

# ESTIMATION OF PALIPERIDONE FROM BIOLOGICAL FLUID EMPLOYING INSTRUMENTAL PLANAR CHROMATOGRAPHY: BIOANALYTICAL METHOD DEVELOPMENT AND VALIDATION

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## ABSTRACT

Paliperidone is an atypical antipsychotic agent widely used for the management of schizophrenia. An instrumental planar chromatography method assisted with liquid-liquid extraction for the estimation of Paliperidone from human plasma was developed. Chromatographic analysis included use of silica coated plates were used as stationary phase. Toluene: ethyl acetate: chloroform: methanol (2.5:2.5:2.5:2.5 v/v/v/v) was employed as the solvent system and detection was performed at 278 nm. The developed method was validated as per bioanalytical method validation M10 and analytical method validation Q2(R2) guidelines. The method exhibited a linear response over the concentration range of 12-48 ng/mL (60-240 ng/band). The method was found to be specific, sensitive, accuracy and reproducibility. The method found to satisfy all validation parameters and capable to of being applied for real sample analysis. This validated HPTLC method for estimation of Paliperidone in biological fluid provides an analytical basis for the quantitative determination of Paliperidone in biological matrices and can support the bioanalytical evaluation of Paliperidone-loaded nanostructured multiparticulate formulations and all other formulations of paliperidone.

**KEYWORDS:** Antipsychotic, Bioanalysis, Instrumental planar chromatography, Liqui-liquid extraction, Paliperidone, Validation, HPTLC.

## INTRODUCTION

Chromatography is a powerful separation technique which is widely used for the separation, identification and accurate quantification of analytes. Chromatographic techniques can be broadly classified into column chromatography and planar chromatography. Amongst column chromatography, the most popular techniques are high performance liquid chromatography (HPLC) and gas chromatography (GC) are widely used. Amongst planar chromatography, thin layer chromatography (TLC) and high performance thin layer chromatography (HPTLC)/ instrumental planar chromatography are popular.1-3

Bioanalytical method involves the estimation of drugs from biological fluids such as plasma, serum, saliva, lacrimal fluid, etc. Bioanalytical method is especially important in practical settings involving therapeutic drug monitoring (TDM), bioavailability-bioequivalence (BA/BE), pharmacokinetic profiling studies. International Council for Harmonization Multidisciplinary (ICH M10) gives the detailed guidance to the validation of bioanalytical methods.4-6

Paliperidone is an atypical antipsychotic agent that is widely employed for the management of Schizophrenia disorder. Its chemical formula is  $C_{23}H_{27}FN_4O_3$  and IUPAC name is (RS)-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.7-9

Paliperidone is a highly potent anti-psychotic agent, hence a highly sensitive analytical technique capable of accurately quantifying Paliperidone from bulk, formulation as well as biological samples is needed. The existing literature on Paliperidone for estimation from biological fluids mainly employs HPLC techniques coupled with detection involving photodiode array detector and mass spectrometric detector.10-18 HPLC is associated with long analysis time and higher consumption of solvent. These drawbacks can be overcome by the utilization of instrumental planar chromatography which is a simple, speedy and low-solvent consuming technique.11

Literature review revealed that bioanalytical methods for estimating Paliperidone employing instrumental planar chromatography were not reported. The research work aims to develop and validate a sensitive, selective, speedy and accurate method for the estimation of Paliperidone from human plasma using instrumental planar chromatography that can be applied to analysis of real samples.

## MATERIALS AND METHODS

### Instrumentation

HPTLC system utilized for the study was CAMAG HPTLC (Switzerland) equipped with semi-automatic Linomat 5 applicator, Scanner 4 and 1-100  $\mu$ L Hamilton syringe; linked with visionCATS software (version 4.0). TLC plates precoated with silica gel F254 and aluminium backing (20x20 cm), Merck, USA were utilized in the study.

