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# NEW METHOD DEVELOPMENT AND VALIDATION OF UV-SPECTROPHOTOMETER FOR THE ESTIMATION OF PALIPERIDONE IN BULK AND PHARMACEUTICAL DOSAGE FORM

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**Abstract:** Paliperidone is a dopamine antagonist of the atypical antipsychotic class of medications. Simple, economic, sensitive, reproducible and rapid UV-Spectrophotometric method have been developed and validated for the determination of Paliperidone (PP) in pharmaceutical dosage forms and in bulk drug. The absorption maxima was found to be at 235 nm in methanol and shows linearity over the concentration range of 1-30µg ml-1with regression equation 0.032x + 0.011(r2 = 0.999) and 0.0312x+0.007(r2=0.999) at 278nm. The proposed method can be successfully applied for the determination of Paliperidone in dosage forms. The methods were validated as per the ICH guidelines.

**Keywords:** Paliperidone, spectroscopy, Validation, ICH guidelines

*PAPER-QR CODE*

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## INTRODUCTION

Paliperidone (9-hydroxyrisperidone) is a major active metabolite of risperidone and is indicated for the acute and maintenance treatment of schizophrenia. Paliperidone is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. Literature survey revealed that LC-MS methods, HPTLC, HPLC, UPLC methods were developed for the analysis of Paliperidone in different solvents and UV-spectrophotometric methods were available which developed in 0.1N HCl. In the present study a simple, rapid, precise and accurate UV-spectrophotometric method has been developed for the determination of Paliperidone in pharmaceutical dosage forms and validated as per the ICH guidelines.

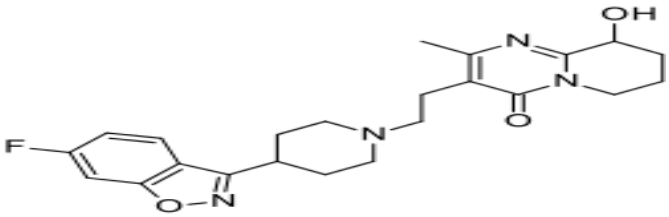


**Figure1. Chemical Structure of Paliperidone**

## MATERIALS AND METHODS

### Instrumentation

A double beam UV-VIS spectrophotometer (UV-1800, Shimadzu, Japan) connected to computer loaded with spectra manager software UV Probe was employed with spectral bandwidth of 1nm and wavelength accuracy of ± 0.3 nm with a pair of 10 mm matched quartz cells. All weights were taken on electronic balance (Contech).

### Chemicals and reagents

Methanol used as diluent. Drug sample of Paliperidone was given as a gift sample by Natco Pharma limited, Hyderabad (India) was used as such without further purification. Tablets of Paliperidone (PALIDO) were procured from local market.

### Preparation of Standard Stock Solution:

The standard solution of Paliperidone was prepared by dissolving accurately about 100 mg of the Paliperidone with Methanol in a 100 ml volumetric flask and sonicated for 20 mins. This stock solution was further diluted with methanol as per the requirement.

**Preparation of Sample Solution:**

Twenty tablets of Paliperidone were taken and into a fine powder of the tablets and the powder equivalent to 10 mg of Paliperidone was weighed accurately and transferred into a 100 ml standard volumetric flask. The contents were dissolved in methanol and sonicated for 30 Minutes. This entire solution was filtered through 0.45 micron Whatmann filter paper (No. 41) and the final solution was made with methanol to get the solution of 1000µg/ ml. This solution was further diluted with methanol as per the requirement.

**Procedure:**

The drug solution was scanned (200-400 nm) against reagent blank i.e. methanol and the absorption spectrum was recorded. The absorption maximum (λmax) was observed at 235 nm and 278nm and the absorbance of a series of solutions (1-30µg $ml^{-1}$) was recorded at that λmax. A graph was plotted by taking the concentration of the drug solutions on the x-axis and the corresponding absorbance values on the y-axis which was shown in figures 4 and 5.

**Assay procedure for the commercial formulations (Tablets):**

Paliperidone is available as tablets of extended release containing 3mg of Paliperidone. Paliperidone is available in the local market with brand names PALIDO (3 mg, TORRENT Pharmaceuticals, India). The sample solution which was prepared earlier was taken and further diluted as per the requirement. A series of solutions were prepared were scanned and the corresponding absorbance values were recorded. The % recovery was calculated from the regression equations obtained from the calibration curves which was shown in table 1 and figures 2 and 3.

