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STABILITY INDICATING NOVEL METHOD FOR THE DETERMINATION OF PALIPERIDONE IN BULK AND DOSAGE FORM BY USING RP-HPLC

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Abstract:

A new precise, accurate, rapid method has been developed for the estimation of PALIPERIDONE in pharmaceutical dosage form by HPLC. The optimum wavelength for the determination of PALIPERIDONE was selected at 284 nm. Various trials were performed with different mobile phases in different ratios, but Ammonium acetate buffer pH-5.0 : Acetonitrile (60:40) was selected as good peak symmetry and resolution between the peaks was observed. The retention times for the drug were considerably less compared to the retention time obtained for the drugs in the other mobile phase. The calibration curve was obtained by plotting peak area versus the concentration over the range of 60-140 µg/mL for PALIPERIDONE. From linearity the correlation coefficient R^2 value was found to be 0.999 for PALIPERIDONE. The proposed HPLC method was also validated for system suitability, system precision and method precision. The %RSD in the peak area of drug was found to be less than 2%. The number of theoretical plates was found to be more than 2000, which indicates efficient performance of the column. The percentage of recovery of PALIPERIDONE was found to be 99.6% respectively shows that the proposed method is highly accurate.

Keywords: *PALIPERIDONE, RP-HPLC, Method Development & Validation.*

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INTRODUCTION:

Paliperidone is an atypical antipsychotic used in the treatment of schizophrenia and other schizoaffective or delusional disorders. IUPAC Name 3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidin-4-one, structure of Paliperidone can be represented as Fig. 1. Paliperidone is the major active metabolite of risperidone. The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown, but it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of central dopamine Type 2 (D2) and serotonin Type 2 (5HT2A) receptor antagonism[1].

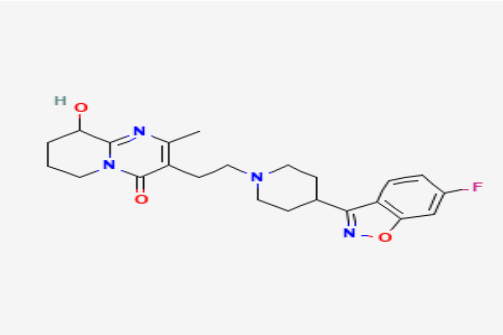


Fig.1: Chemical structure of Paliperidone

EXPERIMENTAL

Table No:1 Instruments used

UV-Visible Spectrophotometer	Nicolet evolution 100
UV-Visible Spectrophotometer software	Vision Pro
HPLC software	Open lab EZ chrome
HPLC	SHIMATZO Technologies
Ultra sonicator	Citizen, Digital Ultrasonic Cleaner
pH meter	Global digital
Electronic balance	Mettler Toledo
Syringe	Hamilton
HPLC Column	Inertsil ODS 3V(150x4.6mm) 4µm

Table No: 2 Reagents used

Water	HPLC Grade
Methanol	HPLC Grade
Ammonium acetate	AR Grade
Acetonitrile	HPLC Grade
Dipotassium hydrogen phosphate	AR Grade
Orthophosphoric acid	HPLC Grade

Optimized Conditions:

Column : Waters X Bridge C18 (150mm×.4.6mm & 5.0µm)
Mobile phase : Ammonium acetate buffer pH-5.0: Acetonitrile
Ratio : 60:40
Flow rate : 1.0 mL/min
Detection wavelength : 235nm
Column oven Temperature : 35°C
Injection volume : 20µL
Run time : 10 min

Ammonium acetate Buffer Preparation (10mM Ammonium acetate buffer)[2]:
Accurately weighed and transferred 0.77g of ammonium acetate in to 1000mL of water and mixed well, adjusted pH 5.0 with glacial acetic acid. Filtered through 0.45µm filter

Diluent: 0.1N HCl
Accurately transferred 8.5mL of Conc HCl in to 1000mL of water and mixed well.

Mobile Phase Preparation:
Mixed 6000mL of Buffer and 400mL of Acetonitrile degassed by sonication.

Preparation of standard solution
Weighed accurately 50mg Paliperidone in 500 ml of volumetric flask and dissolve in 70ml of 0.1N HCl and make up the volume with 0.1N HCl From above stock solution 100µg/ml of Paliperidone was prepared by diluting 5mlto 50ml with 0.1N HCl respectively.

