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APPLICATION OF QUALITY BY DESIGN APPROACH FOR DEVELOPMENT AND VALIDATION OF ANALYTICAL RP-HPLC METHOD FOR LURASIDONE IN BULK AND TABLET DOSAGE FORM

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ABSTRACT

The current research is aimed to study and investigate the estimation of Lurasidone in the bulk drug and its tablet dosage by a developed and validated RP-HPLC method. The method was developed using Quality by Design principles. All the computations for the current optimization study and statistical analysis were performed using Design Expert® software. The 3^3 randomized response surface designs with a Box-Behnken design were used with 17 trial runs to study the impact of three factors on the three key response variables. The Flow rate, pH of mobile phase and Mobile phase composition were selected as independent variables. The retention time, theoretical plate number and tailing factor were selected as dependent variables based on risk analysis. The resulting data was processed into Design Expert 11 software and analysed statistically using analysis of variance (ANOVA).The analysis were carried out using HPLC of Waters, series 2482 (Binary pump, Orochem C18 column, Waters 2489 -UV-Visible Detector, Breeze 2 software) with manually injecting 10 µl of mobile phase consisting of Methanol : Water (85:15), maintaining isocratic flow. The calibration was linear in the range of 200-300µg/ml. The RSD for accuracy, precision and robustness was observed within the range (less than 2%). System suitability parameters were within the limit. The validated limit of quantitation (LOQ) and limit of detection (LOD) was 24.80µg/ml and 8.18µg/ml respectively. The assay result of marketed formulation for Lurasidone was 98.76 %. Hence accurate, precise, and robust method were developed and validated.

KEYWORDS: HPLC, Lurasidone, Quality by Design, Validation, Design Expert.

INTRODUCTION[1-8]

Pharmaceutical industry is constantly in search of new techniques to ensure and enhance product quality in terms of its safety, quality and efficacy. However, still problems with drug recall, manufacturing failure cost, scale up issues and regulatory burden in recent past produces huge challenge for industry. In traditional approach the product quality and performance are predominantly ensured by end product testing, with limited understanding of the process and critical process parameters. Regulatory bodies are therefore focusing on implementing Quality by Design (QbD), a more precise and science-based approach that improves process understanding by reducing process variation and the enabling process control strategies. QbD approach helps to deal quality issue efficiently by analysing problems and their root cause. It comprises of identifying all critical attributes including process parameter and material attributes. These parameters help in getting better process understanding thereby resulting in development of a robust process with least errors. This leads in identifying a design space where all the parameters could result in quality product. Changes in any such parameters during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Working within the design space is not considered as a change. Movement out of the design space is a change and would normally initiate a regulatory post approval change process.

Lurasidone is chemically known as (1R, 2S, 6R, 7S)-4{[1R, 2R)-2-{[4-(1, 2-benzothiazol-3-yl) piperazine-1-yl] methyl}-4-azatricyclo] decane-3, 5-dione and its empirical formula is $C_{28}H_{36}N_4O_2S$. It is having molecular weight 492.676 g/mole. Lurasidone is an atypical antipsychotic that is D2 and 5-HT2A antagonist (mixed serotonin and dopamine activity). It is thought that antagonism of serotonin receptors can improve negative symptoms of psychoses and reduce the extrapyramidal side effects that are often associated with typical antipsychotics.

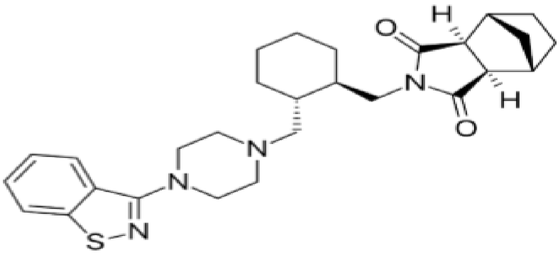

Fig. 1: Structure of Lurasidone.

