

Environmental Assessment and Retrospective Risk Assessment of A Stability-Indicating, Robust, Validated Liquid Chromatographic Method For Lumateperone Tosylate

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ABSTRACT

Reliable quality control of lumateperone tosylate requires an analytical procedure that combines reproducible performance with practical laboratory operation and consideration of environmental impact. This study evaluated an isocratic reversed phase high performance liquid chromatographic method, alongside retrospective risk assessment and complementary greenness metrics. Chromatography was performed using a Kromasil C18 column (150 × 4.6 mm, 5 µm) with potassium dihydrogen orthophosphate buffer and acetonitrile (60:40, v/v), a flow rate of 1.0 mL/min, and a column temperature of 30 °C. Photodiode array detection was conducted at 245 nm within a seven minute run. Calibration concentrations covered 10.5–63 µg/mL. Repeat injection and 24 hour precision yielded relative standard deviations of 0.68% and 0.92%, respectively. Recoveries ranged from 99.17% to 101.18%, with a mean of 100.31%. Reported detection and quantification limits were 0.22 and 0.66 µg/mL. System suitability showed approximately 2,814 theoretical plates and a mean tailing factor of 1.71. Deliberate changes in flow rate, mobile phase composition, and temperature produced relative standard deviations of 0.20–0.50%. Retrospective risk assessment identified mobile phase composition and sample preparation as priorities for analytical control. Environmental evaluation yielded reported AGREE and Analytical Eco-Scale scores of 0.55 and 91, respectively, reflecting different assessment frameworks.

Keywords: Lumateperone tosylate, RP-HPLC; Method validation; Robustness; Retrospective risk assessment; Forced degradation; AGREE; Analytical Eco-Scale.

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INTRODUCTION

Lumateperone is an atypical antipsychotic formulated as the tosylate salt. Although its precise therapeutic mechanism remains unknown, its activity may involve serotonin 5-HT_{2A} receptor antagonism and dopamine D₂ receptor partial agonism [1]. Reliable determination of Lumateperone in pharmaceutical preparations is important for assessing drug content and maintaining consistent product quality. An analytical procedure intended for routine use should therefore provide reproducible measurements while remaining practical to operate and transparent about its environmental burden [4–7].

Published studies have established several approaches for Lumateperone determination. Bavadekar and colleagues developed an HPLC method using prospective analytical quality by design, including experimental design and response-surface optimization. Their procedure employed a Zorbax SB-C18 column (250 × 4.6 mm, 5 µm), ammonium acetate buffer–acetonitrile (80:20, v/v), and detection at 230 nm [2]. Thus, the application of QbD concepts to Lumateperone analysis is already established. Other investigators have explored alternative measurement technologies. A graphene quantum dot fluorescence method incorporated

GAPI, AGREE and BAGI assessments and reported an AGREE score of 0.78, demonstrating that environmental evaluation of Lumateperone assays also precedes the present study [3]. These developments provide a foundation for examining analytical performance, operational risks and environmental considerations within a conventional chromatographic workflow. ICH Q2(R2) and Q14 provide complementary frameworks for analytical validation and procedure development, respectively [4,5]. These guidelines support the generation and documentation of evidence needed to maintain reliable analytical performance throughout the procedure lifecycle. Environmental assessment adds another perspective: AGREE evaluates analytical procedures against twelve principles of green analytical chemistry [6], whereas the Analytical Eco-Scale assigns penalty points associated with reagents, energy consumption and waste [7]. Using both tools allows the environmental profile to be examined through complementary assessment frameworks.

The present study investigates an isocratic RP-HPLC procedure for Lumateperone tosylate using a Kromasil C18 column (150 × 4.6 mm, 5 µm), phosphate buffer–acetonitrile (60:40, v/v), and

photodiode array detection at 245 nm. The method is evaluated through calibration, recovery, repeat-injection precision, measurements after 24 hours, system suitability and deliberate changes in chromatographic conditions. Stress experiments are also included to examine the analytical response following exposure to acidic, alkaline, oxidative, thermal, photolytic and neutral conditions.

The principal contribution of this work is the integration of these experimental assessments with retrospective risk analysis and two complementary environmental metrics. Mobile-phase composition, sample preparation, flow rate, temperature and other operating variables are considered in relation to analytical control. The retrospective assessment organizes available method knowledge and robustness observations without claiming an experimentally established design space. Together, these evaluations provide a practical framework for identifying control priorities, documenting environmental trade-offs and directing further refinement of a routine Lumateperone assay.