Preparation of sample solution:

20tablets (each tablet contains 3mg of Paliperidone) were weighed and taken into a mortar and crushed to fine powder and uniformly mixed. Weighed crushed powder equivalent to 25mg of Paliperidone in 50ml of volumetric flask and dissolve in 35ml of 0.1N HCl by 30min of sonication and make up the volume with 0.1N HCl. Centrifuged sample at 5000rpm for 10min.

Prepared 100µg/mL sample solution by further diluted 5mL above sample stock solution to 25mL with mobile phase and mixed well.

METHOD VALIDATION PARAMETERS[3]:

- System Suitability and system Precision
- Specificity (Blank and Placebo Interference)
- Method Precision – Repeatability
- Intermediate precision-Reproducibility (Rugged)ness
- Linearity and range
- Accuracy and recovery
- Robustness

System suitability results:

. **Table No: 3 System suitability results**

Name of the Standard	Paliperidone	Tailing factor	Plate count
Standard-01	639.42	1.1	4533
Standard-02	641.61		
Standard-03	641.87		
Standard-04	640.55		
Standard-05	641.50		
Average	640.99		
%RSD	0.2		

Observation:: System suitability results were met with acceptance criteria, hence system is suitable

System Precision results:

Table No: 4 System Precision results

Name of the Standard	**Paliperidone**
Standard-01	639.42
Standard-02	641.61
Standard-03	641.87
Standard-04	640.55
Standard-05	641.50
Standard-06	650.441
Average	642.56
%RSD	0.6

Observation:

System Precision results were met with acceptance criteria, hence system is precise.

SPECIFICITY

Blank and Placebo Interference:

Preparation of standard solution

Weighed accurately 50mg Paliperidone in 500 ml of volumetric flask and dissolve in 70ml of 0.1N HCl and make up the volume with 0.1N HCl From above stock solution 100µg/ml of Paliperidone was prepared by diluting 5mlto 50ml with 0.1N HCl respectively.

Preparation of sample solution:

20tablets (each tablet contains 3mg of Paliperidone) were weighed and taken into a mortar and crushed to fine powder and uniformly mixed. Weighed crushed powder equivalent to 25mg of Paliperidone in 50ml of volumetric flask and dissolve in 35ml of 0.1N HCl by 30min of sonication and make up the volume with 0.1N HCl. Centrifuged sample at 5000rpm for 10min.

Prepared 100µg/mL sample solution by further diluted 5mL above sample stock solution to 25mL with mobile phase and mixed well.

Preparation of Placebo solution:

Placebo powderWeighed crushed equivalent to 25mg of Paliperidone in 100ml of volumetric flask and dissolve in 70ml of 0.1N HCl by 30min of sonication and make up the volume with 0.1N HCl. Centrifuged sample at 5000rpm for 10min. Prepared 100µg/mL sample solution by further diluted 5mL above sample stock solution to 50mL with mobile phase and mixed well.

Acceptance Criteria:

No interference should be observed at the retention time of Paliperidoneand Methylsalicylate due to blank and Placebo.

Table no: 5 Specificity

S.No.	Solution details	Area of Paliperidone
1	Standard	638.74
3	Blank	Not Detected
4	Placebo solution	Not Detected
5	Test solution	639.51

Observation:

There was no interference observed at the retention time of Diclofenac and Methylsalicylate due to blank and Placebo Hence System is specific

Fig 2: Chromatogram of Blank

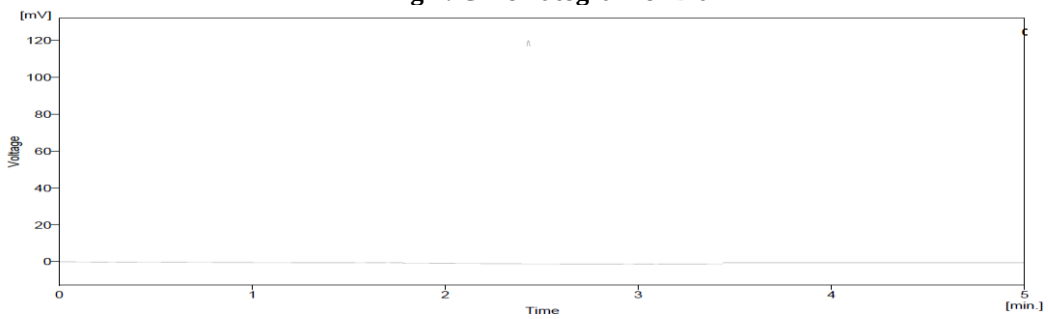
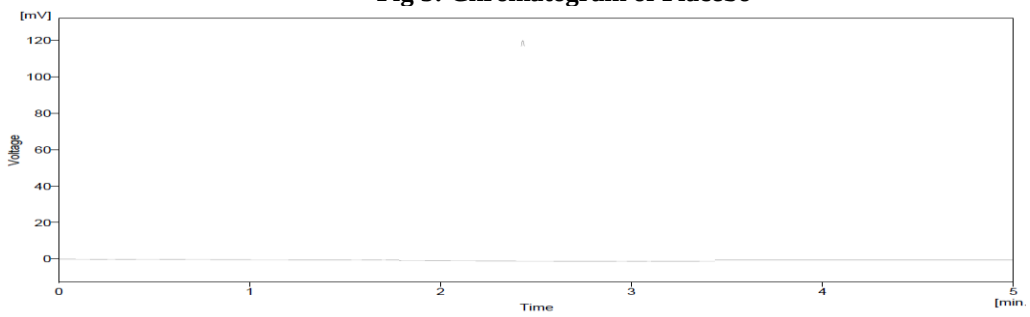


