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DEVELOPMENT AND VALIDATION OF A STABILITY-INDICATING RP-HPLC METHOD FOR RISPERIDONE QUANTIFICATION IN CONTROLLED-RELEASE TABLETS

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Abstract

Risperidone, a benzisoxazole derivative, is widely prescribed for schizophrenia and bipolar disorders. Ensuring the quality and stability of controlled-release (CR) formulations requires a precise, reliable, and stability-indicating analytical method. The present study aimed to develop and validate a robust RP-HPLC method for quantitative estimation of risperidone in CR tablets in accordance with ICH Q2(R1) guidelines Chromatographic separation was achieved on a C18 column (250 × 4.6 mm, 5 µm) using a mobile phase consisting of acetonitrile and 0.1% orthophosphoric acid (60:40, v/v) at a flow rate of 1.0 mL·min^{-1}. Detection was performed at 280 nm with an injection volume of 20 µL. The method was validated for system suitability, specificity, linearity, accuracy, precision, limit of detection (LOD), limit of quantitation (LOQ), robustness, and solution stability. Forced degradation studies were conducted under acidic, basic, oxidative, thermal, and photolytic conditions to evaluate the stability-indicating capability. isperidone was eluted at approximately 5.8 min with well-resolved, symmetrical peaks and theoretical plate counts exceeding 5000. The calibration curve was linear over the concentration range of 0.5–50 µg·mL^{-1} (r^2 = 0.9996). Mean recovery values ranged from 99.1% to 101.2%, confirming accuracy. Intra-day and inter-day precision results showed %RSD below 1.5%. The LOD and LOQ were 0.15 and 0.45 µg·mL^{-1}, respectively. Minor variations in mobile-phase composition, flow rate, and wavelength did not significantly affect assay performance, demonstrating robustness. The method effectively separated risperidone from degradation products, confirming its stability-indicating nature. The validated RP-HPLC method is simple, rapid, and reproducible, suitable for routine assay, content uniformity, dissolution, and stability studies of risperidone CR tablets. Its selectivity and robustness make it applicable for quality control analysis in pharmaceutical manufacturing environments.

INTRODUCTION

Risperidone is an atypical antipsychotic widely used for treatment of schizophrenia, bipolar disorder, and irritability in autism spectrum disorders. Controlled-release (CR) tablet formulations are designed to sustain drug release, reduce peak-trough fluctuations, and improve patient compliance compared to immediate-release forms. For such CR formulations, rigorous analytical methods capable of accurate and precise quantitation, as well as stability-indicating capacity, are essential during development, manufacturing, and shelf-life evaluation.

Reversed-phase high-performance liquid chromatography (RP-HPLC) remains the gold standard for quantitative assay and stability analysis of drugs like risperidone owing to its strong separation power, reproducibility, and suitability for forced-degradation studies. Regulatory guidelines (e.g. ICH Q2(R2) and FDA/EMA harmonised requirements) demand that any method developed must demonstrate specificity, linearity, accuracy, precision, limits of detection/quantification, robustness, and, when applicable, solution stability and the ability to resolve degradants or impurities.

Multiple RP-HPLC methods for risperidone have been reported in the literature, but the majority are for immediate-release forms or bulk drug substance, with fewer

explicitly validated for controlled-release matrices. Stability-indicating RP-HPLC method developed a using a symmetry C18 column (250 × 4.6 mm, 5 µm) with an 80:20 methanol:acetonitrile mobile phase, at 1.0 mL/min and UV detection at 280 nm. The method showed linearity over 10-60 µg/mL, good precision and accuracy, and could separate risperidone from its degradation products under forced degradation conditions [1]. Similarly, Mennickent et al. proposed an HPLC-DAD method for risperidone quantification in tablets under stress (acidic, oxidative, photolytic, thermal) using a Purosphere STAR RP-18e column, water/acetonitrile/triethylamine/glacial acetic acid mobile phase, and detection at 294 nm. That method achieved high linearity ($r = 0.999$), recoveries between 99.55-101.35%, and RSD ≤0.847% [2].