METHODOLOGY

Chemicals and reagents: The Lumateperone standard was purchased from BMR chemicals, Hyderabad. And the standard purity not less than 98% was used for the analysis. Other chemicals used are Water, Acetonitrile, Methanol are of HPLC grade and other chemicals like Orthophosphoric acid (88%), Glacial acetic acid, Triethyl amine, Dimethyl sulfoxide, Perchloric acid, Potassium Di hydrogen Orthophosphate, Sodium hydroxide, Sodium phosphate dibasic anhydrous, Sodium acetate, Ammonium acetate, di-Sodium hydrogen orthophosphate are of analytical grade purchased from RANKEM chemicals. And Instrument HPLC (2695 model) with 2996 PDA detector – Waters was used

Instruments and Equipment

- Waters HPLC 2695 System
- Photodiode Array (PDA) Detector
- Kromasil C₁₈ 150x 4.6mm, 5µm 180Å
- Empower 2 Software – for chromatographic data acquisition and processing

Preparation of reagents

Preparation of Buffer Solution: 0.01N Potassium dihydrogen ortho phosphate (pH 4.8): 1.36gm of Potassium dihydrogen ortho phosphate was taken in to a 1000ml volumetric flask. 900ml of Milli-Q water was added and sonicated. Volume was made up to 1000ml with water and the pH of the solution was adjusted to 4.8 with Glacial acetic acid.

Preparation of Mobile phase: 0.01N Potassium dihydrogen ortho phosphate buffer and were taken in the ratio 60:40.

Preparation of 0.1% Ortho phosphoric acid: 0.1% Orthophosphoric acid was prepared by diluting 1ml of orthophosphoric acid to 1000 ml with Milli-Q water (pH 2.2)

Preparation of Diluent: 0.1% Ortho phosphoric acid solution and Acetonitrile mixed in the ratio 50:50.

Preparation of Standard solution: Accurately weighed 42mg of Lumateperone tosylate standard was transferred into a 100 ml volumetric flask and dissolved initially with diluent of about 10ml and sonicated for 10 min. finally volume was made up to 100ml with diluent. From this solution, 1ml was taken and diluted to 10ml with diluent. Which produces 42µg/ml of Lumateperone

Preparation of sample stock solution: Equivalent weight of the combination powder sample of Lumateperone was Accurately weighed and transferred into a 100ml volumetric flask and dissolved initially with 50 ml of diluent and sonicated for 25 min. the volume was finally made up to 100 ml with diluent and filtered.

Preparation of working sample solution: 1ml of above Sample stock solution, filtered, was taken, and diluted to 10 ml with diluent. Which produces 42µg/ml of Lumateperone

Preparation of Solutions for Forced Degradation Studies

Oxidation: 1ml of Lumateperone stock solution was taken and to it 1ml of 20% hydrogen peroxide was added. Solution kept aside for 30min at 60°C. the resulting solution was diluted for to obtain the concentration of 42ppm and 10µl solution was injected into HPLC system for the assessment of stability of the sample towards oxidation.

Acid Degradation Studies: 1ml of Lumateperone stock solution was taken and to it 1ml of 2N Hydrochloric acid solution was added and refluxed for 30min at 60°C. the resulting solution was diluted to obtain 42ppm and 10µl solution was injected into HPLC system for the assessment of stability of the sample

Alkali Degradation Studies: 1ml of Lumateperone stock solution was taken and to it 1ml of 2N Sodium hydroxide solution was added and refluxed for 30min at 60°C. the resulting solution was diluted to obtain 42ppm and 10µl solution was injected into HPLC system for the assessment of stability of the sample

Dry Heat Degradation Studies: Lumateperone standard solution was taken and placed in an oven at 105°C for 6hrs for dry heat degradation studies. After dried in an oven, the solution was diluted to 42ppm and 10µl solution was injected into HPLC system for the assessment of stability of the sample.

Photo Stability Studies: The drug stability towards photochemical degradation was studied by exposing the solution to UV Light under UV chamber for 7days or 200-watt hours/min. for HPLC study the resulting solution was diluted to 42ppm and 10µl solution was injected into HPLC system for the assessment of stability of the sample.

Neutral Degradation Studies: Under neutral conditions stress testing was studies by refluxing

drug in water for 6hrs at a temperature of 60°C. for HPLC study the resulting solution was diluted to 42ppm and 10µl solution was injected into HPLC system for the assessment of stability of the sample.