### Chemicals and Reagents

Paliperidone (analyte) and Emtricitabine (internal standard-IS) was procured from local pharmaceutical company. Laboratory reagent (LR) grade toluene, ethyl acetate and chloroform were supplied by Research Labs Fine Chem Ltd. Chromatographic grade methanol was supplied by Rankem Pvt. Ltd. Pooled human plasma sample was procured from J. J. Hospital, Byculla, Mumbai.

Figure NO. 01 and Figure No. 02 represent the structure of Paliperidone (drug) and Emtricitabine (IS) respectively.

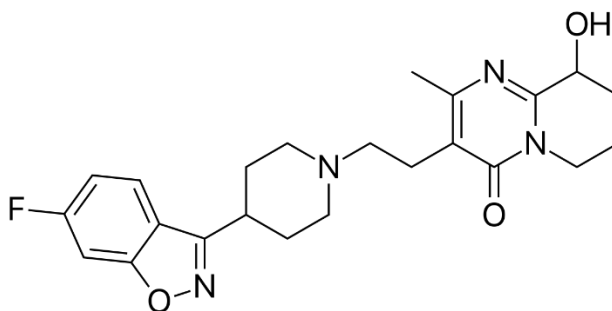


Figure No. 01: Structure of Paliperidone

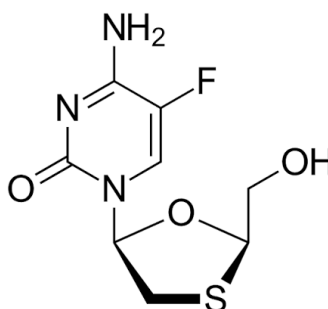


Figure No. 02: Structure of Emtricitabine

### METHOD DEVELOPMENT:

#### Preparation of Analytical Solutions:

##### Stock Solution:

10 mg of Paliperidone and 10 mg of IS were accurately weighed and dissolved in methanol in a 10 mL volumetric flask and sonicated for 5-10 minutes (1000 ppm).

##### Working Standard Solution:

1 mL of Paliperidone stock solution was diluted to 10 mL with methanol to obtain 100 ppm solution. This solution was diluted with methanol to obtain working standard solution of drug. Similarly, 1000ppm stock solution of IS was prepared and subsequently diluted with methanol to obtain 100 ppm solution.

##### Selection of IS

An essential element of bioanalysis is an internal standard which improves the accuracy of the method and compensates for any variation during sample preparation and analysis. Different drugs including paracetamol, caffeine, ibuprofen, ziprasidone, emtricitabine were evaluated for employment as IS based on their chromatographic behavior and availability.

##### Sample Preparation

Sample preparation involved LLE technique employing diethyl ether (DEE) as the extraction solvent. In a 2 mL Eppendorf tube, 500  $\mu$ L of pooled human plasma was added. To this 200  $\mu$ L of working standard solution of drug and 100  $\mu$ L of IS working standard solution was spiked and 300  $\mu$ L of DEE was added. This was mixed using a cyclomixer for 5-7 minutes followed by centrifugation at 7500 rpm for 10 minutes at 4°C. The supernatant was evaporated to dryness and the residue was reconstituted with methanol; the solution was filtered through 0.45  $\mu$ m membrane cartridge filter and subjected to HPTLC analysis.

##### Preparation of Calibration Standards:

500  $\mu$ L of plasma was spiked with 200  $\mu$ L of standard solutions of drug and 200  $\mu$ L of IS working standard solution, 600  $\mu$ L of DEE was added and processed to obtain the calibration stand solutions.

### METHOD VALIDATION:

The developed method was validated as per in-house validation protocol prepared based on ICH M10 and ICH Q2(R2) guidelines. The method was validated for the following parameters:

#### Specificity and Selectivity

Specificity and selectivity of the bioanalytical method indicate the ability of the method of the method detect and distinguish analyte from matrix. It was analyzed by comparing the densitograms for blank plasma, plasma spiked with drug, plasma spiked with IS and plasma spiked with both drug and IS.