Fig 3: Chromatogram of Placebo



PRECISION STUDIES
Method Precision Results

Table no: 6 Method Precision Results:

S.No.	Solution details	%Assay of Paliperidone
1	Test solution preparation-1	100.8
2	Test solution preparation-2	100.9
3	Test solution preparation-3	100.8
4	Test solution preparation-4	100.2
5	Test solution preparation-5	100.0
6	Test solution preparation-6	100.4
Average		100.5
StdDev		0.31
%RSD		0.3

Observation:

- Mean %Assay Obtained between 90.0 to 110.0%for Paliperidone.
- The % RSD of % Assay results obtained from Test solution was obtained less than 2.0% for Paliperidone
- Hence Method is Precise

Linearity and Range:
Preparation of the StandardStock :
Weighed accurately 100mg Paliperidone in 100 ml of volumetric flask and dissolve in 70ml of mobile phase and make up the volume with mobile phase and mixed well.

Table no:7 Linearity

Volume Taken(mL)	Volume diluted to	Concentration(µg/mL)
3	50	60
4	50	80
5	50	100
3	25	120
2.8	20	140

Acceptance criteria:

- The correlation coefficient value should not be less than 0.99 for Paliperidone

Table no: 8 Linearity Results:

S.No	Name of the Solution	Area of Paliperidone
1	Linearity solution, Level-1	416.656
2	Linearity solution, Level-2	535.508
3	Linearity solution, Level-3 (100%)	660.922
4	Linearity solution, Level-4 (120%)	788.644
5	Linearity solution, Level-5 (150%)	922.268
Slope		32.62
Intercept		6.31
Correlation coefficient		0.9995

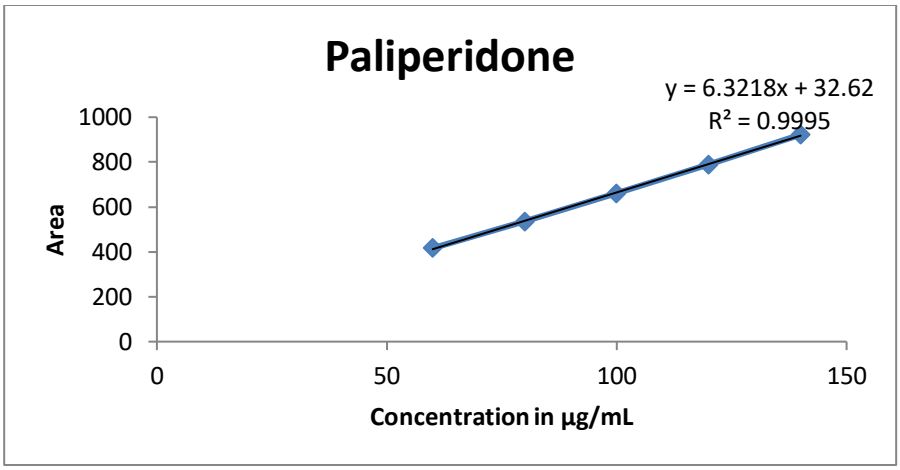


Fig: 4 Linearity Graph

Observation:

- The correlation coefficient value obtained 0.9995 for Paliperidone

Fig: 5 Linearity Chromatogram-01

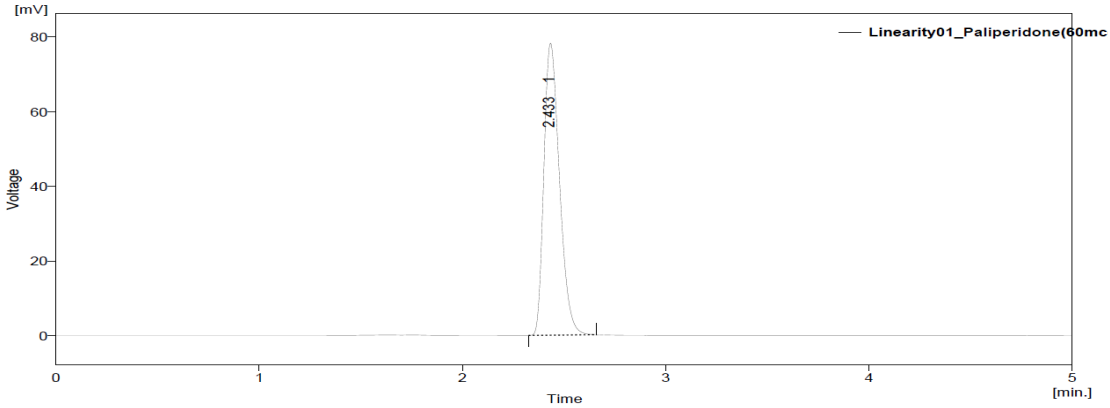


Fig: 6 Linearity Chromatogram-02

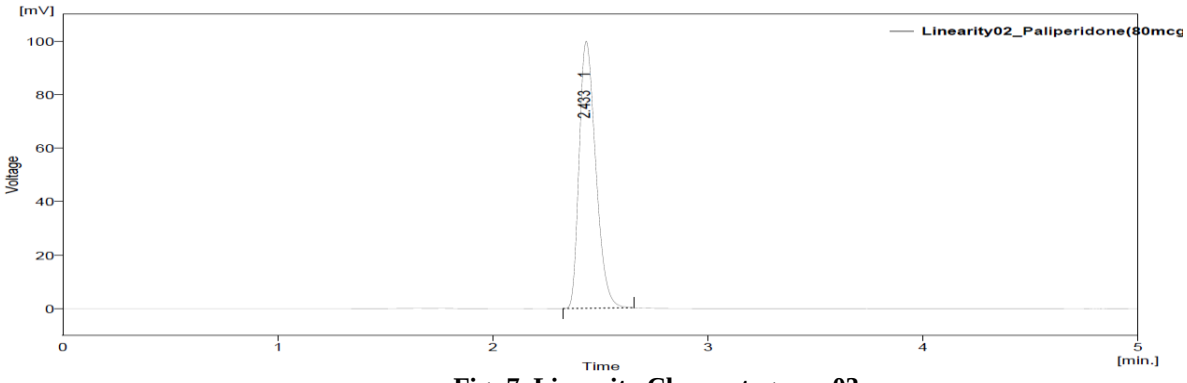


Fig: 7 Linearity Chromatogram-03

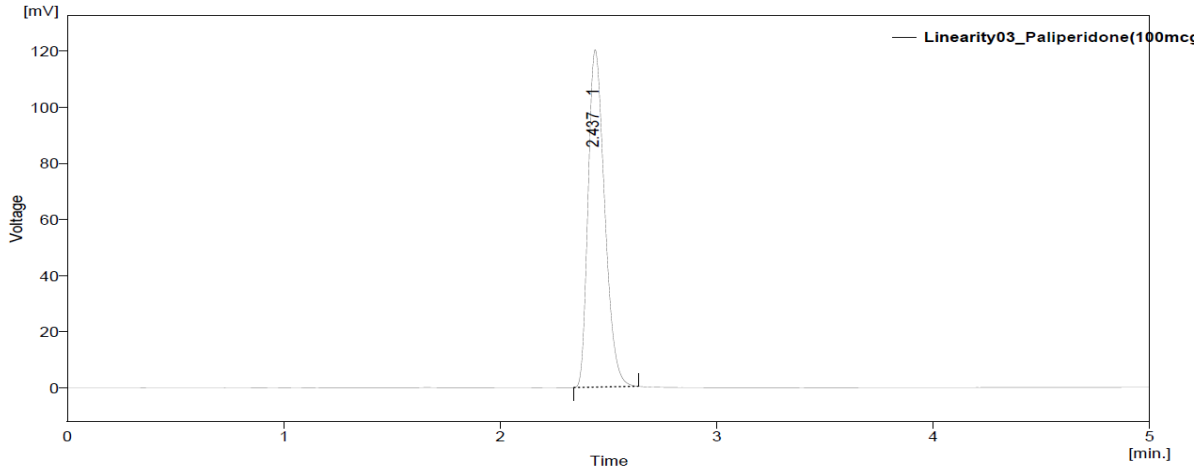


Fig: 8 Linearity Chromatogram-04

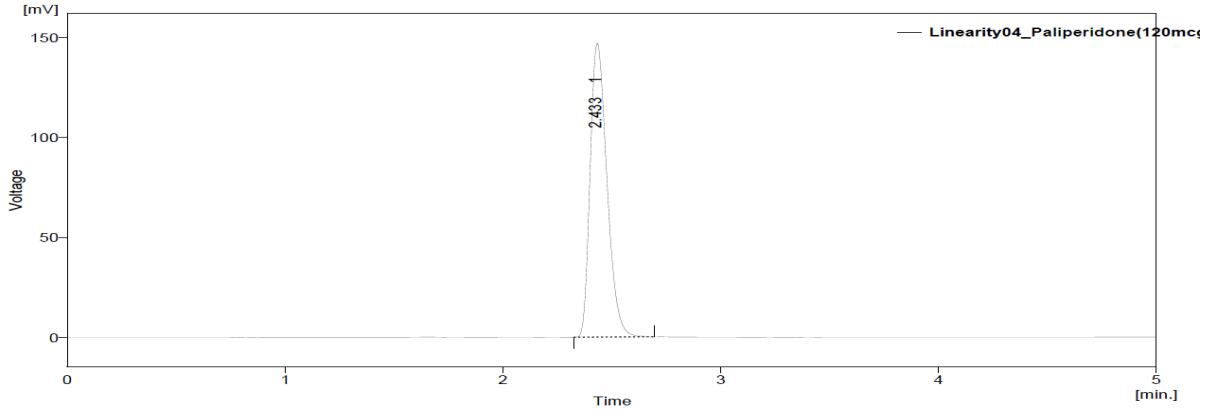