HPLC OPTIMIZED METHOD

Considering the nature and solubility characteristics of Lumateperone, HPLC with reverse phase was better choice of analysis. A series of experiments were performed by making few changes in the solvent system, ratio of mobile phase and composition and the flow rate. Under isocratic conditions, to achieve ideal drug separation Lumateperone separated on an Kromasil C₁₈ 150x 4.6mm, 5µm 180A° column by isocratic elution with a mobile phase consisting of 0.01N Potassium dihydrogen ortho phosphate and acetonitrile at 30 °C in the ratio 60:40. Detection was done by using UV-VIS spectrophotometric detector and detection at 245.0 nm was applied. These conditions found suitable for the separation with good drug recovery. The chromatographic conditions were given in following table 1and chromatogram in Figure 1.

Flow rate	1ml/min
Column	Kromasil C ₁₈ 150x 4.6mm, 5µm 180A°
Detector wave length	245.0 nm
Column temperature	30°C
Injection volume	30.0 µL
Run time	7.0minutes

Table 1: chromatographic conditions of optimized method

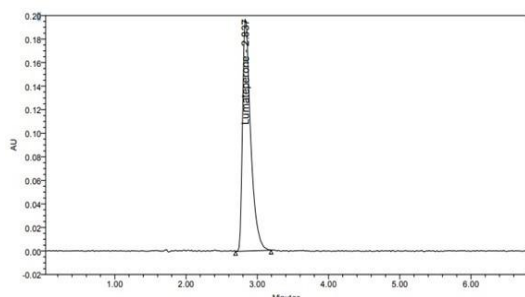


Figure 1: Chromatogram of Lumateperone
RETROSPECTIVE/EXPLORATORY AQBD VISUALIZATIONS DERIVED FROM ROBUSTNESS DATA
 Analytical Target Profile (ATP): The ATP was defined as a simple, precise, accurate and robust RP-HPLC/UV method for estimating Lumateperone in pharmaceutical dosage form across the validated concentration range. Critical method attributes included retention time,

peak area precision, linearity, recovery, tailing factor, plate count and robustness.

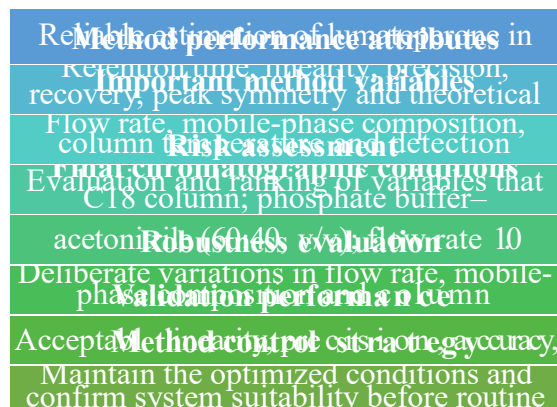


Table 2: Retrospective AQbD workflow illustrating the analytical objective, method variables, risk assessment, robustness evaluation, validation performance and control strategy for the Lumateperone RP-HPLC/UV method.

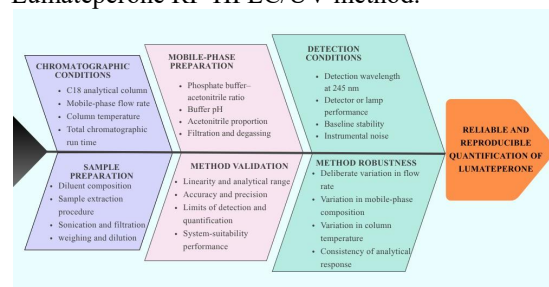


Figure 2: Ishikawa (fishbone) diagram outlining factors influencing the reliability and reproducibility of Lumateperone quantification by liquid chromatography.