### Linearity

Linearity was assessed by constructing calibration curve by analyzing calibration standards over the concentration range of 12-48 ng/mL (60-240 ng/band).

### Accuracy

Accuracy is expressed as the closeness of agreement between the measured value and true value. It was assessed by two ways:

#### Quality Control (QC) Standards:

In this method accuracy was assessed by comparing the measured value with expected true value of the QC standards: Lower limit of quantification (LLOQ), low quality control (LQC), mid quality control (MQC) and high quality control (HQC) and upper limit of quantification (ULOQ). Accuracy studies were performed on the same day (within run) as well as on three consecutive days (between run). Intraday studies involved assessment of the QC samples in triplicate, thrice over the same day. Interday precision involved analysis of QC sample in triplicate on three consecutive days. Three replicates at each concentration level were analyzed and degree of closeness between actual and nominal value was determined.

#### Spiking Study:

This method of determining accuracy involved spiking MQC with 80, 100 and 120% of MQC concentration, each in triplicate, in accordance to the accuracy guidance provided in ICH Q2(R2). The response obtained was used to calculate the percent recovery from the spiked samples. Accuracy studies were performed on the same day (within run) as well as on three consecutive days (between run). Intraday studies involved assessment of the QC samples in triplicate thrice over the same day. Interday precision involved analysis of QC sample in triplicate on three consecutive days.

### Precision

Method precision was assessed at four concentration levels: LLOQ, LQC, MQC, HQC and ULOQ. Precision studies performed included intraday precision and interday precision. Intraday precision involved analysis of the QC samples analysis of the QC samples in triplicate thrice on the same day. Interday precision involved analysis of the QC samples in triplicate over three consecutive days. The precision of the method was assessed by determining the percentage coefficient of variation (%CV).

### Carry-over

Carry-over studies are employed in bioanalysis to ensure that no residue from the previous sample is carried forward to the subsequent sample analysis during analytical run. Carry-over was assessed by injecting blank plasma after ULOQ sample analysis. Carry-over was estimated by determining the response of analyte and IS in blank plasma sample.

### Dilution Integrity

Dilution integrity parameter is used to indicate that the dilution procedure does affect the accuracy and the precision of the measured concentration of analyte. Dilution integrity was assessed by diluting the sample with plasma in 1:1 and 1:2 ratio. Five replicates at each dilution factor level were analyzed, the percent nominal and %CV were determined.

### Extraction Efficiency (Recovery)

Recovery studies were performed using extracted and unextracted QC samples. The extraction efficiency was determined using the following formula:

$$\% \text{Recovery} = (\text{Response of extracted sample} / \text{Response of unextracted sample}) \times 100$$

### Stability Studies

Stability studies were performed to ensure that the preparation, processing and storage of the biological sample do not affect the analyte concentration. Stability studies were performed on LQC and HQC, the results were compared with freshly prepared LQC and HQC samples and the % CV was determined. Three types of stability studies were performed:

#### Bench-to (Short-term) Stability:

Processed LQC and HQC samples were kept on the laboratory for 6 the entire duration of study.

#### Freeze-Thaw Stability:

Processed LQC and HQC samples were subjected to three cycles of freeze-thaw with freezing for 12 hours between the thawing cycles.

#### Long-term Stability:

The processed LQC and HQC samples were subjected to freezing at -20 °C for 28 days.

## RESULTS:

### Method Development

Table 01 depicts the optimised chromatographic parameters.

