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Novel Liquid Chromatography Method with Core Shell Technology Column for Quantification of Lurasidone Hydrochloride in Pharmaceutical Product

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Abstract: This study reports the design and validation of an economical, ultra-high performance liquid chromatography (UPLC) method for the determination of Lurasidone Hydrochloride in pharmaceutical products, with focal interest on the use of core-shell column technology. The employment of core-shell silica column dramatically improved chromatographic performance by providing better resolution, shorter run time, and enhanced peak symmetry than using conventional fully porous columns. Method parameters like mobile phase composition and flow rate were optimized sequentially. ICH guidelines have been followed to validate the method with excellent linearity (r^2 > 0.99), precision (%RSD < 2.0%), accuracy, and robustness. Equivalency has been established between Ultra-Performance Liquid Chromatography (UPLC) and traditional HPLC procedures in comparative studies, validating the method's reliability. The technique is applicable to everyday quality control and impurity profiling of Lurasidone Hydrochloride with the provision of a fast, reproducible, and cost-efficient analytical solution by virtue of core-shell column technology.

Keywords: Lurasidone Hydrochloride, ICH, Ultra-Performance Liquid Chromatography, Validation, Core-Shell

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Introduction

Lurasidone Hydrochloride is an aypical antipsychotic that is used only for the management of schizophrenia in adults and teenagers between 13 and 17 years, also for bipolar depression, either monotherapy or co-administration with lithium or valproate in children and adults 10 to 17 years of age (Loebel *et al.*, 2015; McClellan *et al.*, 2017). Sold under the trade name Latuda, it has the molecular formula $C_{28}H_{37}ClN_4O_2S{\cdot}HCl$ and a molecular weight of about 529.6 g/mol when in the form of its hydrochloride salt. Lurasidone produces its therapeutic effects primarily by blocking dopamine D_2 receptors, thereby controlling the

positive symptoms of schizophrenia. It also opposes serotonin 5-HT_2A and 5-HT_7 receptors, which play a part in enhancing mood and cognitive processes, and is also a partial agonist at 5-HT_1A receptors, which further assists its antidepressant and anxiolytic effects (Meltzer and Massey, 2011; McClellan *et al.*, 2017; Miura *et al.*, 2023).

The pharmaceutical and medical sciences suggested various analytical techniques for the estimation of pharmaceutical products. These techniques include High-Performance Liquid Chromatography (HPLC), Ultra-Performance Liquid Chromatography (UPLC) and spectroscopy techniques, etc. UPLC has emerged as a popular choice because of its improved resolution, speed and sensitivity (Poole, 2004; Sharma, 2020).

UPLC or Ultra-Performance Liquid Chromatography is a modern chromatographic method that makes use of stationary phases with particle sizes usually less than 2 µm and is run at higher pressures compared to conventional HPLC. This result in quicker separations, enhanced resolution, and increased sensitivity. The smaller particle size provides narrower peaks, improved peak shape, and increased efficiency, which makes UPLC very convenient for the quick and precise analysis of Lurasidone hydrochloride in bulk and formulations (Sahu *et al.*, 2018; Bhavyasri *et al.*, 2019; Sharma, 2020).

Core-shell columns provide high resolution at much lower back pressure. They are suitable for both HPLC and UPLC systems, and method development is simplified because of their particular structure, having a solid core surrounded by a thin porous shell. This structure minimizes the diffusion path of analyte molecules, enabling quicker mobile phase flow and increased analysis speed. Compared to traditional fully porous HPLC columns, core-shell columns have a narrower particle size distribution, which leads to higher column efficiency, better resolution, and lower back pressure. Their efficiency is equivalent to UPLC columns.

Validation of the analytical technique is required to confirm accuracy, precision, specificity, linearity, robustness, and reproducibility in compliance with ICH guidelines. A validated technique guarantees accurate results during day-to-day analysis and stability tests of pharmaceutical formulations (Breaux *et al.*, 2003; ICH, 2005; Bhavyasri *et al.*, 2019).