**Table No 1. Assay of commercial formulations**

| Sample no | Formulation | Label claim (mg) | Amount found (mg) | % Recovery |
|---|---|---|---|---|
| 1 | Tablets | 3 | 3.0078 | 100.26 |
| 2 | Tablets | 3 | 3.0048 | 100.16 |

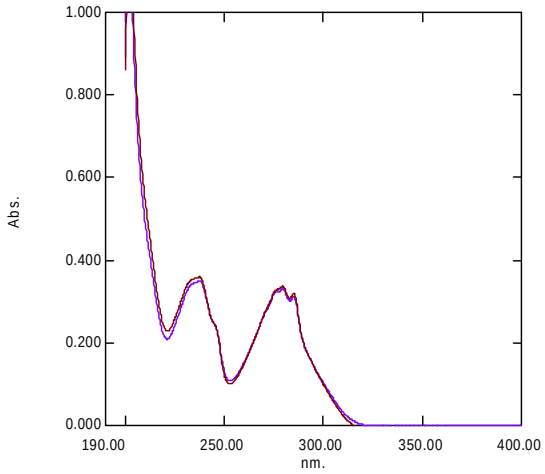


**Figure2. Absorption spectrum of standard and sample drug (10µg/ml)**

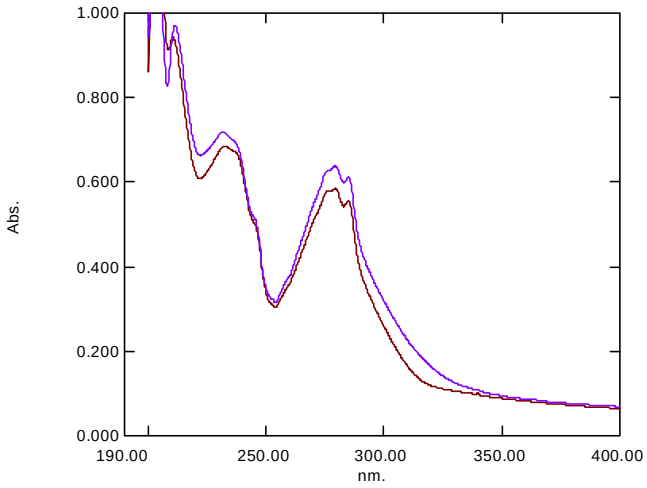


**Figure3. Absorption spectrum of standard and sample drug (20µg/ml)**

**2. Accuracy studies:**

The accuracy of the method, recovery studies were carried out by adding different amounts (80%, 100% and 120%) of bulk samples of Paliperidone within the linearity range were taken and added to the pre-analyzed formulation of concentration 10µg/ml. From that percentage recovery values were calculated. The results were within the range and were found to be highly accurate which was shown in table 2 and 3.

**Table No 2 Accuracy studies (at $\lambda_{235nm}$)**

| Spiked level (%) | Formulation Conc (µg/ml) | Pure Drug Conc (µg/ml) | % Recovery | % Mean recovery | SD | %RSD |
|---|---|---|---|---|---|---|
| 80 | 10 | 8 | 100.16 | 100.21 | 0.244 | 0.243 |
| | 10 | 8 | 100 | | | |
| | 10 | 8 | 100.48 | | | |
| 100 | 10 | 10 | 100.77 | 100.51 | 0.323 | 0.321 |
| | 10 | 10 | 100.62 | | | |
| | 10 | 10 | 100.15 | | | |
| 120 | 10 | 12 | 99.71 | 100.69 | 0.985 | 0.978 |
| | 10 | 12 | 100.70 | | | |
| | 10 | 12 | 101.68 | | | |

**Table No 3 Accuracy studies (at $\lambda_{278nm}$)**

| Spiked level (%) | Formulation Conc (µg/ml) | Pure Drug Conc (µg/ml) | % Recovery | % Mean recovery | SD | %RSD |
|---|---|---|---|---|---|---|
| 80 | 10 | 8 | 100.94 | 100.67 | 0.292 | 0.290 |
| | 10 | 8 | 100.72 | | | |
| | 10 | 8 | 100.36 | | | |
| 100 | 10 | 10 | 101.53 | 101.14 | 0.359 | 0.354 |
| | 10 | 10 | 100.82 | | | |
| | 10 | 10 | 101.08 | | | |
| 120 | 10 | 12 | 100.92 | 100.93 | 0.285 | 0.282 |
| | 10 | 12 | 100.66 | | | |
| | 10 | 12 | 101.23 | | | |