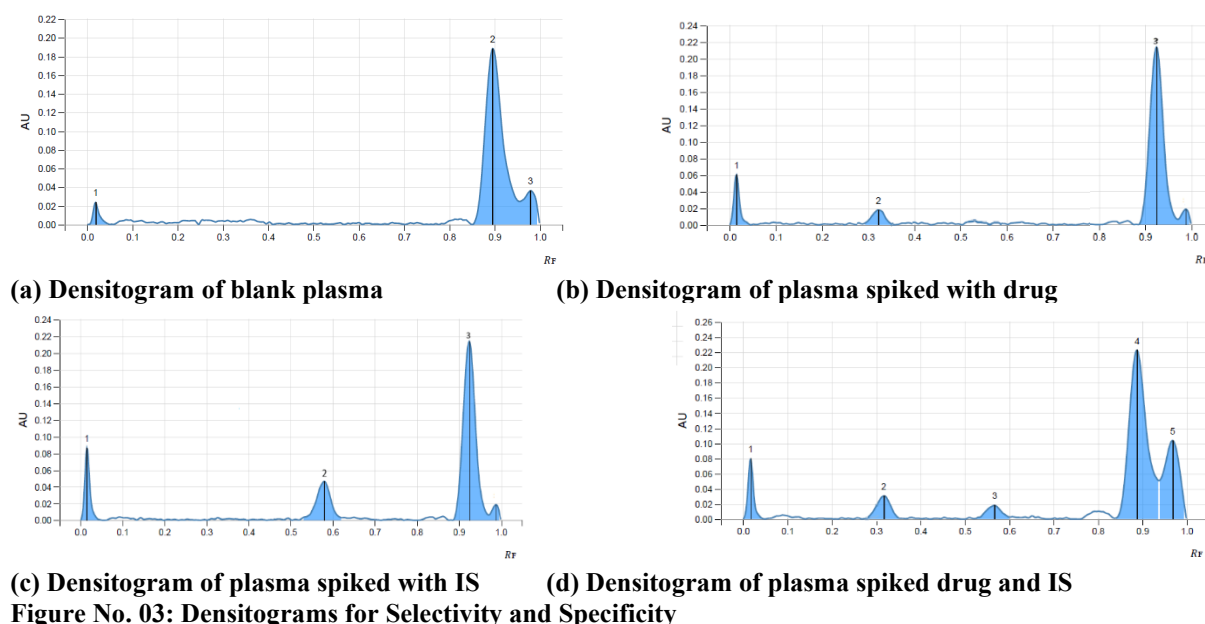
**Table 01: Chromatographic parameters**

| Sr. No. | Parameter      | Condition                                                              |
|---------|----------------|------------------------------------------------------------------------|
| 1.      | Solvent system | Toluene: Ethyl acetate: Chloroform: Methanol (2.5:2.5:2.5:2.5 v/v/v/v) |

|    |                         |                                                 |
|----|-------------------------|-------------------------------------------------|
| 2. | Stationary Phase        | Silica gel F254                                 |
| 3. | Injection Volume        | 50 $\mu$ L                                      |
| 4. | Bandwidth               | 8 mm                                            |
| 5. | Detection Wavelength    | 278 nm                                          |
| 6. | Saturation Time         | 20 min                                          |
| 7. | Retardation Factor (Rf) | Analyte: $0.31 \pm 0.05$<br>IS: $0.57 \pm 0.05$ |

### Specificity and Selectivity

Comparison of the densitograms for blank plasma, plasma spiked with drug, plasma spiked with IS and plasma spiked with both drug and IS showed no overlapping and interfering peaks, hence the method was found to be selective and specific. Figure No. 3(a) depicts the densitogram of blank plasma, Figure No. 3(b) depicts the densitogram of plasma spiked with drug, Figure No. 3(c) depicts the densitogram of plasma spiked with IS and Figure No. 3(d) depicts the densitogram of plasma spiked with both drug and IS.



### Linearity

The results for linearity studies are depicted in Table No. 02. and Table No. 03. Figure No. 04 illustrates the calibration curve for the linearity studies.