This study reports the design and validation of an economical, ultra-high performance liquid chromatography (UPLC) method for the determination of Lurasidone Hydrochloride in pharmaceutical products, with focal interest on the use of core-shell column technology.

Materials and Methods

Sample of Lurasidone Hydrochloride was obtained as a gift from Raks Pharma Ltd. (Ahmedabad, India). Solvents and reagents of analytical grade were purchased from Merck Specialties Pvt. Ltd. in Mumbai, India. Double-distilled water that passed through a membrane filter was used to prepare the solutions.

Chromatographic Conditions

The separation of sample was done on Waters Acquity, H-Class (UPLC) and Shimadzu Prominence-I LC-2030 C, Boltimate C_{18}, (100 X 4.6) mm, 2.7 µm column with the help of isocratic mobile phase, Buffer (pH 3.0) and Acetonitrile in the ratio of 50:50 v/v. Flow rate was maintained at 1.0 ml/min, sample was filtered and degassed before use. Injection volume was 5.0 µl and ambient temperature was maintained throughout the analytical procedure.

Preparation of Mobile phase

Weighed approximately 2.72 g of Potassium dihydrogen phosphate and transferred in appropriate container, added 1 L of water and sonicated to dissolve. Add 2 ml of Triethylamine and mixed well. Adjust pH with ortho phosphoric acid to 3.0 ± 0.05 and mixed well. Mobile phase was prepared by mixing Buffer (pH 3.0): Acetonitrile in the proportion of 50:50 v/v and stirred well. Finally Sonicated to degas and filtered

through 0.22 µm membrane filter. Same system is also used as diluents for further analysis.

Preparation of Standard Solution

Weighed precisely 24.0 mg of Lurasidone Hydrochloride standard and placed in a 25 ml volumetric flask. Added approximately 15 ml of diluent and sonicated to dissolve and diluted up to the mark using same diluent. Transferred 5.0 ml of this solution into 50 ml volumetric flask, diluted volume with diluent and mixed properly.

Preparation of Sample Solution

Weighed 20 tablets accurately, measured their average weight. Grinded all tablets to fine powder in mortar and pestle. Weigh powder precisely equivalent to approximately 160 mg of Lurasidone Hydrochloride and placed into 200 ml volumetric flask. Added approximately 140 ml diluent and sonicated for approximately 20 min with occasional shaking. Transferred 3 ml of this solution into 25 ml volumetric flask, diluted the volume with diluent and mixed well. Filter the sample solution through 0.22 µm syringe filter.

Validation

The suggested UPLC method was validated according to ICH guideline and the different parameters were measured as mentioned below (ICH, 2005; Branch, 2005; Swartz, 2018):

Linearity: The calibration curve was obtained by graphing a concentration versus area of standard and finding the correlation coefficient.

Precision: The accuracy of an analytical method represents to the similarity of agreement among a set of measurements made on different samples through repeated sampling of the same sample under the stated condition.

Accuracy: Accuracy is in concurrence with acceptable true value and result found. Per cent recoveries were conducted with Lurasidone and Placebo at 50%, 100% and 150% level, triplicate at every level and determined by UPLC.

Robustness: Robustness of the method is capacity not to change when minor intentional alterations in chromatographic conditions are made, i.e., variation in proportion of the mobile phase and small alterations in the flow rate, column oven temperature and pH of buffer solution.

Solution Stability

Solution stability study of the method was evaluated as standard and sample solutions were stored at room temperature and injected at different time intervals under the actual conditions of chromatography protocol.

Method Equivalency between UPLC and HPLC

For evaluation of method equivalency between UPLC and HPLC methods, six individual sample solutions and a diluent standard solution were prepared. These samples were tested by the suggested UPLC method, and the same chromatographic conditions were used on the HPLC system for comparison.