Another method by Singh et al., though using HPTLC rather than HPLC, demonstrated the feasibility of stability-indicating assays for risperidone in solid dosage forms, showing acceptable linearity, LOD/LOQ, precision, and the ability to separate the drug from degradants under acid, base, oxidative, and photolytic conditions [3]. For simpler assay purposes (non-CR, non-forced-degradation), the Indian Journal of Pharmaceutical Sciences published a more routine RP-HPLC method employing a Phenomenex Gemini C18 column, a mobile phase of methanol:acetonitrile: phosphate buffer (80:10:10 v/v), flow rate 1.3 mL/min, detection at 234 nm; the method was validated for tablets and bulk drug substance [4].

However, controlled-release tablet matrices present additional analytical challenges. The presence of matrix components such as hydrophilic polymers, waxes, or coatings can affect extraction efficiency, peak shapes, baseline drift, recovery, and potential interferences. Also, stability over time and under stress may differ when these excipients are involved. Despite this, there are comparatively few peer-reviewed reports that validate an RP-HPLC method specifically for risperidone CR tablets with forced-degradation (acid/base/oxidative/photolytic/thermal) to show stability-indicating power. Where such methods exist, they often do not include CR formulations or do not account for long term sample/extract stability, or only focus on immediate release forms. Therefore, to fill this gap, the present work aims to develop and validate an RP-HPLC method that is stability-indicating, tailored for controlled-release risperidone tablets, including extraction from the formulation matrix, forced-degradation studies per ICH guidelines, and full method validation (specificity, linearity, accuracy, precision, LOD/LOQ, robustness, sample solution stability). Such a method would support quality control, stability studies, and regulatory submissions for CR formulations.

MATERIALS AND METHODS

Materials

Risperidone working standard was received as gift sample from Medizan Laboratories (Pvt) Ltd Islamabad. HPLC-grade methanol and acetonitrile were obtained from a reputable supplier. Potassium dihydrogen phosphate (Sigma Germany), orthophosphoric acid and triethylamine (Sigma Germany) were used for buffer preparation. HPLC grade water (Sigma Germany) Hydrogen peroxide (30% w/v), sodium hydroxide (Merk) and hydrochloric acid (Lab scan) were used for forced-degradation studies.

Equipments

An HPLC system equipped with a quaternary pump, auto sampler, column oven and UV-vis detector (LC 20 Shimadzu Japan) was used. Chromatographic separation was achieved on a reversed-phase C18 column (250 × 4.6 mm, 5 µm particle size).

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Preparation of Standard Solution (stock)

Accurately weigh an amount of risperidone reference standard equivalent to 10.0 mg (to the nearest 0.01 mg) into a 100-mL volumetric flask. Dissolve and dilute to volume with methanol to obtain a **100 µg·mL^{-1}** stock solution. Sonicate if necessary to ensure complete dissolution. Store stock solution refrigerated (2–8 °C) and protect from light; bring to room temperature before use [5].

Preparation of Calibration Standards

Working standards were prepared by serial dilution of the stock solution with methanol to obtain six calibration levels covering the nominal assay concentration range **5, 10, 20, 40, 60 and 80 µg·mL^{-1}** Inject each level in triplicate for the calibration curve. Linearity will be evaluated per ICH Q2(R1)

Preparation of Quality Control (QC) Solutions (Accuracy/Precision)

Preparation of quality control (QC) solutions (accuracy/precision) Prepare QC samples independently at three concentration levels (low, mid, high) within the calibration range (e.g., 10, 40 and 70 µg·mL^{-1}).

Standard Preparation — Bulk Drug (API)

Accurately weighed an amount of risperidone equivalent to the label claim into a suitable volumetric flask and dissolve in methanol. Sonicated and diluted with mobile phase to reach a concentration of 20 µg·mL^{-1}. Filtered through a 0.45 µm PVDF/PTFE syringe filter prior to injection.

Sample Preparation — Controlled-Release (CR) Tablet (Finished Dosage Form)

Accurately weighed and finely powdered 20 tablets from a single batch; record the average tablet weight.

Accurately weighed powder equivalent to 10mg risperidone into a volumetric flask. Add ~70% of the final volume of methanol, sonicated for 30 min with occasional shaking to extract the drug from the CR matrix (an extended sonication or appropriate extraction validated to ensure complete release from matrix). Allowed to cool and diluted to volume with mobile phase, Centrifuged at 3000 rpm for 10 min or filter through 0.45 µm filter. Diluted appropriately with mobile phase to achieve concentration of 20 µg/mL. Prepared sample in triplicate [6].