Various analytical methods have been reported for the assay of Lurasidone. They include UV spectrometric method and RP-HPLC. Literature survey reveals that no analytical method for determination of Lurasidone by Quality by Design (QbD) approach is reported. Therefore in present study the analytical method is developed to quantify Lurasidone while meeting the method performance criteria based on regulatory requirements, such as linearity, accuracy, precision, system suitability, and robustness.

MATERIAL AND METHOD

Material and Instruments

Reference standards of Lurasidone were obtained as gift samples. Marketed formulation of Lurasidone was procured from local market. HPLC grade water was obtained from Merck (India).HPLC grade Methanol was obtained from Finar Pvt Ltd. Analytical grade Ortho Phosphoric Acid was purchased from Finar Pvt Ltd. The wavelength for analysis was selected with the help of Shimadzu UV-Visible spectrophotometer (UV-2450, Software- UV probe). The HPLC system consisted Manual Injecting port and UV-Visible detector (Water corp.). The mobile phase was sonicated with Digital Ultrasonic Cleaner (Citizen). The pH of mobile phase was measured with the help of Ana lab Instruments, pH cal Digital pH meter. The output signal was monitored and compiled using Breeze 2 manager software (Waters HPLC, Waters 1525 binary pump, Waters 2489 UV-Visible Detector). All the computations for the current optimization study and statistical analysis were performed using Design Expert® software (Design Expert trial version 11; State-Ease Inc., Minneapolis, MN, USA).

Chromatographic Conditions

The separation was achieved on Orochem C18 column. Isocratic elution with mobile phase composition of methanol: water (85:15% v/v) at the flow rate of 1.2 ml/min was carried out. The detection was monitored at 316 nm and injection volume was 10 µl. The peak purity was checked with the UV/Visible detector.

Preparation of standard stock solution

Accurately weighed quantity of Lurasidone 50 mg was transferred to 50 ml volumetric flask, shaken vigorously for five minutes and volume was made up to mark with diluent. From 50 ml, pipette out 2 ml and diluted upto 10 ml with diluent, which is equal to 200 µg/ml of Lurasidone.

Preparation of sample solution of Lurasidone

To determine the content of the drugs in pharmaceutical formulations, 20 tablets were weighed and pulverized using a mortar and pestle to get fine powder. An amount equivalent to 50 mg of Lurasidone was transferred to 50 ml standard volumetric flask, and volume was added till the mark by adding methanol and sonicated for 10 minutes. An aliquot portion of the filtrate was further diluted to get final concentration of 200µg/ml 10 ml of Methanol were added and sonicated for 10 minutes. Equal volumes of standard and sample solutions were injected separately after equilibrium of stationary phase. The chromatograms were recorded and the response i.e. peak area of major peaks were measured.

RESULT AND DISSCUSSION

The purpose of the present study was to study and investigate the estimation of Lurasidone in the bulk drug and its tablet dosage by a developed and validated RP-HPLC method using QbD principles. The method was developed and validated using orochem c18 column with UV detection at 316 nm.

Method optimization

The pure drug of Lurasidone was injected into the HPLC system and run in different solvent systems. Mixture of different solvents were tried in order to determine optimum chromatographic conditions for effective elution of Lurasidone. After several permutation and combination, it was found that the methanol and water gives satisfactory results as compared to other mobile phases. Finally, the optimal composition of the mobile phase selected as per design, which gives acceptable peak shape and symmetry of Lurasidone.

Application of Design of experiments for method optimization

The 3^3 randomized response surface designs with a Box-Behnken design were used with 17 trial runs to study the impact of three factors on the three key response variables. In this design 3 factors were evaluated, each at 3 levels, and experimental trials were performed at all possible combinations. The 1) Flow rate, 2) pH of mobile phase, 3)Mobile phase composition were selected as independent variables and Retention Time (RT), Theoretical Plate number (TPN) and Tailing Factor were selected as dependent variables based on risk analysis. The resulting data was processed into Design Expert 11 software and analysed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to determine the influence of flow rate, pH and mobile phase composition on dependent variables.

Table No. 1: Translation of Coded level in actual value.