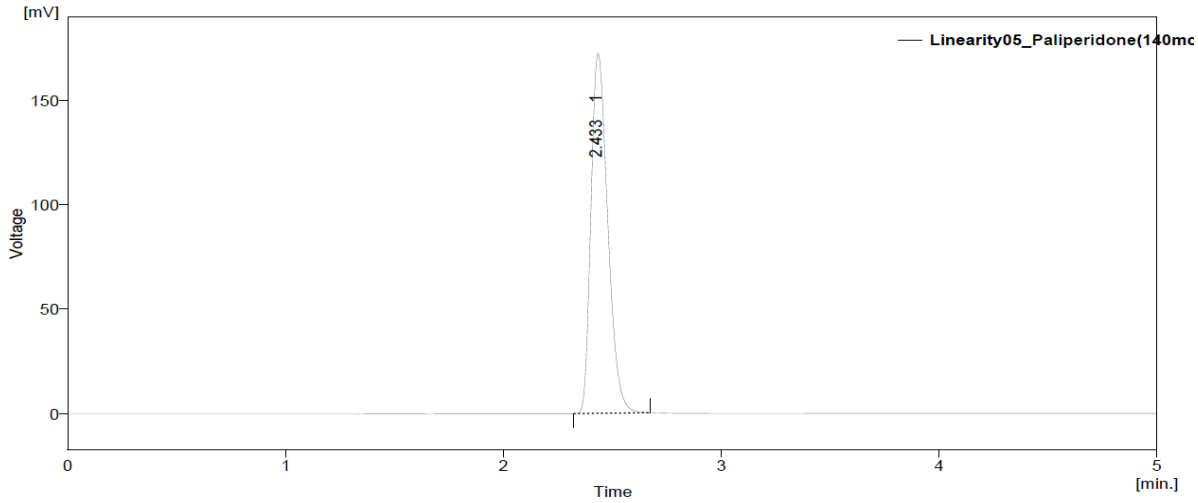


Fig: 9 Linearity Chromatogram-05



Recovery results:

Table no: 9 Recovery results

Name of the Solution	%Recovery of Paliperidone
Recovery-50%-01	101.3
Recovery-50%-02	100.9
Recovery-50%-03	100.8
Recovery-100%-01	99.8
Recovery-100%-02	99.0
Recovery-100%-03	100.1
Recovery-150%-01	99.7
Recovery-150%-02	99.6
Recovery-150%-03	99.7
Average	99.6
Stddev	0.73
%RSD	0.7