RISK ASSESSMENT MATRIX

Risk factor	S	O	D	RP N	Risk level	Control strategy
Mobile-phase composition	4	4	2	32	High	Maintain the phosphate buffer-acetonitrile ratio at 60:40 (v/v) and verify performance during robustness

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						s testing; observed %RSD was 0.3– 0.5%.
Sample and diluent preparati on	3	3	3	27	High	Use the validated diluent composit ion, accurate volumetr ic preparati on, controlle d sonicatio n and appropria te filtration; monitor recovery and solution response.
Flow rate	4	3	2	24	Medi um	Maintain the flow rate at 1.0 mL/min and verify performa nce followin g deliberat e variation

						s; observed %RSD was 0.2– 0.4%.
Column temperat ure	3	3	2	18	Medi um	Maintain the column temperat ure at 30 °C and evaluate the effect of deliberat e temperat ure changes; observed %RSD was 0.2– 0.4%.
Detectio n wavelen gth	4	2	2	16	Medi um	Maintain detection at 245 nm and monitor baseline stability and detector response before analysis.
Column conditio n and performa nce	4	2	2	16	Medi um	Confirm system suitabilit y before analysis;

						the mean theoretical plate count was 2,814 and the mean tailing factor was 1.71.
Buffer pH and preparation	4	3	2	24	Medium	Prepare the buffer using calibrated glassware, adjust the pH accurately, and filter and degas the aqueous phase before use.
Injection volume	3	2	2	12	Medium	Maintain the validated injection volume and verify autosampler precision and absence of

						carryover
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Table 3: Risk assessment of variables affecting the Lumateperone RP-HPLC/UV method

S: Severity

O: Occurrence

D: Detectability

RPN: Risk Priority Number = $S \times O \times D$

Suggested classification: Low = 1–10; Medium = 11–24; High ≥ 25

Experimental design table

R un co de	Experi mental conditio n	A: Fl ow rate	B: Mobile -phase compo sition	C: Colum n temper ature	Pea k- are a %R SD
N	Nominal method condition	0	0	0	0.70
F–	Lower flow rate	–1	0	0	0.40
F+	Higher flow rate	+1	0	0	0.20
M–	Lower mobile-phase level	0	–1	0	0.30
M+	Higher mobile-phase level	0	+1	0	0.50
T–	Lower column temperature	0	0	–1	0.40
T+	Higher column temperature	0	0	+1	0.20

Table 4: Robustness-derived experimental conditions and peak-area precision

Coded levels: -1 = minus condition, 0 = nominal condition, +1 = plus condition. The response variable was peak-area precision expressed as %RSD.

Deliberate variations in flow rate, mobile-phase composition, and column temperature produced peak-area %RSD values ranging from 0.20% to 0.50%, compared with 0.70% under the nominal condition. These findings indicate that the evaluated variations did not adversely affect method precision and support the robustness of the chromatographic procedure within the tested ranges.

ACTUAL RATIO LEVELS

Factor	Lower level (-1)	Nominal level (0)	Higher level (+1)
Flow rate	Actual value	1.0 mL/min	Actual value
Mobile-phase composition	Actual ratio	60:40 (v/v)	Actual ratio
Column temperature	Actual value	30 °C	Actual value

Table 5: Nominal conditions and lower (-1) and higher (+1) factor levels for robustness assessment of the Lumateperone RP-HPLC method.

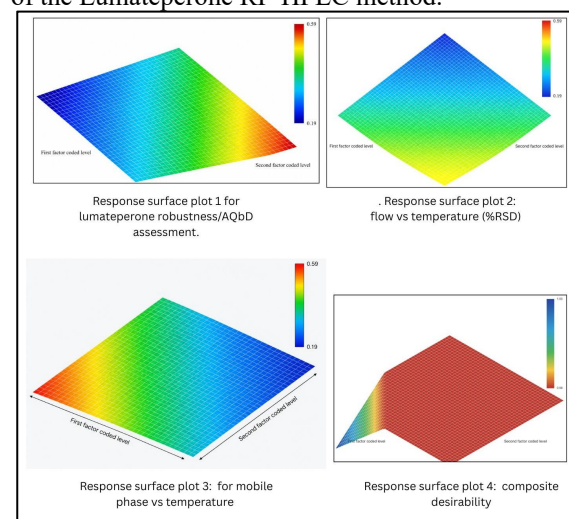


Figure 3: response surface plots for the Lumateperone RP-HPLC method.