Level of variables	Flow rate (ml/min)	pH	Mobile phase composition ratio (methanol: water)
Low level (-1)	1	2.8	75:25
Medium level (0)	1.2	3.0	85:15
High level (+1)	1.4	3.2	95:05

Table No. 2: Layout of Actual Design of DOE ANOVA for response surface quadratic model (Retention Time).

		Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3
Std	Run	A: Mobile Phase	B: pH	C: Flow Rate	Retention Time	Plate count	Tailing
9	1	85	2.8	1	4.3	6244	1.11
5	2	75	3	1	5.5	6421	1.25
10	3	85	3.2	1	6.3	5325	1.1
14	4	85	3	1.2	3.96	6564	1.03
3	5	75	3.2	1.2	6.59	6582	0.89
8	6	95	3	1.4	3.16	4779	0.96
1	7	75	2.8	1.2	4.58	5739	1.26
11	8	85	2.8	1.4	3.03	4379	1.07
2	9	95	2.8	1.2	3.43	4699	0.95
13	10	85	3	1.2	3.97	6564	1.03
6	11	95	3	1	4.43	5167	0.88
7	12	75	3	1.4	4.09	5215	1.21
16	13	85	3	1.2	3.96	6464	1.03
17	14	85	3	1.2	3.99	6667	1.02
12	15	85	3.2	1.4	4.56	5008	0.84
15	16	85	3	1.2	3.85	5419	1.2
4	17	95	3.2	1.2	4.91	4106	1

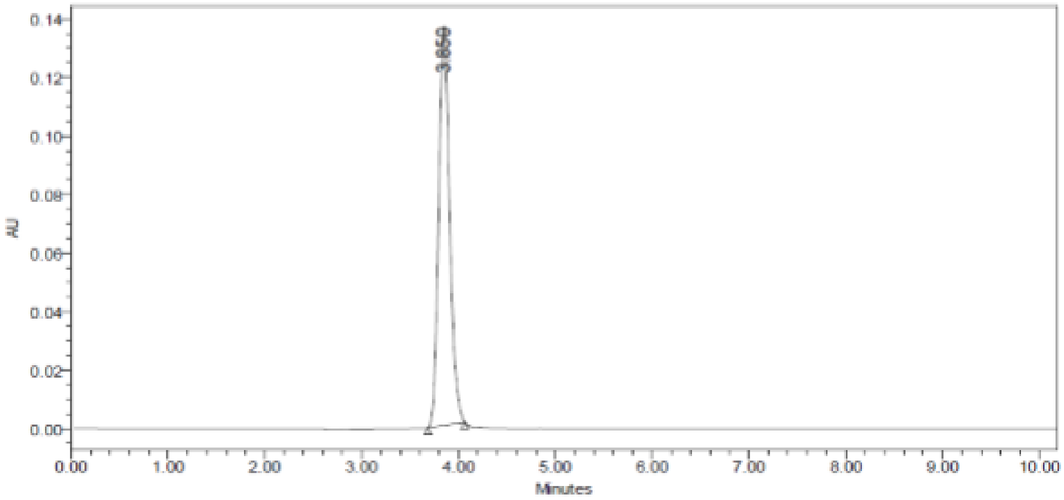

Fig. 2: Chromatogram of Lurasidone.

System suitability

System suitability test is a pharmacopoeia requirement and it is used to verify, whether the resolution and reproducibility of the chromatographic system are adequate for analysis to be done. The tests were performed by collecting data from five replicate injections of standard drug solution.

Table No.3: System Suitability Parameters.