## 2. Precision

Precision of an analytical method is usually expressed as standard deviation or relative standard deviation. The standard deviation and % relative standard deviation are calculated from statistical formula. The standard deviation and relative standard deviation for the absorbance values were calculated from statistical formula which was shown in tables 4 and 5.

### A). Repeatability

**Table No 4 Repeatability studies (at $\lambda_{235nm}$)**

| Concentration [µg/ml] | Absorbance at235nm | Absorbance Mean | SD | %RSD |
|---|---|---|---|---|
| 10 | 0.342 | | | |
| 10 | 0.343 | | | |
| 10 | 0.343 | 0.342 | 0.001 | 0.306 |
| 10 | 0.344 | | | |
| 10 | 0.341 | | | |
| 10 | 0.342 | | | |

**Table No 5 Repeatability studies (at $\lambda_{278nm}$)**

| Concentration [µg/ml] | Absorbance at279nm | Absorbance Mean | SD | %RSD |
|---|---|---|---|---|
| 10 | 0.340 | | | |
| 10 | 0.341 | | | |
| 10 | 0.344 | 0.341 | 0.001 | 0.399 |
| 10 | 0.342 | | | |
| 10 | 0.341 | | | |
| 10 | 0.342 | | | |

**B) Inter day Precision**

To check the reproducibility of the method, the same procedure was followed as that of precision of the method on the next day. Absorbance of each solution was scanned and the spectra were recorded. The standard deviation and relative standard deviation for the absorbance values using the statistical formula and the results were shown in tables 6 and 7.

**Table No 6 Interday precision (at λ235nm)**

| Sample no | Inter day | |
|---|---|---|
| 1 | 0.363 | |
| 2 | 0.364 | |
| 3 | 0.365 | Mean=0.364 |
| 4 | 0.362 | S.D=0.0029 |
| 5 | 0.366 | %RSD=0.808 |
| 6 | 0.362 | |
| 7 | 0.366 | |
| 8 | 0.371 | |

**Table No 7 Interday precision (at$\lambda_{278nm}$)**

| Sample no | Inter day | |
|---|---|---|
| 1 | 0.358 | |
| 2 | 0.359 | |
| 3 | 0.355 | Mean=0.358 |
| 4 | 0.358 | S.D=0.0015 |
| 5 | 0.360 | %RSD=0.445 |
| 6 | 0.358 | |
| 7 | 0.360 | |
| 8 | 0.359 | |

**C). Intraday Precision**

To check the reproducibility of the method, the same procedure was followed as that of precision of the method on the same day. Absorbance of each solution was scanned and the spectra were recorded. The standard deviation and relative standard deviation for the absorbance values using the statistical formula and the results were shown in tables 8 and 9.

**Table No 8 Intraday precision (at λ235nm)**

| Sample no | Intra day | |
|---|---|---|
| 1 | 0.360 | |
| 2 | 0.359 | |
| 3 | 0.355 | Mean=0.358 |
| 4 | 0.359 | S.D=0.0019 |
| 5 | 0.359 | %RSD=0.537 |
| 6 | 0.360 | |
| 7 | 0.360 | |
| 8 | 0.356 | |

**Table No 9 Intraday precision (at$\lambda_{278nm}$)**

| Sample no | Intra day | |
|---|---|---|
| 1 | 0.365 | |
| 2 | 0.363 | |
| 3 | 0.365 | Mean=0.365 |
| 4 | 0.361 | S.D=0.0028 |
| 5 | 0.371 | %RSD=0.784 |
| 6 | 0.366 | |
| 7 | 0.365 | |
| 8 | 0.366 | |

**3. Specificity:** The analyte was assessed in the presence of the components and it was found that there was no interaction with the analyte.