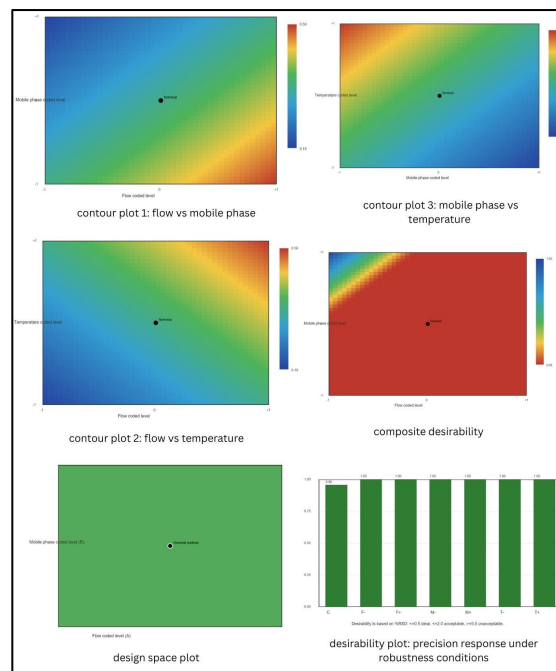


Figure 4: Retrospective robustness and desirability plots for the Lumateperone RP-HPLC method.

RESULTS AND DISCUSSION

ANALYTICAL METHOD VALIDATION : The method developed was entirely validated for, accuracy, precision, selectivity, linearity, solution stability and solubility at 24hrs, LOD and LOQ as per ICH guidelines. forced degradation studies were also performed to establish drug degradation pathways which reveals chemical behaviour of Lumateperone and samples obtained from degradation studies were analysed. The degradation parameters include oxidation of drug with 20% hydrogen peroxide (H₂O₂), Acid Degradation using 2N Hydrochloric acid, Alkali Degradation with 2 N sodium hydroxide, dry heat degradation, neutral degradation, and photo stability studies.

Linearity: Six injections were eluted with 25, 50, 75, 100, 125, 150 % of the linearity levels and repeated for six sets. The average area found foreach level was given in the table. Linearity was constructed and the slope was found to be 34625 with y- intercept 2192.5 giving out the correlation coefficient 0.9995. The % of Linearity Level, Concentration of drug, Area of the peak were given in Table 6 and linearity graph was given in Fig 5.

% of Linearity Level	Concentration of drug	Area of the peak
0	0	0
25	10.5	771299
50	21	1567430
75	31.5	2334920
100	42	3074612
125	52.5	3838110

150	63	4609055
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Table 6: Linearity results of Lumateperone

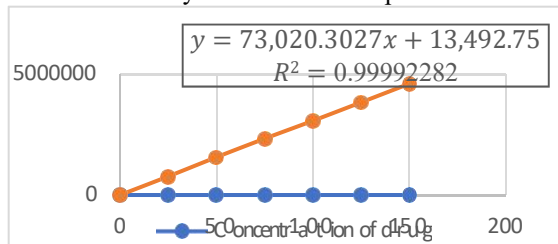


Figure 5: Linearity

plot

Method Precision or Repeatability:

Serial number of injections	Area of the peak
1	1434925
2	1429383
3	1423240
4	1443206
5	1422143
6	1444940
AVG	1432973
SD	9763.6
% RSD	0.7

Table 7: Method precision data

Working Sample solution are injected six times and eluted for the repeatability of the solution at a concentration of 42 µg/ml. The average peak area of the solutions, standard deviation, %RSD values are given in the table 7.

Day To Day Precision or Intermediate Precision:

Working Sample solution are injected six times next day of the preparation of the solution at 24 hrs of intermediate precision at a concentration of 42 µg/ml to perform intermediate precision. The average peak area of the solutions, standard deviation, %RSD values are given table 4 and chromatogram after 24hrs of intermediate precision was given in figure 6.

Serial number of injections	Area of the peak
1	1415109
2	1389403
3	1386227
4	1411730
5	1391820
6	1387622
AVG	1396985

SD	12910.9
% RSD	0.9

Table 8: Intermediate precision data

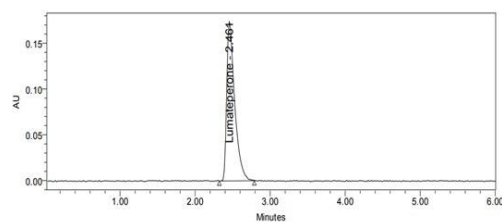


Figure 6: Lumateperone at 24 hrs of intermediate precision

Limit of detection and limit of Quantification:

Drug concentrations of range 2.5 to 12.5 µg/ml which is expected detection limit range. Calibration curve was drawn using these concentrations. Y-Intercepts of regression line, Standard deviation was calculated and submitted in the following equations to find out the limit of detection and limit of quantification of the drug. The values were given in table 9.

$$\text{Limit of detection} = \sigma \times 3.3/S$$

$$\text{Limit of quantification} = \sigma \times 10/S$$

σ = Standard deviation

S = Slope

Test name	values
Limit of detection	0.22 µg/ml
Limit of quantification	0.66 µg/ml

Table 9: Data of LOD and LOQ OF Lumateperone

Accuracy: Three concentrations levels for accuracy of 50%, 100%, 150% were prepared and each level of concentration were injected three times and percentage recovery, standard deviation was calculated. The percentage recovery at each level of accuracy and the standard deviation and relative standard deviation ns data is shown in table 10.