Results and Discussion

This study achieved optimum efficiency while used specified column and solvent system. Drug was successfully estimated in pharmaceutical formulation using developed UPLC method. The chromatograms of standard and sample solutions are shown in Figures 1 and 2. The identical peaks for both the solutions assure optimal functioning of selected chromatographic conditions.

Validation

The aim of this exercise was to demonstrate that the in-house UPLC method is valid for the assay testing of Lurasidone Hydrochloride tablets. The method validation was carried out in accordance with ICH guidelines.

Linearity

Linearity of Lurasidone Hydrochloride was confirmed by analyzing linearity solutions of varying concentrations ranging from 50% to 150 %. Linearity curve was plotted between peak area *vs.* concentration. Linearity result is shown in Table 1 and Figure 3. The linearity data meets the acceptance criteria indicates that the method is linear within the concentration range from 50% to

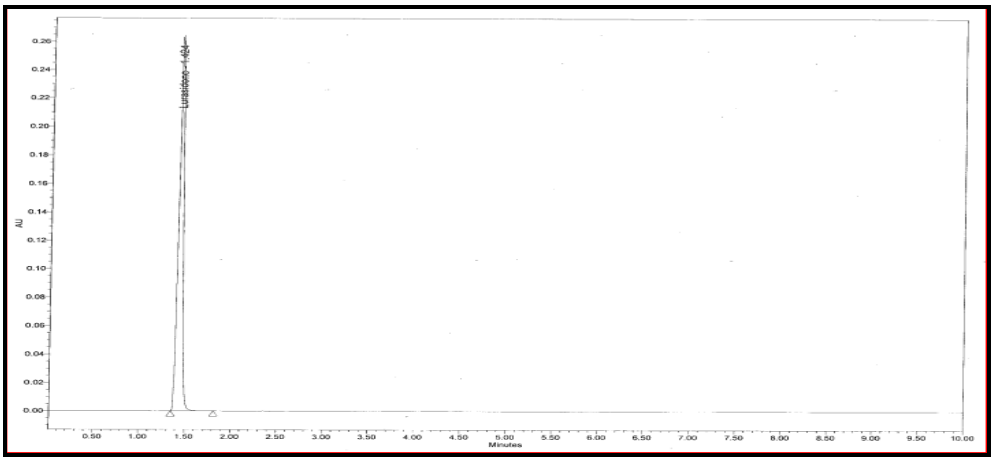

Fig. 1: Chromatogram of Standard Solution.

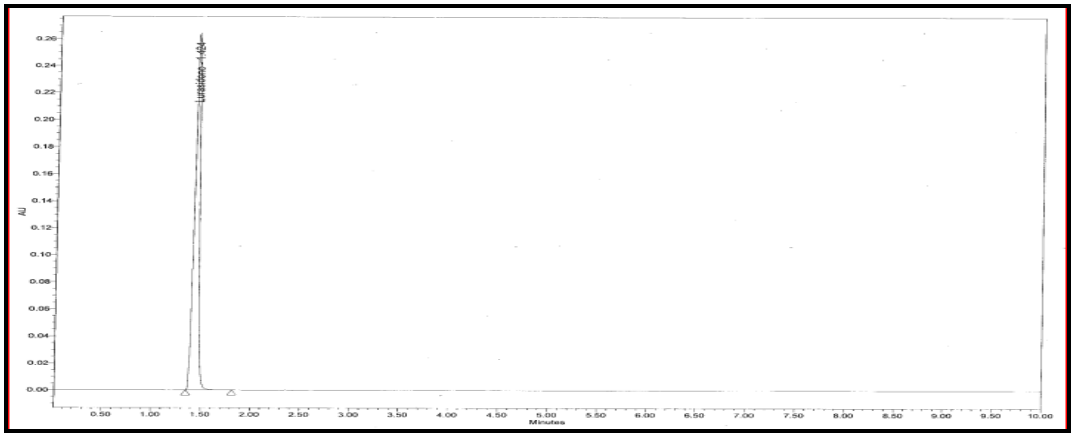

Fig. 2: Chromatogram of Sample Solution.