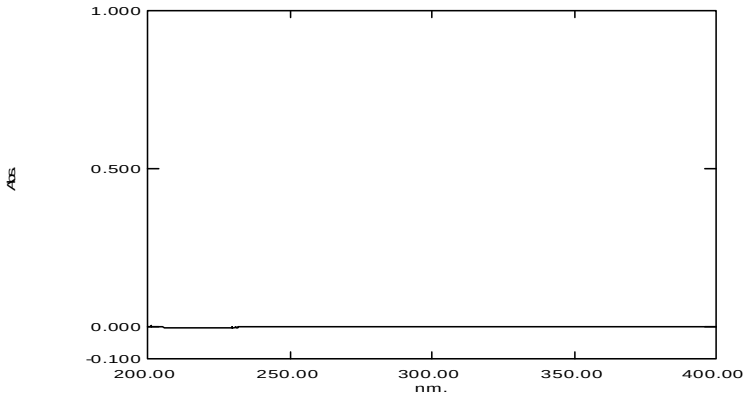


**Figure 4. Specificity**

**4. Limit of Detection and Limit of Quantification**

The LOD and LOQ were calculated based on the standard deviation of the response and the slope of the constructed calibration curve, as described in International Conference on Harmonization guidelines Q2 (R1) was shown in table no 18.

**5. Linearity:**

The linearity of the analytical method is determined by mathematical treatment of test results obtained by analysis of samples with analyte concentrations across the claimed range. Absorbance was plotted graphically as a function of drug concentration. Absorbance of each solution was scanned and the spectra were recorded. Calibration curve was plotted for both the drugs individually using the absorbance obtained at the different concentration levels. The linearity of the drug Paliperidone was observed at 1-30µg/ml was shown in table 10 and 11 and figure 5 and 6.

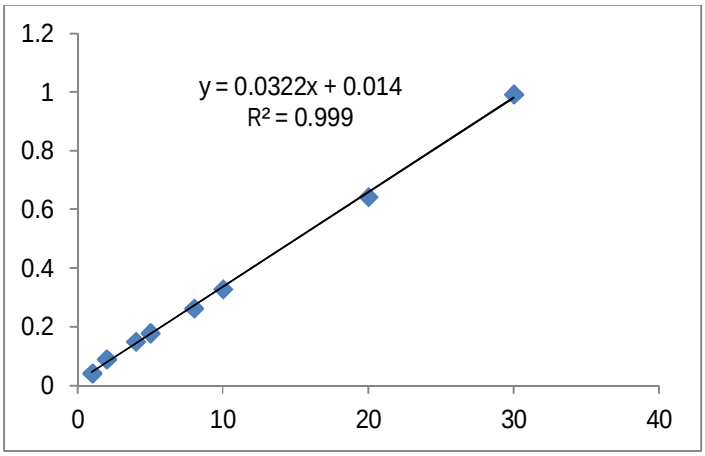


**Figure 5. Linearity graph (at $\lambda_{235nm}$)**

**Table No 10 linearity (at $\lambda_{235nm}$)**

| Conc. (µg/ml) | Absorbance (235nm) |
|---|---|
| 1 | 0.044 |
| 2 | 0.068 |
| 4 | 0.157 |
| 5 | 0.180 |
| 8 | 0.278 |
| 10 | 0.341 |
| 20 | 0.645 |
| 30 | 0.996 |

**Table No 11 linearity (at λ278nm)**

| Conc. (µg/ml) | Absorbance (278nm) |
|---|---|
| 1 | 0.042 |
| 2 | 0.05 |
| 4 | 0.147 |
| 5 | 0.178 |
| 8 | 0.261 |
| 10 | 0.327 |
| 20 | 0.643 |
| 30 | 0.973 |