% Level	Add ppm	% Recovery
ACCURACY_50%	21	100.52
	21	100.89
	21	100.48
ACCURACY_100%	42	101.18
	42	99.63
	42	100.58
ACCURACY_150%	63	99.17
	63	100.00
	63	100.37
Average % recovery	AVG	100.31
	STDEV	0.62

	%RSD	0.62
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Table 10: Accuracy data OF Lumateperone

System Suitability: working standard solution of Lumateperone was prepared as per the procedure and six injections were given for attaining system suitability parameters. Area of the peak, USP plate count and the tailing factor were calculated and shown in the table 11.

S No	RT in Min	Area of the peak	USP Plate count	USP Tailing
1	2.879	1428519	2810	1.72
2	2.721	1421736	2798	1.72
3	2.821	1444436	2730	1.72
4	2.829	1429844	2893	1.70
5	2.831	1452117	2857	1.70
6	2.833	1422530	2794	1.72

Table 11: System suitability data OF Lumateperone

Robustness: To achieve robustness, small changes in the chromatographic conditions were employed. These changes were applied according to ICH guidelines and the change in flowrate, mobile phase composition, and temperature were applied and injected, %RSD was found within limits specified in table 12.

Parameter	%RSD
Flow minus	0.4
Flow plus	0.2
Mobile phase minus	0.3
Mobile phase plus	0.5
Temperature minus	0.4
Temperature plus	0.2

Table 12: Robustness data

Degradation studies:

Acid Degradation studies: Degradation in acid was performed and after study it was found that there is no degradation in the drug and good drug recovery, and theoretical plates. Purity plot was also given for the acid study. The chromatograms of the acid degradation study and the purity plot are given in figure 6 and figure 7.

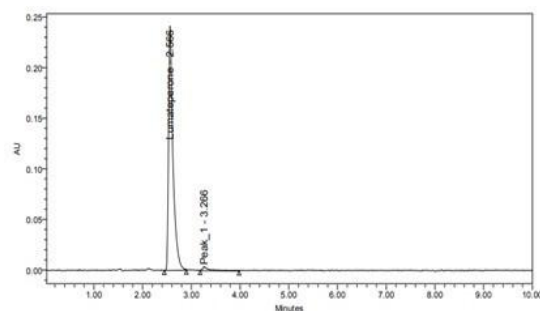


Figure 6: Acid degradation chromatogram

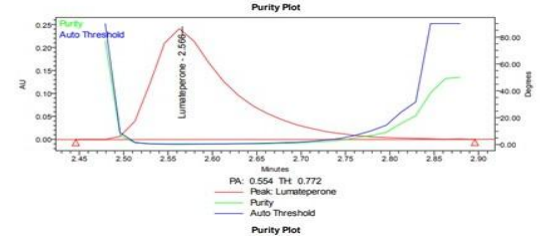


Figure 7: purity plot for Acid degradation study

Alkali degradation studies: Degradation in base was performed and after study it was found that there is no degradation in the drug. good drug recovery, and theoretical plates was achieved. Purity plot was also given for the alkaline study. The chromatograms of the base degradation study and the purity plot are given in Figure 8 and figure 9.

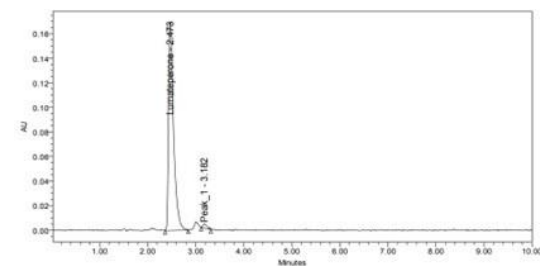


Figure 8: Alkali degradation chromatogram

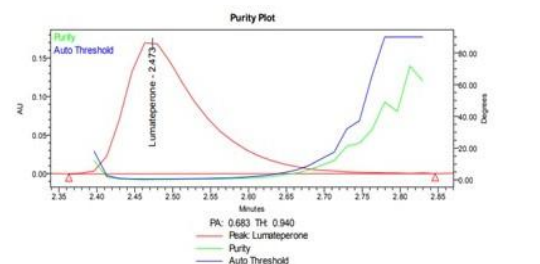


Figure 9: Purity plot for Alkali degradation study

Peroxide degradation studies: Peroxide degradation was performed and no degradation in the drug was seen. good drug recovery, and theoretical plates was achieved. Purity plot was also drawn for peroxide degradation study. The chromatograms of study and the purity plot are given figure 10 and figure 11.