Sample name	Retention time (min)	Area	Plate Count	Tailing Factor
Lurasidone	3.968	1032820.6	6273	1.078

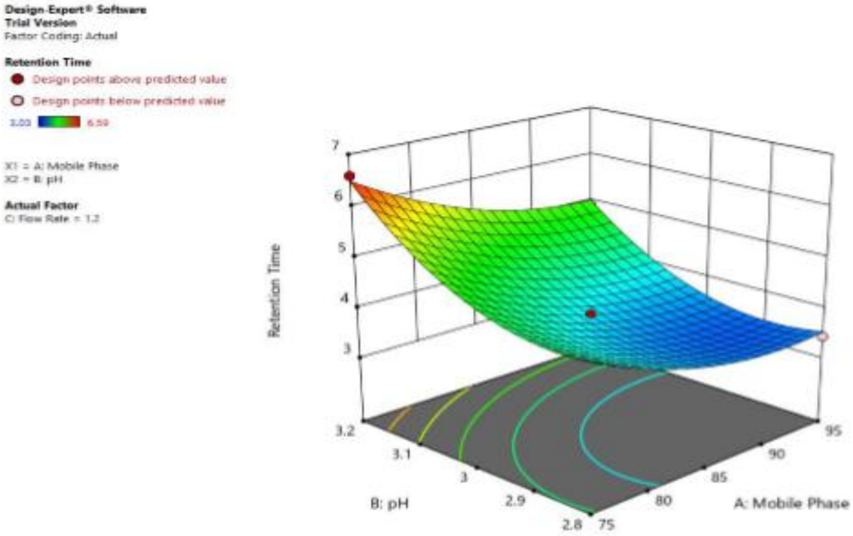

Fig. 3: Response plot for retention time against pH and Mobile Phase.

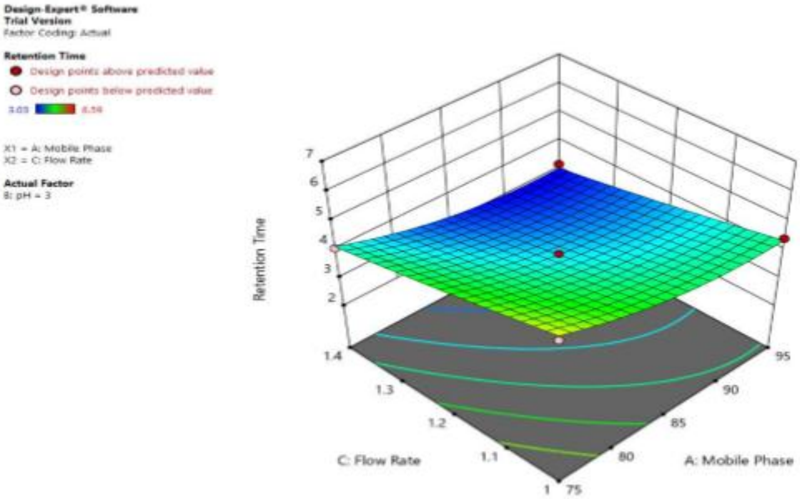

Fig. 4: Response plot for retention time against Flow Rate and Mobile Phase Composition.

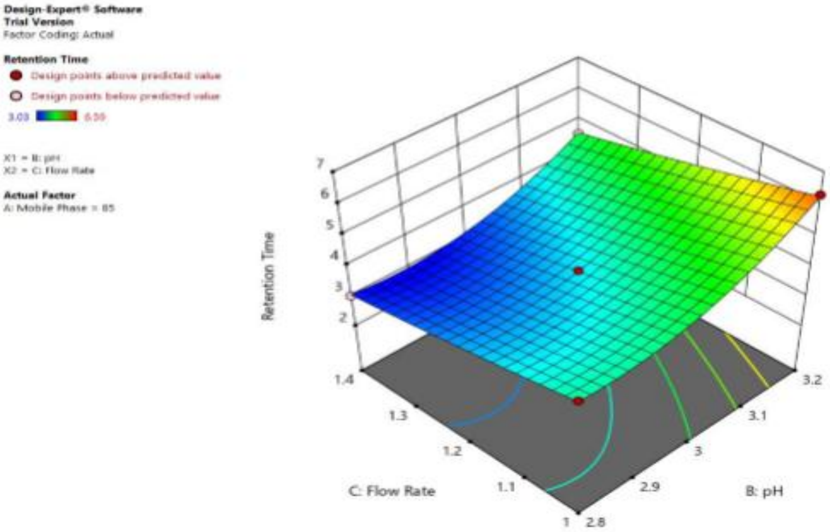

Fig. 5: Response plot for retention time against pH and Flow rate.