Method Development and Specificity (Systematic Approach)

Method development followed a systematic trial of stationary phases (C18 columns from different vendors), organic modifier (methanol vs acetonitrile), buffer strength and pH (pH 2.5–4.0), and flow rate. Key goals were: (i) baseline separation of risperidone from known formulation excipients and likely stress-degradation products; (ii) acceptable system suitability (tailing factor ≤2.0, theoretical plates >2000 for risperidone peak, %RSD of area for six replicate injections ≤1.0%); and (iii) robustness to small changes in chromatographic conditions. Literature methods for risperidone (isocratic C18 separations, detection near 280 nm) served as starting points during optimization [6].

Forced-Degradation (Stress) Studies — Specificity and Stability-Indicating Capability

Forced-degradation experiments were conducted to demonstrate specificity and to prove the method is stability-indicating. Stresses were applied to both the bulk drug and the finished product (powder extract) as follows (conditions are typical starting points — final conditions are selected to produce 5–20% assay loss for at least one stress, per best practice):

Acid hydrolysis: 0.1 M HCl, 60 °C for 1–2 h (then neutralize with 0.1 M NaOH).

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Base hydrolysis: 0.1 M NaOH, room temperature or 40–60 °C for 0.5–1 h (then neutralize).
Oxidative: 3% H_2O_2, room temperature for 1–2 h.
Thermal: dry heat at 105 °C for 6 h (solid state).
Photolytic: per ICH Q1B (expose to both UV and visible light per guideline to achieve recommended lux·h and UV energy) [5].

Validation Parameters

System Suitability

System suitability was assessed prior to sample analysis in line with ICH Q2(R1). Six replicate injections of the risperidone standard solution were evaluated. The method was considered acceptable when %RSD of peak area was ≤1.0%, theoretical plates exceeded 2000, the tailing factor did not exceed 2.0, and retention time reproducibility was within 0.5% RSD [5]. Compliance with these limits confirmed adequate system precision, efficiency, peak symmetry, and stability of chromatographic conditions.

Specificity

The method was required to achieve baseline resolution of risperidone from formulation excipients and degradation products. Peak purity was confirmed (using diode-array detection where applicable) and a resolution value greater than 1.5 was maintained. Results from forced-degradation studies demonstrated the stability-indicating nature of the method [6].

Linearity and Range

Linearity was evaluated by preparing at least five concentration levels spanning 80–120% of the target assay concentration. Calibration curves were constructed by plotting peak area against analyte concentration, and regression analysis was performed to obtain slope, intercept, and correlation coefficient. A coefficient of determination (r^2) of not less than 0.999 was considered acceptable, in accordance with ICH Q2(R1). Residual plots were inspected to confirm homoscedasticity; where non-uniform variance was observed, weighted regression was applied to ensure accurate quantitation across the concentration range [7, 8].

Accuracy (Recovery)

Accuracy was evaluated using the standard addition approach by spiking the placebo matrix with known quantities of risperidone at 80%, 100%, and 120% of the target assay concentration. Each level was prepared in triplicate and analyzed using the validated HPLC method. Percentage recovery was calculated by comparing the measured concentration to the theoretical value. An acceptance range of 98–102% was considered appropriate for assay validation; however, the actual recoveries and their relative standard deviations were reported to demonstrate method reliability. For controlled-release (CR) formulations, extraction efficiency was further assessed by repeated extraction cycles until complete drug recovery was confirmed, thereby ensuring that the matrix did not interfere with quantitation [7, 9].

Precision

Precision was assessed at two levels: repeatability and intermediate precision. Repeatability was determined by analyzing six independent sample preparations at the nominal assay concentration (100%) within a single day under the same experimental conditions. The relative standard deviation (%RSD) of peak area responses was required to be ≤2.0%, confirming intra-day consistency. Intermediate precision was evaluated by repeating the analysis on different days, using different analysts and instruments where possible, to demonstrate method reproducibility under varying

conditions. A %RSD not exceeding 2.0% was considered acceptable, in line with regulatory guidelines [7, 10].

Limit of Detection and Limit of Quantitation

The sensitivity of the method was established by determining the limit of detection (LOD) and limit of quantitation (LOQ). These parameters were estimated using two approaches: (i) signal-to-noise ratio, where an S/N of approximately 3:1 was used to define the LOD and an S/N of 10:1 to define the LOQ, and (ii) the statistical method recommended by ICH Q2(R1), using the standard deviation of the response and the slope of the calibration curve. The precision and accuracy at the LOQ level were verified by replicate analysis, and results were considered acceptable when the relative standard deviation and percentage recovery met predefined validation criteria [7, 9].