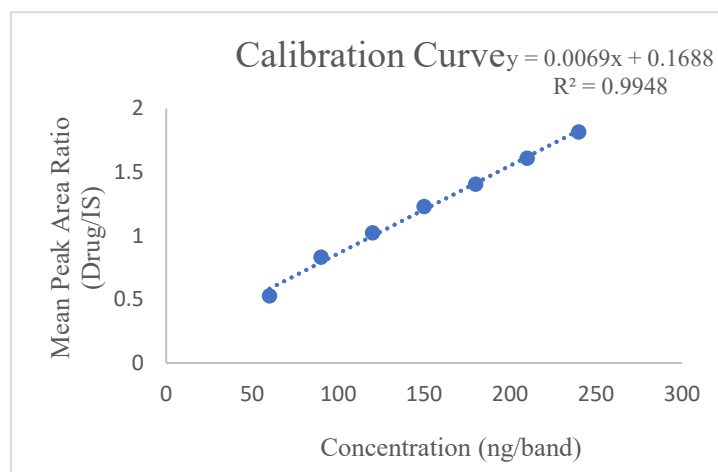
**Table No. 02: Results for Linearity Studies**

| Concentration of Calibration Standards (ng/mL) | Concentration of Calibration Standards (ng/band) | Mean Peak Area Ratio (Drug/IS) | Back-calculated Concentration | % CV     | % Nominal |
|------------------------------------------------|--------------------------------------------------|--------------------------------|-------------------------------|----------|-----------|
| 12 (LLOQ)                                      | 60                                               | 0.526667                       | 51.8648                       | 4.384939 | 86.43     |
| 18 (LQC)                                       | 90                                               | 0.830627                       | 95.9170                       | 6.556464 | 106.57    |
| 24                                             | 120                                              | 1.022549                       | 123.7317                      | 5.275027 | 103.11    |
| 30 (MQC)                                       | 150                                              | 1.229888                       | 153.7809                      | 10.73608 | 102.52    |
| 36 (HQC)                                       | 180                                              | 1.40522                        | 179.1913                      | 3.465205 | 99.55     |
| 42                                             | 210                                              | 1.60898                        | 208.7217                      | 4.997654 | 99.39     |
| 48 (ULOQ)                                      | 240                                              | 1.815652                       | 238.6742                      | 3.055511 | 99.45     |

**Table No. 03: Results of Linearity Studies**

|                                              |                              |
|----------------------------------------------|------------------------------|
| Range                                        | 12-48 ng/mL (60-240 ng/band) |
| Coefficient of Correlation (R <sup>2</sup> ) | 0.9948                       |
| Equation of Line                             | $y = 0.0069x + 0.1688$       |

The coefficient of correlation was found to be 0.9948. The %nominal values were found to be within the acceptable limits of  $\pm 20\%$  for LLOQ and  $\pm 15\%$  for all other concentration levels as per the validation protocol.



**Figure No. 04: Calibration Curve**

### Accuracy

#### QC samples:

Table No. 04 and Table No. 05 depicts the results for intraday and interday accuracy studies.

**Table No. 04: Results for Accuracy Studies (by QC Standards)**

| Concentration Level | Mean Peak Area Ratio (Drug/IS) |            | % Nominal |          |
|---------------------|--------------------------------|------------|-----------|----------|
|                     | Intraday                       | Interday   | Intraday  | Interday |
| LLOQ                | 0.504246197                    | 0.52670383 | 81.01     | 86.45    |
| LQC                 | 0.949272204                    | 0.92377433 | 94.26     | 91.18    |
| MQC                 | 1.105384375                    | 1.20957725 | 90.49     | 100.53   |
| HQC                 | 1.495502248                    | 1.45847151 | 106.82    | 103.84   |
| ULOQ                | 1.841737986                    | 1.84124455 | 101.02    | 100.99   |

The results for accuracy studies showed that the %nominal was found to be within the acceptance criteria of  $\pm 20\%$  for LLOQ and  $\pm 15\%$  for all other concentration levels.