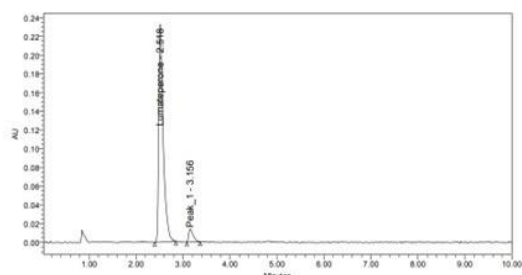


Figure 10: Peroxide degradation chromatogram

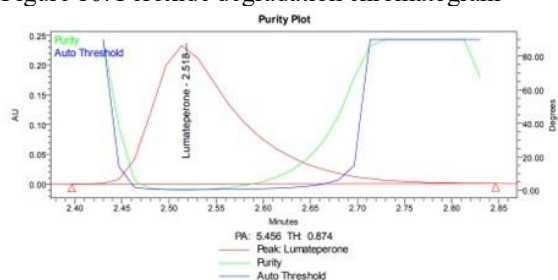


Figure 11: Purity plot for peroxide degradation study
Photolytic degradation study: Degradation in ultra-violet was performed and after study it was found that there is no degradation in the drug. good drug recovery, and theoretical plates was achieved. Purity plot was also given for the study. The chromatograms and the purity plot are given in figure12 and figure 13.

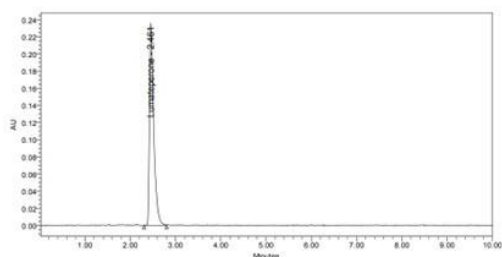


Figure 12: Photolytic degradation study chromatogram

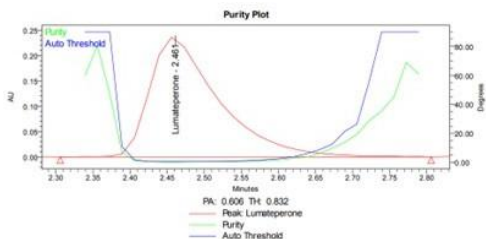


Figure 13: Purity plot for photolytic degradation study

Neutral degradation study: Degradation in water was performed and after study it was found that there is no degradation in the drug. good drug recovery, and theoretical plates was achieved. The chromatograms of the neutral degradation study and the purity plot are given in figure 14 and figure 15.