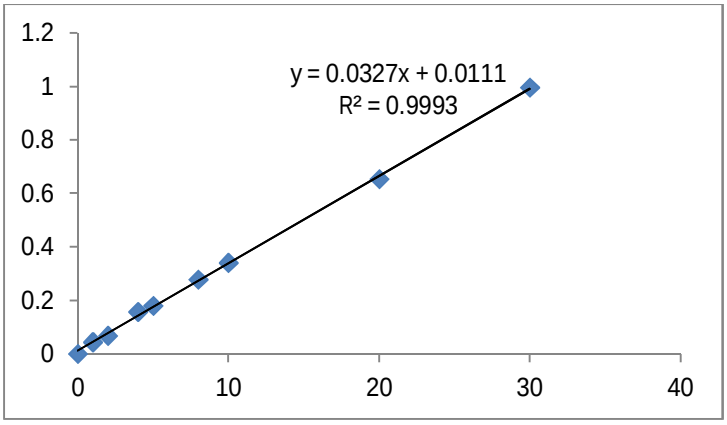


**Figure6. Linearity graph (at $\lambda_{278nm}$)**

**6. Range:** The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity. The range was found between 1-30µgm/ml.

**7. Robustness:**

The Robustness of the method was determined by making slight changes in the experimental conditions such as the temperature and scanning the samples maintained at room temperature and cooled to 18℃ as shown in table 12 and 13.

**Table No 12 Robustness (at $\lambda_{278nm}$)**

| Sample no | Room temperature (Abs) | | Cooling temperature 18˚C (Abs) | |
|---|---|---|---|---|
| 1 | 0.360 | | 0.360 | |
| 2 | 0.359 | Mean=0.358 | 0.356 | Mean=0.357 |
| 3 | 0.355 | S.D=0.00186 | 0.358 | S.D=0.00242 |
| 4 | 0.359 | %RSD=0.519 | 0.355 | %RSD= 0.677 |
| 5 | 0.359 | | 0.361 | |
| 6 | 0.360 | | 0.356 | |

**Table No 13 Robustness (at $\lambda_{235nm}$)**

| Sample no | Room temperature (Absorbance) | | Cooling temperature at 18˚C (Absorbance) | |
|---|---|---|---|---|
| 1 | 0.365 | Mean=0.365 | 0.387 | Mean=0.385 |
| 2 | 0.363 | S.D=0.0033 | 0.385 | S.D=0.0026 |
| 3 | 0.365 | %RSD=0.923 | 0.385 | %RSD 0.689 |
| 4 | 0.361 | | 0.381 | |
| 5 | 0.371 | | 0.389 | |
| 6 | 0.366 | | 0.385 | |

**8. Ruggedness:**

The ruggedness of the method was determined by carrying out the experiment on different instrument like Lab India double beam UV- spectrophotometer and Shimadzu UV-Visible spectrophotometer and by different analysts. The results were analyzed and was shown in table 14.

**Table No 14 Ruggedness by two different instruments**

| Lab India double beam UV- spectrophotometer | | | | | Shimadzu UV-Visible spectrophotometer | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Sample no** | Absorbance | | | | Absorbance | | | | |
| | 235nm | 278nm | | 235nm | 278nm | 235nm | 278nm | | 235nm | 278nm |
| **1** | 0.342 | 0.339 | | | | 0.342 | 0.339 | | | |
| **2** | 0.343 | 0.331 | Mean | 0.342 | 0.336 | 0.344 | 0.340 | Mean | 0.342 | 0.340 |
| **3** | 0.343 | 0.336 | S.D | 0.001 | 0.004 | 0.343 | 0.336 | S.D | 0.001 | 0.004 |
| **4** | 0.344 | 0.340 | %RSD | 0.306 | 1.21 | 0.342 | 0.336 | %RSD | 0.306 | 1.17 |
| **5** | 0.341 | 0.331 | | | | 0.343 | 0.349 | | | |
| **6** | 0.342 | 0.339 | | | | 0.341 | 0.340 | | | |

**Table No 15 Ruggedness by two different analyst**

| **Analyst-1** | | | | | **Analyst-2** | | | |
|---|---|---|---|---|---|---|---|---|
| **Sample no** | Absorbance | | | | Absorbance | | | |
| | 235n | 278n | 235n | 278n | 235n | 278n | 235n | 278n |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | m | m | | m | m | m | m | m | m |
| **1** | 0.343 | 0.339 | | | | 0.341 | 0.342 | | |
| **2** | 0.341 | 0.338 | Mean | 0.341 | 0.339 | 0.340 | 0.339 | Mean | 0.341 | 0.340 |
| **3** | 0.344 | 0.336 | S.D | 0.0014 | 0.002 | 0.339 | 0.338 | S.D | 0.0014 | 0.001 |
| **4** | 0.340 | 0.338 | %RSD | 0.430 | 0.791 | 0.342 | 0.340 | %RSD | 0.414 | 0.415 |
| **5** | 0.341 | 0.344 | | | | 0.343 | 0.341 | | | |
| **6** | 0.342 | 0.339 | | | | 0.341 | 0.340 | | | |

The ruggedness was performed by taking the percentage difference in the means of assay results between the ruggedness parameters of two different instruments and two different analysts from the above table 14 and 15.