Observation:

- The % Recovery obtained between 98.0 to 102.0% for Paliperidone
- Mean % Recovery obtained between 98.0 to 102.0% for Paliperidone
- %RSD obtained for All %recoveries less than 2.0%.
- Hence method is Accurate

Table no: 10 Drugs used

Paliperidone (API)	Gift Samples obtained from Chandra labs, Hyd.
PALIP XR 3MG	Sample obtained from local pharmacy

Forced Degradation studies[4]:

Acceptance Criteria:

- Peak purity should be Pass
- Value should be in positive

Table no: 11 Forced Degradation results For Paliperidone:

Name of the Degradation	Condition	Peak Purity	Peak Purity Value	%Assay
Photolytic degradation	1.2mill/LUX Hours	PASS	+	99.8
Thermal Degradation	60°C/7Days	PASS	+	100.4
Acid Degradation	5mL of 5N HCl/2Hrs at 60°C	PASS	+	99.8
Base Degradation	5mL of 5N NaOH	PASS	+	93.5
Peroxide Degradation	5mL of 20% H_2O_2/4Hrs at Bench top	PASS	+	99.7
Control Sample	NA	PASS	+	100.1

Observation:

- Peak purity was obtained Pass
- Purity value obtained in Positive
- %degradation 5.8% obtained in Acid degradation
- No interference was observed with treated Blank