Table 1: Result of Linearity Study

Linearity level	Concentration (µg/ml)	Area
50 %	48.36	465271
80 %	77.376	744434
100 %	96.720	930542
120 %	116.064	1116650
150 %	145.080	1395813
Correlation Coefficient	0.99667	

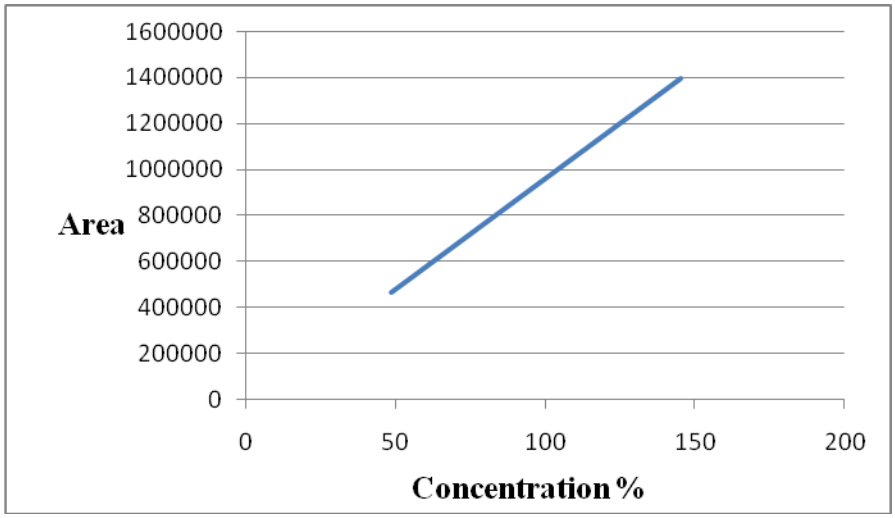

Fig. 3: Linearity Graph of Lurasidone Hydrochloride.

Table 2: Results of Method Precision

Injections Sets	% Assay (Results in %)
1	99.9
2	100.1
3	100.0
4	100.2
5	100.0
6	99.9
Mean	100.0
% RSD	0.11

150% of test concentrations.

Precision

In this precision study, it was concluded that there was no significance difference in % assay and mean % RSD, which were calculated under 2.0 % (Table 2). Therefore, it indicates that the analytical procedure was precise for its intended use.

Accuracy

Recovery samples were prepared in triplicate by spiking Lurasidone Hydrochloride into 50 %, 100 % and 150 % with respect to working concentration of assay method. The result is presented in Table 3. The study found that the mean recovery was 99.6 %. The acceptable range for mean percentage recovery is 98-102%. The results fall within this range, it showed that the analytical method was precise for its specific application.

Robustness

Robustness of an analytical procedure is a measure of its ability to stay unchanged by small, but intentional changes in method parameters and gives an idea of its reliability under normal

Table 3: Results of Accuracy Study

Recovery Level	Amount Added (µg/ml)	Amount Found (µg/ml)	% Recovery	Mean % Recovery	% RSD
50 % Set-1	48.272	47.677	98.8	99.1	0.3
50 % Set-2	48.128	47.832	99.4		
50 % Set-3	48.221	47.864	99.3		
100% Set-1	96.329	96.049	99.7	99.7	0.1
100% Set-2	96.416	96.041	99.6		
100% Set-3	96.167	96.061	99.9		
150% Set-1	144.275	144.001	99.8	100.1	0.3
150% Set-2	144.383	144.878	100.3		
150% Set-3	144.567	144.989	100.3		
Overall average % recovery				99.6	