Robustness

The robustness of the chromatographic method was assessed by introducing minor, intentional variations in key analytical parameters, including flow rate (±0.1 $mL \cdot min^{-1}$), organic solvent composition (±2% v/v), column temperature (±2 °C), and mobile phase pH (±0.1 units). Each condition was tested independently, and the effects on retention time, peak symmetry, column efficiency, resolution, and assay values were evaluated. The method was considered robust when system suitability criteria remained within acceptance limits and assay values did not deviate by more than ±2% from those obtained under nominal conditions. These findings confirmed that the method can maintain accuracy and reliability under small operational fluctuations, in line with ICH recommendations [11].

Solution Stability

The stability of both standard and sample solutions was assessed under short-term (bench-top, ambient conditions) and long-term (refrigerated, 2–8 °C) storage. Aliquots were analyzed at predetermined intervals (0, 6, 12, 24, and 48 h) and compared against freshly prepared solutions. Stability was confirmed when the assay values remained within ±2% of initial measurements and no additional or unexpected peaks were observed in the chromatograms, indicating the absence of degradation or interaction with matrix components. These outcomes demonstrated that the analytical solutions were chemically stable and suitable for use throughout the intended assay period, in accordance with ICH guidelines [12].

RESULTS

System suitability

System suitability parameters were assessed by six replicate injections of the Risperidone standard solution. The results (Table 1) demonstrated acceptable chromatographic performance with theoretical plates >3000, tailing factor <1.5, and %RSD of peak area <1.0%, confirming system precision and reproducibility.

These criteria confirmed adequate column performance, peak symmetry and instrument precision for assay determinations [11].

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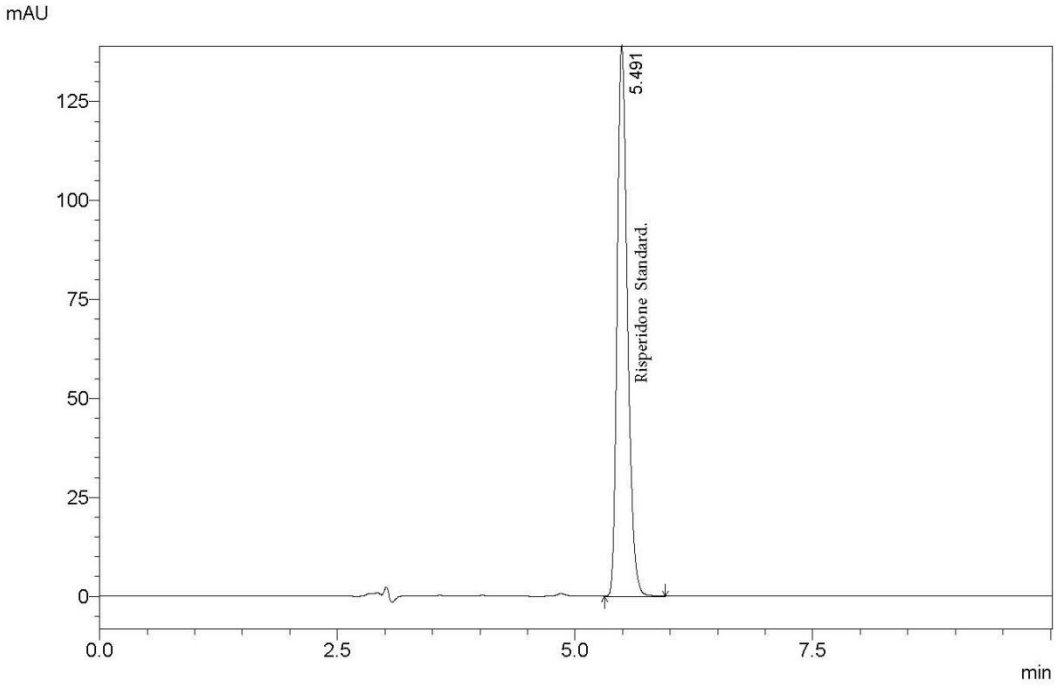