#### Spiking Studies:

**Table No. 05: Results for Accuracy Studies (by Spiking Studies)**

| Concentration Level | Mean Peak Area Ratio (Drug/IS) |            | % Recovery |          |
|---------------------|--------------------------------|------------|------------|----------|
|                     | Intraday                       | Interday   | Intraday   | Interday |
| MQC + 80%           | 1.950218097                    | 1.97728514 | 95.61      | 97.01    |
| MQC + 100%          | 2.189370423                    | 2.18191987 | 97.61      | 97.25    |
| MQC + 120%          | 2.340415224                    | 2.3400365  | 95.37      | 95.35    |

The results of accuracy from spiking study showed that the % recovery for both intraday and interday accuracy was within the acceptable limits of 95-105%.

### Precision

Table No. 06 depicts the results for intraday and interday precision studies.

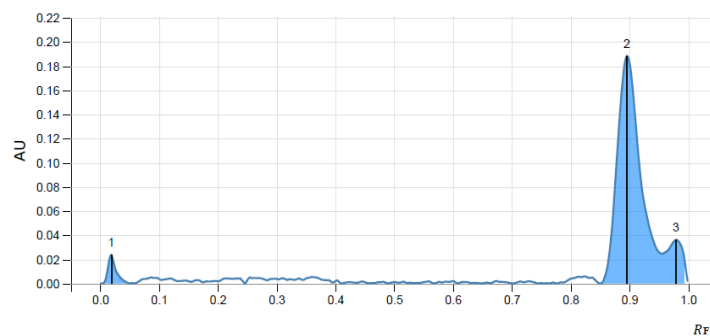
**Table No. 06: Results for Precision Studies**

| Concentration Level | Mean Peak Area Ratio (Drug/IS) |             | % CV     |          |
|---------------------|--------------------------------|-------------|----------|----------|
|                     | Intraday                       | Interday    | Intraday | Interday |
| LLOQ                | 0.505965509                    | 0.492030948 | 1.01     | 3.67     |
| LQC                 | 0.961993841                    | 0.960903294 | 1.73     | 1.79     |
| MQC                 | 1.044451125                    | 1.051864313 | 5.77     | 3.54     |
| HQC                 | 1.369980064                    | 1.330057428 | 2.60     | 7.12     |
| ULOQ                | 1.810192873                    | 1.807785063 | 2.05     | 1.10     |

The results for precision studies showed that the %nominal was found to be within the acceptance criteria of  $\pm 20\%$  for LLOQ and  $\pm 15\%$  for all other concentration levels.

### Carry-Over

The densitogram of blank plasma showed no response of both analyte as well as IS, hence there was no carry-over reported. Figure No. 05 shows the densitogram for blank plasma analyzed immediately following ULOQ analysis.



**Figure No. 05: Densitogram of Blank Plasma after ULOQ Analysis**

### Dilution Integrity

The results for dilution integrity studies are elucidated in Table No. 07.

**Table No. 07: Results for Dilution Integrity Study**

| Dilution Level                | 1:1         | 1:2         |
|-------------------------------|-------------|-------------|
| Back-calculated Concentration | 471.9218308 | 410.4614626 |
| %CV                           | 6.02        | 1.89        |
| %Nominal                      | 98.32       | 85.5128047  |

### Extraction Efficiency

Extraction efficiency study for all QC samples was performed and %recovery values obtained are illustrated in Table No. 08

**Table No. 08: Results for Extraction Efficiency Study**

| Concentration Level | Mean Peak Area Ratio (Drug/IS) |                  | % Recovery |
|---------------------|--------------------------------|------------------|------------|
|                     | Unextracted Sample             | Extracted Sample |            |
| LLOQ                | 0.543010753                    | 0.496774194      | 91.48      |
| LQC                 | 1.052910053                    | 0.973509934      | 92.46      |
| MQC                 | 1.27027027                     | 1.127516779      | 88.76      |
| HQC                 | 1.478723404                    | 1.364238411      | 92.26      |
| ULOQ                | 1.895604396                    | 1.828947368      | 96.48      |

The acceptance criteria for %recovery as per validation protocol is that the recovery must not be 100%, but should be consistent. From the extraction efficiency study, the recovery of both drug, and IS was found to be accurate and consistent.