Method Validation

- ***Linearity***

Linearity was performed by diluting standard stock solution. From stock solution aliquots of 2.00, 2.25, 2.50, 2.75, 3.00 ml diluted to 10ml with diluent such that the final concentration of Lurasidone in the range of 200 to 300 µg/ml.

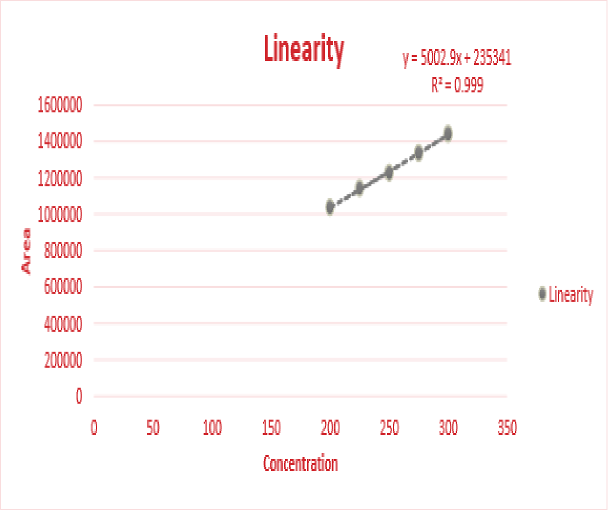

Fig. 6: Linearity graph of Lurasidone.

- ***Accuracy***

The accuracy of an analytical method is determined by applying the method to analysed samples, to which known amounts of analyte have been added. The accuracy is calculated from the test results as the percentage of analyte recovered by the assay. Accuracy of the method was demonstrated at three different levels i.e. 80, 100 and 120% by spiking known quantity of standard drugs into an analysed sample in triplicates.

Table No. 4: Recovery Study of Lurasidone.

Sample	Amount Added	%Recovery	%RSD
80%	100	99.50	0.3896
100%	125	100.45	0.5859
120%	150	100.20	0.79

- ***Precision***

Prepare six different test solution of the 100% test concentration from the same sample matrix. Inject duplicate injections of each test solution. Precision of an analytical method is usually expressed as standard deviation or relative standard deviation.

Table No. 5: Method Precision for Lurasidone.

Sample Name	Concentration (µg/ml)	%RSD
Lurasidone	200	0.9629

- ***Robustness***

Robustness of an analytical method is determined by analysis of aliquots from homogenous lots by differing physical parameters that may differ but are still within the specified parameters of the assay. Demonstrate the robustness of the method, deliberate changes in chromatographic conditions were carried out viz. change in wavelength maxima (±2 nm) and change in mobile phase composition (± 2.0 ml).

Table No. 6: Robustness.

Parameters	%RSD		
Change in wavelength maxima(± 2 nm)	**316 nm**	**318 nm**	**314nm**
	0.1941	0.1904	0.1781
Change in mobile phase composition(± 2.0 ml)	85+15	87+13	83+17
	0.1941	0.1904	0.1781

- ***Limit of Detection and Limit of quantification***

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantified as an exact value. The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. It is calculated based on standard deviation (SD) of the response and slope of the curve(S).

Table No. 7: LOD and LOQ.

Sample	LOD	LOQ
Lurasidone	8.18 µg/ml	24.80g/ml

CONCLUSION

The RP-HPLC method developed and validated for estimation of Lurasidone using Quality by Design approach as per the guidelines given by ICH from pharmaceutical dosage form. The proposed high-performance liquid chromatographic method has also been evaluated for accuracy, precision and robustness and proved to be convenient and effective for the quality control of Lurasidone. The developed method can be applied for the assay of commercial tablets containing Lurasidone.

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