**Table No 16 Mean Assay of Ruggedness**

| **Different Instrument-1** | | | | | **Different Instrument-2** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Sample no** | %Assay | | | | %Assay | | | | |
| | 235nm | 278nm | | 235nm | 278nm | 235nm | 278nm | | 235nm | 278nm |
| **1** | 100.26 | 100.26 | | | | 100.26 | 99.97 | | | |
| **2** | 100.26 | 99.97 | Mean | 100.21 | 100.49 | 100.55 | 100.85 | Mean | 100.35 | 100.45 |
| **3** | 99.39 | 100.26 | S.D | 0.502 | 0.419 | 100.85 | 101.1 | S.D | 0.302 | 0.466 |
| **4** | 99.97 | 100.55 | %RSD | 0.500 | 0.417 | 99.97 | 100.55 | %RSD | 0.301 | 0.464 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **5** | 100.55 | 100.85 | | 100.26 | 100.26 | |
| **6** | 100.85 | 101.1 | | 100.26 | 99.97 | |

| | At 235nm | At 278nm |
|---|---|---|
| **Over All Mean** | 100.28 | 100.47 |
| **Mean S.D** | 0.402 | 0.442 |
| **Mean %R.S.D** | 0.400 | 0.439 |

Percentage Difference of Mean Calculations: **(at $\lambda_{235nm}$)**

% Difference of means = (Mean% assay of Instrument-1)–(Mean% assay Instrument-2)

Mean% assay Instrument-1

= 100.21-100.35

100.21

=0.0013

Percentage Difference of Mean Calculations: **(at $\lambda_{278nm}$)**

% Difference of means= (Mean% assay of Instrument-1)–(mean% assay Instrument-2)

Mean% assay Instrument-1

= 100.49-100.45

100.49

=0.0003

**Table No 17 Mean Assay of Ruggedness**

| **Analyst-1** | | | | | **Analyst-2** | | | |
|---|---|---|---|---|---|---|---|---|
| **Sample no** | %Assay | | | | %Assay | | | |
| | 235nm | 278nm | 235nm | 278nm | 235nm | 278nm | 235nm | 278nm |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 99.97 | 100.8 | | | | 100.55 | 100.4 | | | |
| **2** | 100.26 | 101.4 | Mean | 100.01 | 101.15 | 100.26 | 100.5 | Mean | 100.06 | 100.66 |
| **3** | 100.26 | 101.7 | S.D | 0.339 | 0.516 | 99.39 | 100.7 | S.D | 0.396 | 0.258 |
| **4** | 99.39 | 100.5 | %RSD | 0.338 | 0.510 | 99.97 | 100.8 | %RSD | 0.395 | 0.256 |
| **5** | 100.26 | 101.7 | | | | 100.26 | 101.1 | | | |
| **6** | 99.97 | 100.8 | | | | 99.97 | 100.5 | | | |

| | **At 235nm** | **At 278nm** |
|---|---|---|
| **Over All Mean** | 100.03 | 100.90 |
| **Mean S.D** | 0.367 | 0.387 |
| **Mean %R.S.D** | 0.366 | 0.383 |

Percentage Difference of Mean Calculations: **(at $\lambda_{235nm}$)**

% Difference of means = (Mean% assay of Analyst-1)–(Mean% assay Analyst-2)

Mean% assay Analtst-1

= 100.01-100.06

100.01

=0.0004

Percentage Difference of Mean Calculations **(at $\lambda_{278nm}$)**

% Difference of means = (Mean% assay of Analyst-1)–(Mean% assay Analyst-2)

Mean% assay Analyst-1

= 101.15-100.66

101.15

=0.0048

## 9. Forced Degradation Study

Drug samples were subjected to alkaline hydrolysis using 0.1N NaOH, Acid hydrolysis using 0.1N HCl, and peroxide oxidation using 3% $H_2O_2$, treated samples were scanned and their respective spectra were recorded and the Changes in absorbance value were recorded and the results were shown in table 17 and the absorption spectra were shown in figures 7,8,9,10.