Fig : 10 Chromatogram of Acid degradation

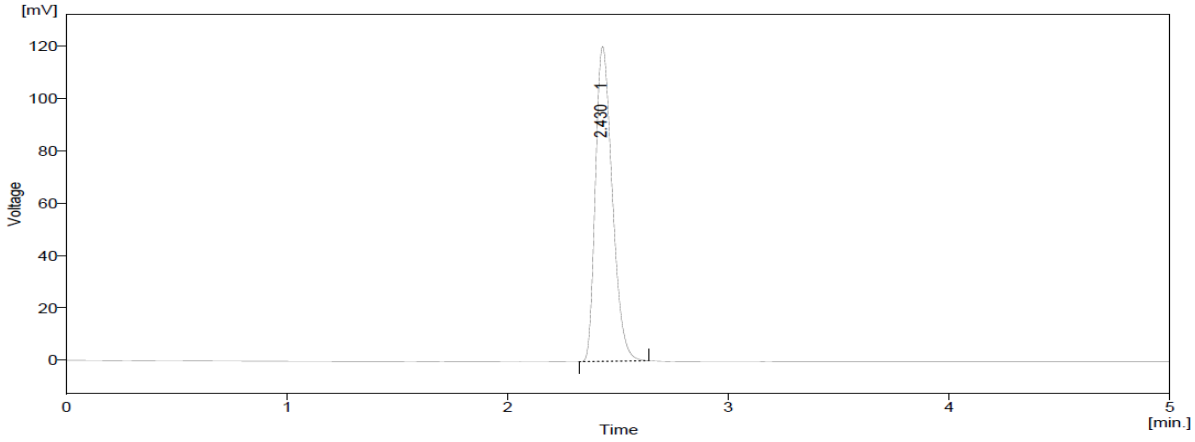


Fig :11 Chromatogram of Base degradation

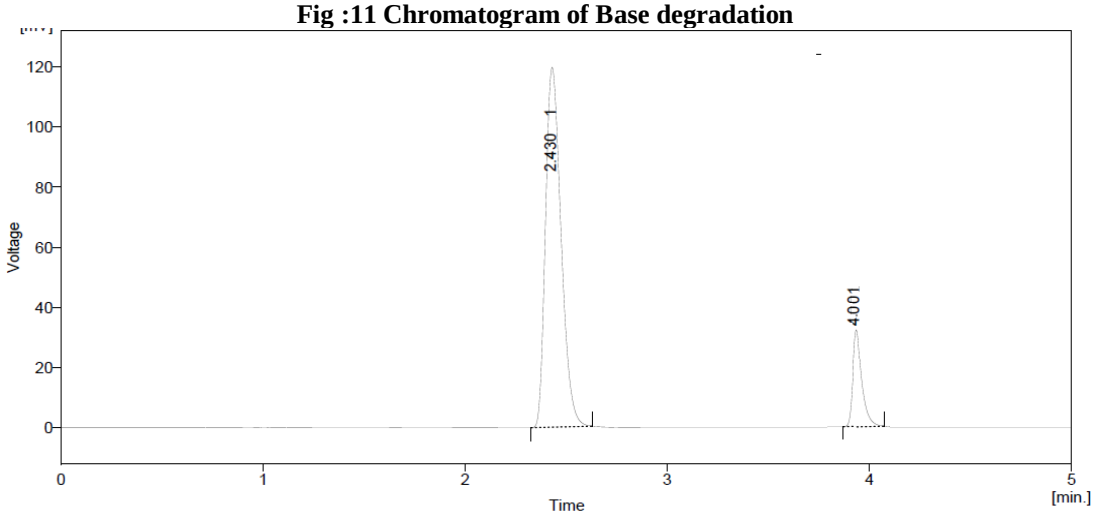


Fig :12 Chromatogram of Peroxide degradation

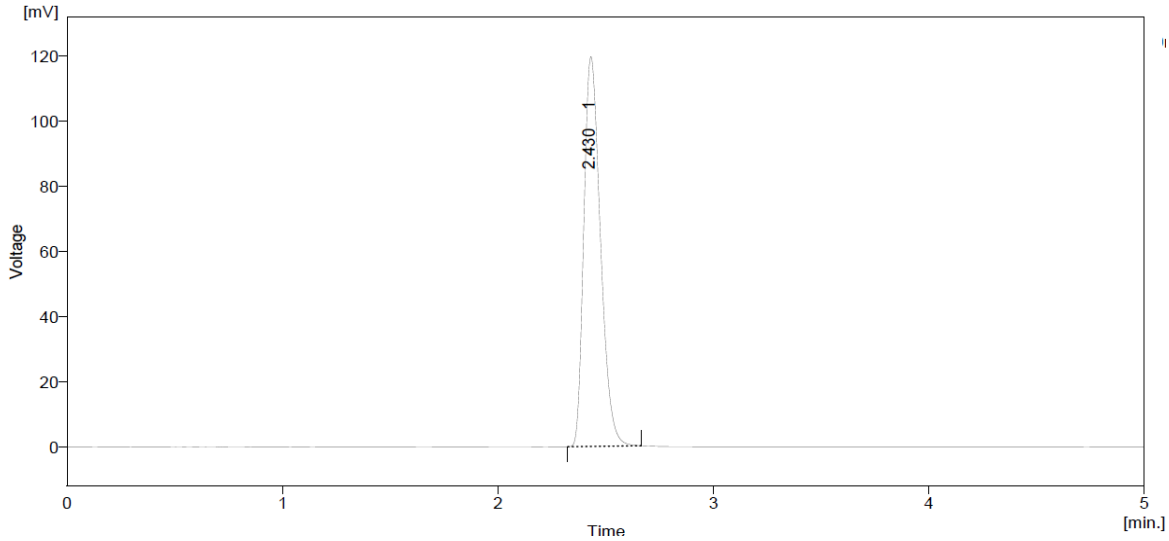


Fig :13 Chromatogram of Photolytic degradation

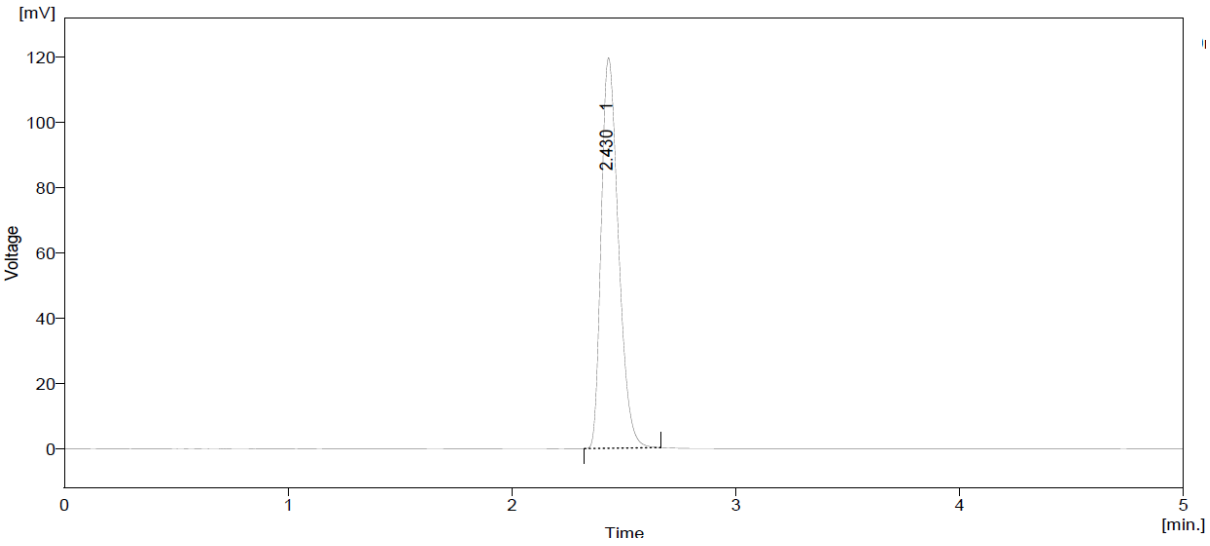
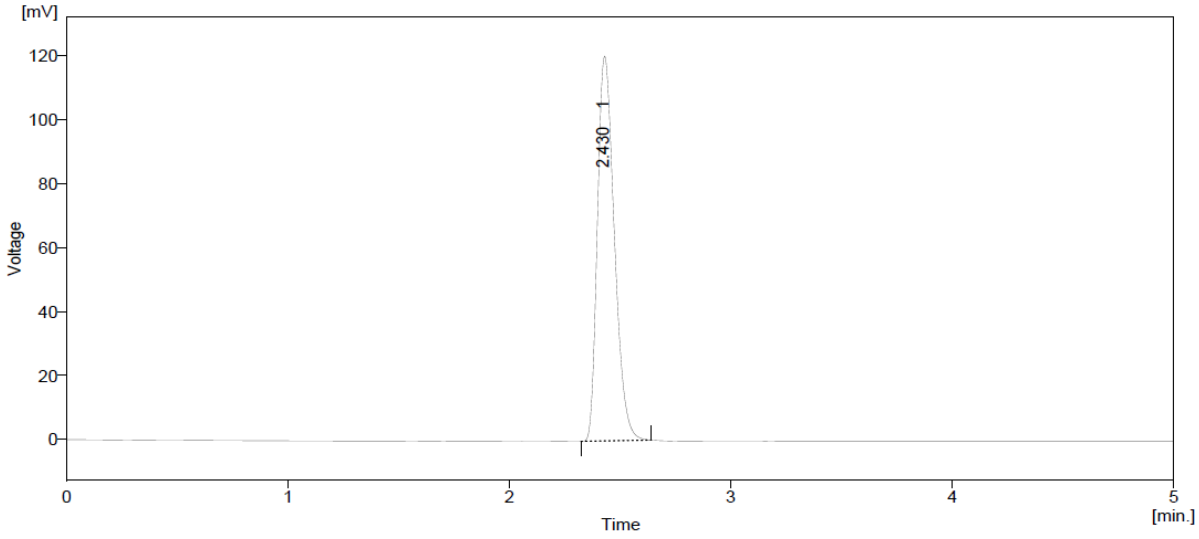


Fig :14 Chromatogram of Thermal degradation



RESULTS & DISCUSSION:

The optimum wavelength for the determination of PALIPERIDONE was selected at 284 nm. Various trials were performed with different mobile phases in different ratios, but Ammonium acetate buffer pH-5.0 : Acetonitrile (60:40) was selected as good peak symmetry and resolution between the peaks was observed. The retention times for the drug were considerably less compared to the retention time obtained for the drugs in the other mobile phase.

The different analytical performance parameters such as linearity, precision, accuracy, and specificity were determined according to International Conference on Harmonization ICH Q2B guidelines. The calibration curve was obtained by plotting peak area versus the concentration over the range of 60-140 µg/mL for PALIPERIDONE. From linearity the correlation coefficient R^2 value was found to be 0.999 for PALIPERIDONE. The proposed HPLC method was also validated for system suitability, system precision and method precision. The %RSD in the peak area of drug was found to be less than 2%. The number of theoretical plates was found to be more than 2000, which indicates efficient performance of the column. The percentage of recovery of PALIPERIDONE was found to be 99.6% respectively shows that the proposed method is highly accurate. Hence the proposed method is highly sensitive, precise, and accurate and it successfully applied for the

quantification of API content in the commercial formulations of PALIPERIDONE in Educational institutions and Quality control laboratories.

CONCLUSION:

A new precise, accurate, rapid method has been developed for the simultaneous estimation of PALIPERIDONE in pharmaceutical dosage form by HPLC.

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