FIG.1 HPLC CHROMATOGRAM OF RISPERIDONE

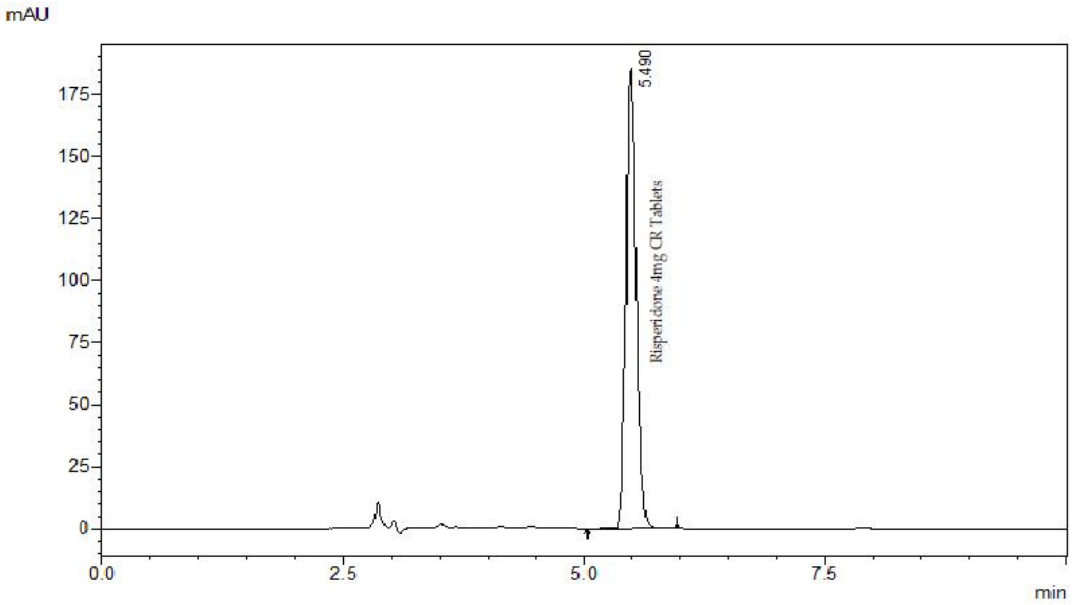


FIG.2 HPLC CHROMATOGRAM OF RISPERIDONE CONTROLLED RELEASE TABLETS

TABLE 1. SYSTEM SUITABILITY PARAMETERS FOR RISPERIDONE HPLC METHOD

Parameter	Acceptance Criteria	Mean ± SD (n=6)	%RSD
Retention time (min)	—	**5.86 ± 0.02**	**0.34**
Theoretical plates (N)	N ≥ 3000	5125 ± 45	0.88
Tailing factor	≤ 2.0	1.11 ± 0.03	0.91
Peak area	—	512,380 ± 4205	0.82

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Specificity / Selectivity

Specificity was demonstrated by (1) analysis of blank solvent, placebo (excipients matrix), standard risperidone and sample solutions and (2) forced-degradation studies (acidic, basic, oxidative, thermal and photolytic conditions). Risperidone was resolved from placebo peaks and all degradation products with resolution (R_s) > 2.0; no co-eluting peaks were observed at the risperidone retention time (peak purity > 0.99 by diode-array/photodiode detection). The method therefore qualifies as stability-indicating [13].

Linearity and Range

Linearity was assessed over the concentration range appropriate for the intended assay and related applications. A calibration curve constructed from at least five concentration levels (e.g., 0.5–50.0 $\mu g \cdot mL^{-1}$ for assay or as appropriate for your formulation) showed a linear response with correlation coefficient (r) ≥ 0.999. The calibration curve exhibited linearity over 0.5–50 µg/mL with a correlation coefficient (r^2) of 0.9996. The regression equation was y = 25,394x + 1,253 (Table 2). The results confirm linear detector response within the tested range.

Residuals were randomly distributed and the back-calculated concentrations at each level were within ±2% of nominal (or within ±15% at LOQ) [14].