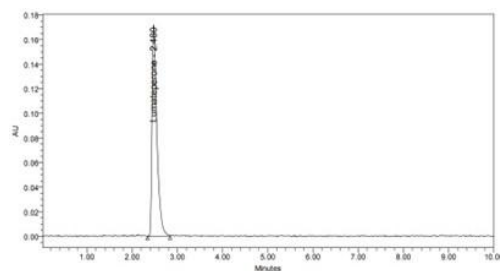


Figure 14: Neutral degradation study chromatogram

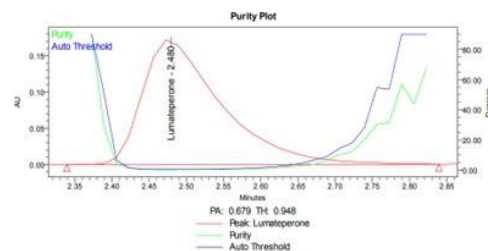


Figure 15: Purity plot for neutral degradation study
GREEN ANALYTICAL EVALUATION

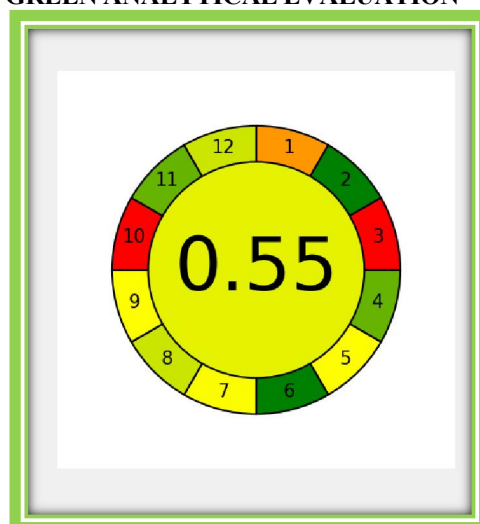


Figure 15: AGREE software-generated score

Score Range	Interpretation
0.00–0.40	Poor Greenness
0.41–0.60	Moderate Greenness
0.61–0.80	Good Greenness
0.81–1.00	Excellent Greenness

Table 13: Proposed interpretation of AGREE scores for analytical method greenness.

The greenness of the developed RP-HPLC method for Lumateperone was evaluated using the Analytical GREENness Metric Approach (AGREE). AGREE assessment is based on the twelve principles of Green Analytical Chemistry and provides a comprehensive evaluation of the environmental impact of an analytical procedure. The developed method achieved an AGREE score of 0.55, indicating moderate compliance with green analytical chemistry principles. The acceptable greenness profile was mainly attributed to the short chromatographic run time (7.0 min), low solvent

consumption, automated instrumental operation, simple sample preparation procedure, and the absence of derivatization steps. However, the overall score was moderately reduced due to the use of acetonitrile as an organic modifier and the off-line nature of the analytical procedure. The AGREE pictogram demonstrated that the developed RP-HPLC method possesses an acceptable environmental profile and can be considered a moderately green analytical procedure suitable for routine quality control analysis of Lumateperone.

Analytical Eco-Scale Assessment

The environmental sustainability of the developed RP-HPLC method for Lumateperone was evaluated using the Analytical Eco-Scale approach. The Analytical Eco-Scale is based on an ideal green analytical procedure with a score of 100, from which penalty points are deducted according to the hazards associated with reagents, energy consumption, and waste generation. The developed chromatographic method employed 0.01 N potassium dihydrogen orthophosphate buffer and acetonitrile in the ratio of 60:40 (v/v) as the mobile phase, with a flow rate of 1.0 mL/min and a run time of 7 min. Accordingly, the total solvent waste generated per analysis was approximately 7 mL, consisting of 2.8 mL of acetonitrile and 4.2 mL of phosphate buffer.

Parameter	Penalty Points
Acetonitrile usage	3
Phosphate buffer	2
Energy consumption	1
Waste generation	3
Total penalty	9
Eco-Scale Score	91

Table 14. Analytical Eco-Scale assessment of the developed RP-HPLC method for Lumateperone.

The developed RP-HPLC method achieved an Analytical Eco-Scale score of 91, indicating an excellent green analytical profile. The high score was primarily attributed to the short chromatographic run time, moderate solvent consumption, and simple analytical procedure. Penalty points were assigned for the use of acetonitrile as the organic modifier and phosphate buffer in the mobile phase. According to the Analytical Eco-Scale classification, analytical procedures with scores greater than 75 are considered excellent green methods. Therefore, the proposed method can be regarded as an environmentally acceptable and sustainable analytical approach suitable for routine quality control analysis of Lumateperone.

CONCLUSION

The developed isocratic RP-HPLC method showed promising performance for the determination of Lumateperone tosylate within a seven-minute run.

Mean recovery of 100.31%, together with repeat-injection and 24-hour precision values of 0.68% and 0.92% RSD, respectively, supported accurate recovery and consistent analytical response. Deliberate changes in flow rate, mobile-phase composition and column temperature yielded peak-area RSD values of 0.20–0.50%, indicating maintained precision under the tested conditions.

The study's principal contribution is the integration of analytical performance with retrospective risk assessment and environmental evaluation. Mobile-phase composition and sample preparation emerged as priorities for method control. Reported AGREE and Analytical Eco-Scale scores of 0.55 and 91, respectively, provided complementary perspectives on the method's environmental profile and identified opportunities for further improvement. Together, these findings support the method's potential for routine pharmaceutical quality control. Reconciliation of the calibration statistics, documentation of actual robustness factor levels and quantitative verification of degradation behaviour remain necessary to strengthen the final validation and stability-indicating claims.

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