Table 4: Results of Robustness

Change in Parameters	Value	Mean Results (in %)	% Difference
Actual	As Such	99.9	N/A
Flow rate (± 10 %)	0.9 ml/ min	99.8	0.1
	1.1 ml/ min	100.0	0.1
Column Oven Temperature (±5 °C)	Temperature 35°C	100.1	0.2
	Temperature 45°C	99.7	0.2
Mobile Phase Composition	+ 10 ml Acetonitrile	100.0	0.1
	- 10 ml Acetonitrile	99.6	0.3
Buffer pH	+ 0.2 pH	99.7	0.2
	- 0.2 pH	100.1	0.2

conditions. Robustness study is conducted by comparing the results obtained with changed conditions with the results obtained using normal chromatographic conditions. Robustness was conducted by the variations in the various chromatographic conditions with reference to normal condition and results are given in Table 4. Within acceptance criteria established under the study of robustness, results fall well within it. From robustness result, the test procedure can be considered as sufficiently robust as supported by modifying flow rate, column oven temperature

Table 5: Results of stability study

Time Interval	Results in %	% Difference
Initial	100.0	NA
37 Hours	99.9	0.1
80 Hours	100.3	0.3

Table 6: Results of Method Equivalency between UPLC and HPLC

S. No.	Results (%)	
	UPLC (Precision)	HPLC (Precision)
1	99.9	100.1
2	100.1	100.0
3	100.0	99.9
4	100.2	100.2
5	100.0	100.1
6	99.9	100.2
Mean	100.0	100.1
% RSD	0.11	0.12

and Buffer pH.

Stability of Analyte in Solution

Stability of analyte in solution was done for standard and sample solutions. Standard and sample solutions were made and run according to test procedure. Some parts of these solutions were left at room temperature and tested at varied time intervals. Results at the long term period were compared to initial results and results of standard and sample solutions are depicted in Table 5. The result shows stability of both the solutions sample as well as standard, even after the duration of 80 h.

Method Equivalency between UPLC and HPLC

For evaluation of method equivalency between UPLC and HPLC methods, six individual sample solutions and a diluent standard solution were prepared. These samples were tested by the suggested UPLC method, and the same chromatographic conditions were also used on the HPLC system for comparison. Both the UPLC and HPLC systems were injected with all six samples as per the developed methodology. The finding of the method equivalency study is presented in Table 6. According to the result of this research, there was no appreciable difference in the % values of dissolution, and the average % RSD was less than 2.0%, meaning that the analytical technique was accurate and appropriate for its intended purpose.

Conclusion

Analytical method worked out for the quantitation of Lurasidone Hydrochloride has been suitably validated on the basis of the conventional validation parameters. Linearity was proven in the range of 50% to 150% of the target concentration with a good relationship between the peak area and concentration as indicated by correlation coefficient 0.99667. This is an indication of the method being appropriate for quantitative determination. Accuracy was established by recovery studies at three levels of concentrations with a mean recovery of 99.6%, which was within the acceptable range of 98% to 102%, and hence the method was considered reliable for accurate measurement. Precision was established by repeated assay, giving a % RSD of 0.11%, which was well within the acceptable limit of 2.0%,

showing that the method is consistent and reproducible. The ruggedness of the method was verified by deliberate variations in parameters like flow rate, column oven temperature, mobile phase ratio, and buffer pH. Results were as consistent and within the desired limits as always, demonstrating the method's ability to withstand minor variations in conditions of analysis. Further, solution stability experiments verified that the standard and sample solutions remained stable for a period up to 80 h at room temperature and were within a negligible variation. The method equivalency study between UPLC and HPLC showed no significant difference in % dissolution, with mean % RSD below 2.0%, confirming the accuracy and suitability of the analytical method for its intended purpose. In general, the method was found to be linear, accurate, precise, stable, and robust, and thus considered ideal for the repeated analysis of Lurasidone Hydrochloride in drug formulations. Equivalency has been established between UPLC and traditional HPLC procedures in comparative studies, validating the method's reliability.

Ethical Statement

No animal or microbes have been used or sacrificed for this study, hence Ethical Approval not required.

Author Contributions

Each author has equally contributed in planning the study, performing the analysis, writing and editing the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

The authors declare no conflicts of interest.

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