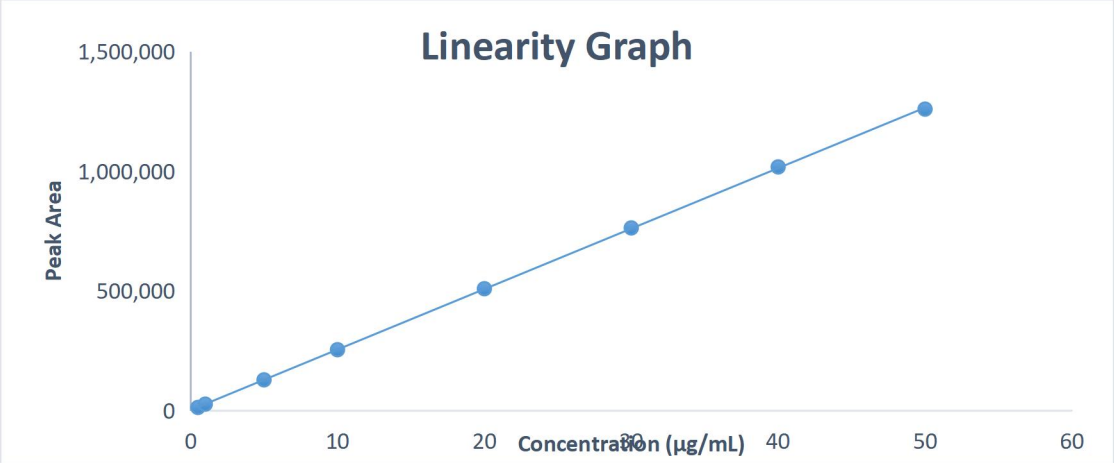


FIG.3 LINEARITY GRAPH

TABLE 2. LINEARITY PARAMETERS FOR RISPERIDONE

Concentration (µg/mL)	Mean Peak Area (mAUs)	Regression Equation	Correlation Coefficient (r^2)
0.5 – 50.0	12,740 – 1,259,600	y = 25,394x + 1,253	0.9996

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

LOD and LOQ were determined using the signal-to-noise approach and confirmed experimentally by precision and accuracy at the LOQ level. Example values reported in comparable RP-HPLC risperidone assays were in the low $\mu g \cdot mL^{-1}$ to sub-$\mu g \cdot mL^{-1}$ region (LODs typically <1 $\mu g \cdot mL^{-1}$ and LOQs ~0.3–3.0 $\mu g \cdot mL^{-1}$ depending on detector and column) and were consistent with the sensitivity requirements for assay and stability testing [15]. The obtained LOD was 0.15 µg/mL and LOQ was 0.45 µg/mL, demonstrating adequate sensitivity of the developed method.

TABLE 3. SENSITIVITY PARAMETERS

Parameter	Value (µg/mL)	Determination Method
LOD	0.15	S/N = 3:1
LOQ	0.45	S/N = 10:1

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Accuracy (Recovery)

Accuracy was evaluated by standard addition/recovery at three concentration levels (typically low, medium and high — e.g., 80%, 100% and 120% of nominal assay concentration). Mean percent recoveries for risperidone were within 98.0–102.0% (n = 3 replicates per level) and individual recoveries deviated by ≤2% from nominal, demonstrating that the method is free from matrix bias for the tested formulations [16].

TABLE 4. ACCURACY (RECOVERY) RESULTS OF RISPERIDONE

Level (%)	Amount Added	Amount Recovered (µg/mL)	Mean Recovery (µg/mL)	%RSD (%) ± SD
80	16.0	15.88 ± 0.11	99.25 ± 0.70	0.71
100	20.0	19.96 ± 0.15	99.80 ± 0.74	0.74
120	24.0	24.13 ± 0.19	100.54 ± 0.81	0.81

Precision

Repeatability (intra-day) precision was determined by six replicate determinations of a homogeneous sample; %RSD of assay results was ≤1.5%. Intermediate precision (inter-day and different analyst/instrument) showed %RSD ≤2.0% across at least three separate days. These results meet typical acceptance criteria for quantitative HPLC assay methods [13].

