platinum and palladium**

| Sample code | Platinum content | | | | | Palladium content | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Initial conc. (µg/ml) | Spiked conc. (µg/ml) | Theo. conc. (µg/ml) | Obs. conc. (µg/ml) | % Rcov. | Initial conc. (µg/ml) | Spiked conc. (µg/ml) | Theo. conc. (µg/ml) | Obs. conc. (µg/ml) | % Recov |
| | 0.459 | 0.2 | 0.659 | 0.61 | 92.56 | 0.249 | 0.1 | 0.349 | 0.312 | 89.39 |
| **B** | 0.459 | 4.0 | 4.459 | 4.214 | 94.50 | 0.249 | 2 | 2.249 | 2.101 | 93.41 |
| | 0.459 | 8.0 | 8.459 | 8.151 | 96.35 | 0.249 | 4 | 4.249 | 4.081 | 96.04 |
| | 0.501 | 0.2 | 0.701 | 0.626 | 89.30 | 0.264 | 0.1 | 0.364 | 0.311 | 85.44 |
| **C** | 0.501 | 4.0 | 4.501 | 4.407 | 97.91 | 0.264 | 2 | 2.264 | 2.115 | 93.41 |
| | 0.501 | 8.0 | 8.501 | 8.211 | 96.58 | 0.264 | 4 | 4.264 | 4.198 | 98.45 |
| | 0.519 | 0.2 | 0.719 | 0.671 | 93.32 | 0.253 | 0.1 | 0.353 | 0.306 | 86.68 |
| **D** | 0.519 | 4.0 | 4.519 | 4.41 | 97.58 | 0.253 | 2 | 2.253 | 2.118 | 94.00 |
| | 0.519 | 8.0 | 8.519 | 8.318 | 97.64 | 0.253 | 4 | 4.253 | 4.131 | 97.11 |

**Table 7: Studies for specificity of platinum and palladium in presence of each other**

| Solution composition, (µg/ml) | Mean obs. conc. (µg /ml) (n=3) | | Mean % Rcov (n=3) | Mean % Rcov (n=3) |
|---|---|---|---|---|
| | Pt | Pd | Pt | Pd |
| Pt: 0.2 | 0.198 | - | 99.0 ± 1.118 | - |
| Pd: 0.2 | - | 0.195 | - | 97.5 ± 1.409 |
| Pt: 0.2 + Pd: 0.2 | 0.197 | 0.194 | 98.5 ± 1.664 | 97.0 ± 1.281 |
| Pt: 0.2 + Pd: 2.0 | 0.196 | 2.016 | 98.0 ± 1.414 | 100.8 ± 1.320 |
| Pt: 0.2 + Pd: 8.0 | 0.199 | 7.986 | 99.5 ± 1.178 | 99.82 ± 1.113 |
| Pt: 2.0 | 2.019 | - | 100.9 ± 1.443 | 100.5 ± 1.318 |
| Pd: 2.0 | - | 2.016 | - | 100.8 ± 1.426 |
| Pt: 2.0 + Pd: 0.2 | 2.014 | 0.193 | 100.7 ± 1.310 | 96.5 ± 1.693 |
| Pt: 2.0 + Pd: 2.0 | 2.012 | 2.012 | 100.6 ± 1.244 | 100.6 ± 1.461 |
| Pt: 2.0 + Pd: 8.0 | 2.006 | 8.011 | 100.3 ± 1.515 | 100.1 ± 1.388 |
| Pt: 8.0 | 7.994 | - | 99.9 ± 1.420 | - |
| Pd: 8.0 | - | 7.941 | - | 99.3 ± 1.215 |
| Pt: 8.0 + Pd: 0.2 | 7.981 | 0.191 | 99.7 ± 1.315 | 95.5 ± 1.613 |
| Pt: 8.0 + Pd: 2.0 | 8.006 | 1.991 | 100 ± 1.266 | 99.5 ± 1.241 |
| Sample B (Pd-0.247 & Pt-0.459) + Pd: 0.2 + Pt 8.0 | 8.206 | 0.421 | 97.0 ± 1.102 | 94.2 ± 1.518 |
| Sample B (Pd-0.247 & Pt-0.459) + Pd: 8.0 + Pt 0.2 | 0.621 | 8.219 | 94.23 ± 1.314 | 99.46 ± 1.469 |

**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 0.1 µg/ml for platinum and 0.05 µg/ml for palladium. Limit of quantification (LOQ) was obtained as 0.2 µg/ml for platinum and 0.1 µg/ml for palladium evaluated on the basis of minimum concentration for which a reproducible signal was obtained with % RSD less than 5 for five replicates.

## CONCLUSION

Since the quality of any pharmaceutical formulation would be dependent upon the quality of raw material used during the manufacturing of the product, it is therefore utmost essential that the raw material is analyzed for the presence of any impurities in it. It has been found that raw material of Donepezil may contain platinum and palladium as impurities which would certainly contaminate the pharmaceutical formulation prepared from this raw material thereby causing adverse effects on human health. Therefore, it is important that the experimental data clearly depicts that the developed and validated analytical method is precise, accurate, sensitive and selective for the simultaneous quantitative determination of platinum and palladium in the raw material of Donepezil hydrochloride using inductively coupled plasma – optical emission spectroscopy (ICP-OES).

The method provides wide range of linearity, specificity without interference from endogenous impurities. 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. Thus, the present study suggests that ICP-OES has the advantages over other analytical methods for the determination of platinum and palladium because of sensitivity i. e. the lower limit of detection, for both platinum and palladium in the raw material of Donepezil hydrochloride. Therefore, the method can easily be adopted for routine quantitative analysis of platinum and palladium, present as residual impurities in raw materials of Donepezil hydrochloride.

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## CONFLICT OF INTERESTS

Declared None

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