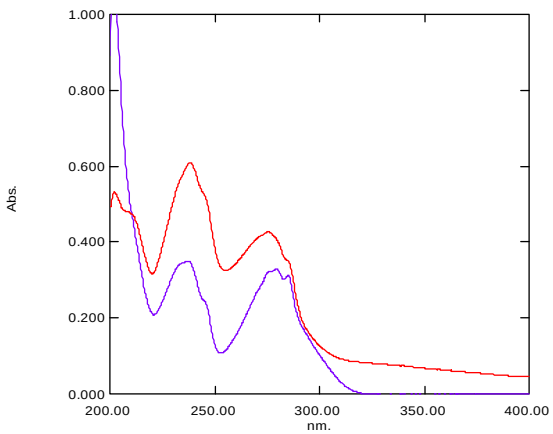


**Figure7. 0.1N HCl (Acidic condition)**

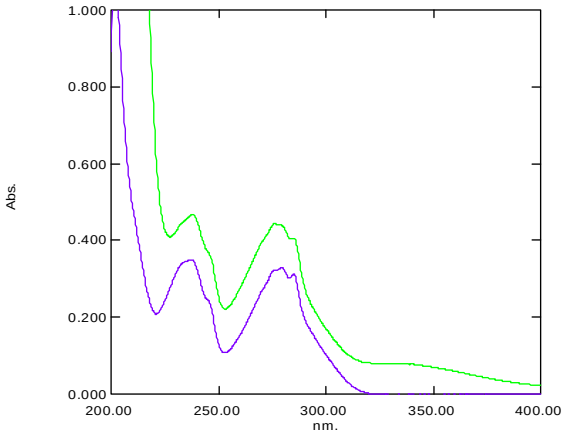


**Figure8 0.1N NaOH (Basic condition)**

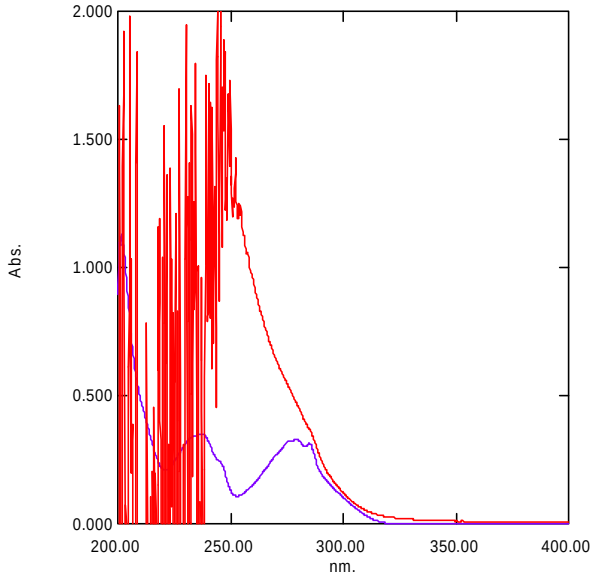


Figure9 3%$H_2O_2$ (Oxidation)

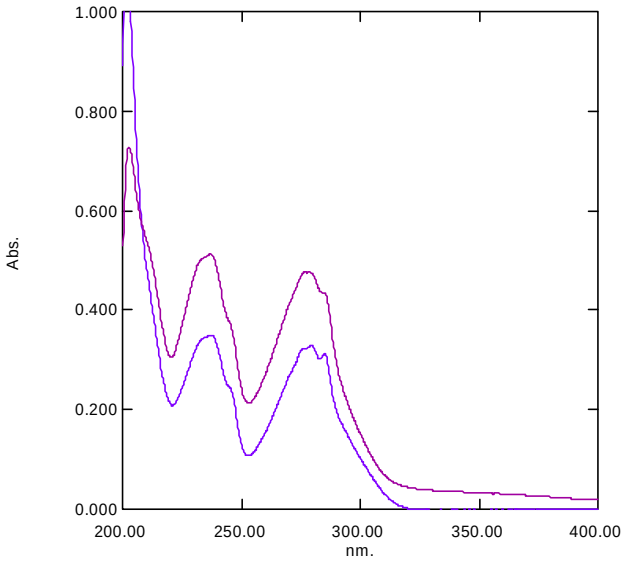


Figure10 Water (Neutral condition)