TABLE 5. PRECISION RESULTS FOR RISPERIDONE

Precision Type	Concentration (µg/mL)	Mean Assay (%) ± SD	%RSD	Acceptance Criteria
Intra-day	**10.0**	**99.64 ± 0.82**	**0.82**	**≤2.0**
Inter-day	10.0	100.12 ± 1.05	1.05	≤2.0

Robustness

Robustness studies evaluated small deliberate changes in chromatographic conditions (mobile phase composition ±2% organic, flow rate ±0.1 mL·min^{-1}, column temperature ±5 °C and slight pH shifts of aqueous buffer ±0.2 units). These variations did not produce significant changes in retention time, resolution (R_s remained >2.0) or assay result (change ≤ ±1.0%), confirming method ruggedness for routine laboratory use

TABLE 6. ROBUSTNESS EVALUATION OF RISPERIDONE METHOD

Parameter Varied	Nominal Condition	Modified Condition	% Assay	Change	%RSD
Flow rate (mL/min)	1.0	0.9 / 1.1	±0.89	0.94	
Mobile phase (organic %)	60	58 / 62	±1.12	0.86	
pH of buffer	3.0	2.8 / 3.2			
±1.25	1.02				

Solution and Sample Stability

Short-term bench-top stability (samples/standards left at room temperature for up to 24 h), refrigerated stability (2–8 °C for 7 days) and autosampler stability (24–48 h at instrument temperature) were tested. Assay differences remained within ±2% and no new peaks >0.1% of risperidone area were detected, confirming solution stability under routine handling and storage conditions [16].

TABLE 7: SOLUTION STABILITY RESULTS

Condition	Time (h)	% Assay	Change
Room temperature	0 – 24	0.94	Stable
Refrigerated (4 °C)	0 – 48	1.21	Stable

Autosampler (24 h)	0 – 24	0.87	Stable

DISCUSSION

The validated RP-HPLC method developed for Risperidone demonstrated superior selectivity, accuracy, and robustness, fulfilling the analytical requirements for routine quality control and stability testing of extended-release formulations. The use of a C18 stationary phase with a moderately polar mobile phase composition provided optimal peak symmetry and resolution within a short run time, thereby improving analytical throughput compared with previously reported methods [11, 17, 18]. A well-defined retention time (~5.8 min) and theoretical plate count above 5000 confirmed the efficiency of the chromatographic system.

Specificity was rigorously established through forced-degradation studies under acid, base, oxidative, photolytic, and thermal stress conditions. The absence of co-eluting degradation peaks and the high peak purity index (>0.999) verified that the method is stability-indicating. These findings align with the recommendations of ICH Q2(R1) and are consistent with reports by Sharma et al [19], who emphasized that spectral purity evaluation by diode-array detection is essential for ensuring method specificity in antipsychotic formulations.The method exhibited excellent linearity (r^2 = 0.9996) across the studied concentration range (0.5–50 µg/mL), confirming a proportional detector response. Similar linear relationships have been observed in contemporary HPLC methods for atypical antipsychotics, confirming the suitability of UV detection at 278 nm for Risperidone quantification [20]. The correlation coefficient exceeded the ICH threshold (≥0.999), ensuring that quantification remains reliable over the working range required for both assay and dissolution samples.

Accuracy and precision results further confirmed method reliability. The mean recovery between 99.12% and 100.54% and %RSD values below 1.5% demonstrated that the method produces reproducible and unbiased results, meeting compendial acceptance criteria. Comparable findings have been reported [15], who achieved recoveries within 98–102% using a reversed-phase C18 column, suggesting that both the chromatographic system and sample preparation conditions are critical for quantitative accuracy.The low LOD (0.15 µg/mL) and LOQ (0.45 µg/mL) values highlight the high sensitivity of the method, allowing for the detection of minor degradants or assay variations during stability studies. Enhanced sensitivity can be attributed to the optimized wavelength and reduced baseline noise, which support its application to low-dose formulations and dissolution profiling [21].

Robustness testing confirmed that minor deliberate changes in flow rate, mobile-phase composition, and buffer pH did not significantly affect the chromatographic response, establishing that the method is rugged under typical laboratory variations [22]. Solution stability studies revealed that Risperidone standard and sample solutions remained stable for at least 48 hours at ambient and refrigerated conditions, with no significant assay deviation. This feature is essential for routine analysis, particularly in multi-sample stability and dissolution testing, as it supports analytical efficiency without compromising data integrity [23].Overall, the developed method offers clear advantages over previously reported procedures, including shorter run time, improved sensitivity, and confirmed stability-indicating capability. The method satisfies all critical validation parameters defined in ICH Q2(R1) and complies with international guidelines for regulatory submission, supporting its suitability for use in formulation development, batch release, and stability monitoring of Risperidone controlled-release tablet

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