### Stability Studies

Table 09 depicts the results for stability studies.

**Table No. 09: Results for Stability Studies**

| Stability                      | Bench-top |          | Freeze-thaw |           | Long-term |            |
|--------------------------------|-----------|----------|-------------|-----------|-----------|------------|
|                                | LQC       | HQC      | LQC         | HQC       | LQC       | HQC        |
| Mean Peak Area Ratio (Drug/IS) | 0.8741101 | 1.314801 | 0.873504    | 1.2710453 | 0.8727925 | 1.25007730 |
| %CV                            | 8.41      | 5.06     | 2.49        | 6.79      | 5.66      | 1.42       |
| %Nominal                       | 85.18     | 92.27    | 85.10       | 88.66     | 85.01     | 87.05      |

From the stability studies results, the QC samples were found to be stable throughout the study duration.

### DISCUSSION:

A rapid, sensitive, selective and accurate instrumental planar chromatographic method was developed and validated for the estimation of Paliperidone from pooled human plasma. The chromatographic analysis was performed using toluene: ethyl acetate: chloroform: methanol (2.5:2.5: 2.5:2.5 v/v/v/v) as the solvent system and silica gel F254 as the stationary phase. based on the different IS evaluated for employment in bioanalysis, Emtricitabine was selected as the IS as it gave a well-resolved peak and showed consistent chromatographic behavior. Emtricitabine showed consistent recovery from processed samples similar to Paliperidone.

Amongst the different extracting solvents studied, DEE gave maximum extraction of Paliperidone from human plasma and gave consistent results, hence DEE was selected as the extraction solvent for LLE assisted estimation of Paliperidone from human plasma.

The developed bioanalytical method was validated as per the in-house validation protocol prepared based on ICH M10 and ICH Q2(R2) guidelines. the developed method was found to selective and specific for the estimation of Paliperidone from plasma. The method demonstrated acceptable accuracy and precision. The samples showed good stability over the study duration. Thus, the developed method caters to the requirement of a speedy, sensitive, selective and accurate method

for the estimation of Paliperidone from biological fluids. The method can thus be applied to analysis of real samples of Paliperidone.

## CONCLUSION

A sensitive, selective, rapid and accurate method capable of quantifying Paliperidone from human plasma was developed and validated. The validation of the method was performed as per the in-house validation protocol, the method gave acceptable results for all the validation parameters studied. The method gave reproducible results and consistent recovery for both drug and IS. The sampling technique involved was suitable to maintain the properties of both drug and IS as the samples were found to be stable throughout the duration of study. Hence, a sensitive, speedy and selective bioanalytical method was developed and validated for Paliperidone that can be applied to routine analysis of real samples. This bioanalytical HPTLC method can be employed for Bioanalytical Estimation of Paliperidone in biological fluid for evaluation of a nanostructured multiparticulate drug delivery system, other nano or micro formulations, novel drug delivery systems and all other formulations of Paliperidone.