**Table No 18 Forced degradation studies of Paliperidone**

| Degradation parameters | Absorbance | | Concentration (µg/ml) | | %Drug Decomposed | | Degradation time |
|---|---|---|---|---|---|---|---|
| Standard drug | 235nm | 278nm | 235nm | 278nm | 235nm | 278nm | |
| | 0.341 | 0.327 | 10 | 10 | 0 | 0 | |
| Acid degradation (0.1N HCl) | 0.610 | 0.427 | 17.88 | 13.05 | 78.88 | 30.5 | 90mins |
| Alkali degradation (0.1N NaOH) | 0.467 | 0.443 | 13.69 | 13.54 | 36.95 | 35.4 | 60mins |
| Peroxide degradation (3%$H_2O_2$) | 1.008 | 0.480 | 29.56 | 14.07 | 95.6 | 47 | 40mins |
| Neutral conditions (Water) | 0.507 | 0.476 | 14.86 | 14.55 | 48.68 | 45.5 | 40mins |

## RESULTS AND DISCUSSION

Beer Lambert's law was obeyed over the concentration range 1–30µgml$^{-1}$in the proposed method. The linear regression equations were found to be y = 0.032x + 0.011 (r2 = 0.999) at 235nm and 0.0312x+0.007(r2=0.999) at 279nm. The %RSD values in precision studies were found to be 0.537 at 235nm and 0.783 at 278nm which are less than 2% indicating that the method is more precise. The % RSD values in accuracy studies were also found to be less than 2% indicating that the method is more accurate. The degradation studies were performed using 0.1N HCl, 0.1N NaOH, 3%$H_2O_2$ and water in acidic, alkaline, peroxidation and neutral conditions respectively. The drug has been totally degraded in peroxidation condition when compared to the other acid, alkaline and neutral conditions.

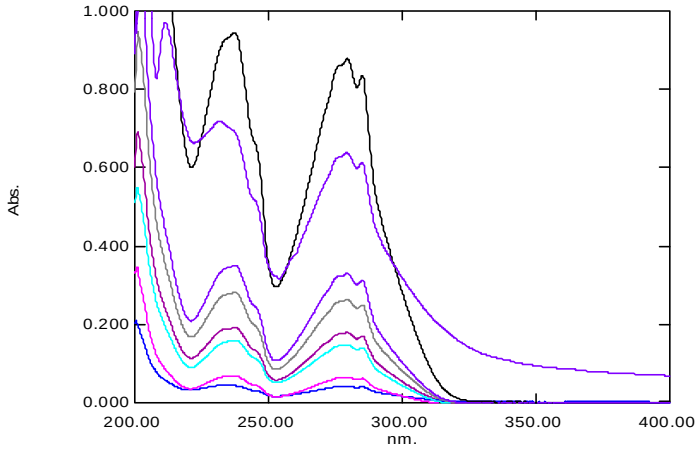


**Figure11 Overlay spectra**

**Table No 19 optical characteristics of Paliperidone**

| PARAMETERS | METHOD | |
|---|---|---|
| λmax (nm) | 235 | 278 |
| Beers law limit µg/ml | 1-30 | 1-30 |
| Molar absorbivity (L mol$^{-1}$cm$^{-2}$) | 3.41×10$^4$ | 3.27×10$^4$ |
| Correlation coefficient ( r$^2$) | 0.999 | 0.999 |
| Regression equation (y=mx+c) | 0.032x+0.011 | 0.0312x+0.007 |
| Slope (m) | 0.032 | 0.0312 |
| Intercept(c) | 0.011 | 0.007 |

| | | |
|---|---|---|
| **Accuracy** | 99.71-101.68 | 100.36-101.53 |
| **Precision (%RSD)** | 0.537 | 0.784 |
| **LOD (µg/ml)** | 0.297 | 0.299 |
| **LOQ (µg/ml)** | 0.901 | 0.480 |
| **Sandell's sensitivity (µ $cm^{-2}$/0.001 absorbance units)** | 0.0293 | 0.03058 |
| **90 % Confidence limits** | (+)0.364 (-) 0.268 | (+)1.199 (-) 0.856 |
| **95% Confidence limits** | (+)0.313 (-) 0.217 | (+)1.0303 (-)0.691 |

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