## REFERENCES

1. Badri S, Kumar R, Siva P, et al. A review on comparison of HPLC and HPTLC. *J Innov Appl Pharm Sci*. 2023;8(3):18-23.
2. Gupta DB, Shenoy L, Tripathy AS. HPLC and HP-TLC. *Adv Anal Tech Forensic Investig*. 2024:241-269.
3. Gope ER, Begum SM, Anisetti PP, et al. A review of principles, applications, and recent developments in HPTLC and HPLC. *J Pharma Insights Res*. 2024;2(6):56-64.
4. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH harmonised guideline M10: bioanalytical method validation and study sample analysis [Internet]. Geneva: International Council for Harmonisation; 2022 [cited 2026 Sep 28]. Available from: ICH M10 guideline
5. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH harmonised guideline Q2(R2): validation of analytical procedures [Internet]. Geneva: International Council for Harmonisation; 2023 [cited 2026 Sep 28]. Available from: ICH Q2(R2) Guideline
6. European Medicines Agency, Committee for Medicinal Products for Human Use. Guideline on bioanalytical method validation [Internet]. London: European Medicines Agency; 2011 [cited 2026 Sep 28]. Available from: EMA Guideline on Bioanalytical Method Validation
7. National Center for Biotechnology Information. PubChem Compound Summary for CID 115237, Paliperidone [Internet]. Bethesda (MD): National Library of Medicine (US); [cited 2026 Sep 28]. Available from: <https://pubchem.ncbi.nlm.nih.gov/compound/115237>
8. Wang SM, Han C, Lee SJ, Patkar AA, Pae CU, Fleischhacker WW. Paliperidone: a review of clinical trial data and clinical implications. *Clin Drug Investig*. 2012;32(8):497-512. doi:10.2165/11634440-000000000-00000
9. Mauri MC, Paletta S, Maffini M, Colasanti A, Dragogna F, Di Pace C, Altamura A. Clinical pharmacology of atypical antipsychotics: an update. *EXCLI journal*. 2014 Oct 13;13:1163.
10. Wesołowska A, Jastrzębska-Więsek M, Cios A, Partyka A. The preclinical discovery and development of paliperidone for the treatment of schizophrenia. *Expert Opinion on Drug Discovery*. 2020 Mar 3;15(3):279-92.
11. Shirode A, Garade C, Kadam V. DEVELOPMENT AND VALIDATION OF HPTLC METHOD FOR QUANTITATIVE ESTIMATION OF PALIPERIDONE. *Indian Drugs*. 2018 Sep 1;55(9):34.
12. Jeremić A, Milosavljević F, Vladimirov S, Batinić B, Marković B, Jukić M. Validation of a quick and simple chromatographic method for simultaneous quantification of sertraline, escitalopram, risperidone and paliperidone levels in the human plasma. *Arhiv za farmaciju*. 2021;71(5):365-77.
13. Nozawa H, Minakata K, Hasegawa K, Yamagishi I, Miyoshi N, Yuyama K, Suzuki M, Kitamoto T, Kondo M, Suzuki O. Quantification of risperidone and paliperidone by liquid chromatography–tandem mass spectrometry in biological fluids and solid tissues obtained from two deceased using the standard addition method. *Legal Medicine*. 2024 Jul 1;69:102340.
14. Farooq JS, Khan FN. QbD-Driven Development and Validation of a Bioanalytical LC–MS Method for Quantification of Paliperidone in Human Plasma. *Int. J. Exp. Res. Rev*. 2023;36:47-57.
15. Ahmed Baig ML, Ali SA. LC-MS/MS method for the estimation of paliperidone in human plasma. *Analytical Chemistry Letters*. 2017 Mar 4;7(2):228-40.
16. Bocato MZ, Simões RA, Calixto LA, de Gaitani CM, Pupo MT, de Oliveira AR. Solid phase microextraction and LC–MS/MS for the determination of paliperidone after stereoselective fungal biotransformation of risperidone. *Analytica chimica acta*. 2012 Sep 12;742:80-9.
17. Ruan CJ, Guo W, Zhou M, Guo GX, Wang CY, Li WB, de Leon J. Quantitative determination of risperidone, paliperidone and olanzapine in human serum by liquid chromatography–tandem mass spectrometry coupled with on-line solid-phase extraction. *Biomedical Chromatography*. 2018 Jul;32(7):e4209.
18. Panda SS, Beg S, Ravi K, Varaha V, Priyadarshini S. Analytical quality-by-design compliant ultrafast liquid chromatographic method for determination of paliperidone in extended release tablet dosage form. *Journal of Bioanalysis & Biomedicine*. 2015 Aug 5;7.
19. Tambe R, Mankar S, Dighe S. Analytical Method Development and Validation of Paliperidone: A Review. *Research Journal of Science and Technology*. 2020;12(1):23-35.