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DEVELOPMENT AND VALIDATION OF STABILITY INDICATING ASSAY METHOD FOR ESTIMATION OF LURASIDONE HYDROCHLORIDE IN TABLET DOSAGE FORM

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KEYWORDS:

Lurasidone HCl, Stability indicating RP-HPLC Method, Validation.

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ABSTRACT

A simple, rapid, economical, precise and accurate stability indicating RP-HPLC method for Lurasidone HCl In its Pharmaceutical Dosage Form has been developed. The separation was achieved by Inertsil ODS 3V (250× 4.6mm) column and Water: Methanol (10:90) as mobile phase, at a flow rate of 1 ml/min. Detection was carried out at 285 nm. Retention time of Lurasidone HCl was found to be 5.050 min. The method has been validated for linearity, accuracy and precision. Linearity observed for Lurasidone HCl 5-15µg/ml. Developed method was found to be accurate, precise and rapid for estimation of Lurasidone HCl in its Pharmaceutical Dosage Form. The drug was subjected to stress condition of hydrolysis, oxidation, photolysis and Thermal degradation. The proposed method was successfully applied for the estimation of the drug in commercial Pharmaceutical dosage form.

INTRODUCTION:

Lurasidone is an atypical antipsychotic that is a D2 and 5-HT2A (mixed serotonin and dopamine activity) to improve cognition. Chemically Lurasidone HCl is (3aR,4S,7R,7aS)-2-[[(1R,2R)-2-[[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl] methyl] cyclohexyl] methyl] hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione Hydrochloride (figure 1). 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[1-2]

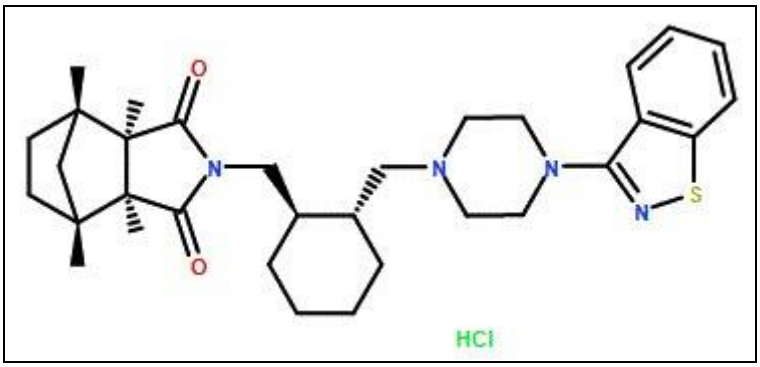

Figure 1: Chemical structure of Lurasidone HCl

A literature survey for the determination of Lurasidone hydrochloride in pure and formulations revealed that various methods such as HPLC[3], RP-HPLC[4-8], UV spectrophotometric[10-13] methods and LC/MS[9] method for determining in rat plasma were available. However, some of these methods have certain drawbacks like longer run time, complexity in the composition of the mobile phase, a higher amount of buffer that can affect column performance. It affects sensitivity, precision and accuracy of the method. So, an attempt was made to develop simple, fast and validated RP-HPLC method for the estimation of Lurasidone hydrochloride in marketed tablet formulation.

MATERIALS AND METHODS

Apparatus and Instruments

The HPLC system (LC-20AT) consisting of a column {Inertsil ODS 3V (250× 4.6mm)}, 20µL fixed loop Injector, SPD 20A UV Detector and LC software.

Reagents and Materials

Methanol and water used were of HPLC. Lurasidone HCl was procured from Yash Pharmaceuticals.

Preparation of standard solutions

Lurasidone HCl (Standard stock solution: 100µg/ml)

A 10 mg of Lurasidone HCl was weighed and transferred to a 100 ml volumetric flask. Volume was made up to the mark with methanol.

Lurasidone HCl (Standard working solution: 10µg/ml)

Take 1 ml from the Lurasidone HCl stock solution and transferred to 10 ml volumetric flask. 5 ml of diluent was added to it and sonicated. Then final volume was made with mobile phase which was used in particular trials.

Sample preparation

Take Tablet powder equivalent to 10mg Lurasidone HCl and Transfer to 100ml volumetric flask and add 60ml of mobile phase. It was sonicated for 30 min with intermediate shaking and diluted to the volume with mobile phase (Sample stock solution 100µg/ml). Then the solution was filtered through 0.45 µm poly tetra fluoro ethylene (PTFE) filter by discarding first 2 ml of the filtrate. Take 1ml from this solution and transfer to 10ml volumetric flask and make the volume with mobile phase (Sample working solution 10µg/ml).

Selection of wavelength

Lurasidone HCl standard solution (10µg/ml) prepared in Methanol. This solution was then scanned in UV region of 200-400 nm and maximum Absorbance was recorded.

Chromatographic separation

Standard solution of 10µg/ml of Lurasidone HCl was injected in column {Inertsil ODS 3V (250× 4.6mn)} with 20µl micro-syringe. The chromatogram was run for appropriate time with previously degassed mobile phase Water: Methanol (10:90) with flow rate 1.0 ml/min. The detection was carried out at wavelength 285 nm. The chromatogram was stopped after separation achieved completely. Data related to peak like area, height, retention time, resolution etc. were recorded using software.

System suitability

System suitability is generally performed to check whether the developed method suits the intended purpose or not. It can be demonstrated by injecting five replicates of standard solution (10µg/ml) into HPLC system and the results obtained were used to express the system suitability of the developed method.

Forced degradation study of Lurasidone HCl by RP-HPLC

I. Acid degradation

Acid decomposition studies were performed by refluxing 1ml of stock solution (Standard and Sample). This was taken in a separate 10 ml of volumetric flask. 2 ml of 0.1 N HCl solutions was added in each and mixed well and put for 7 hrs at 70 ºC in 250 ml Round bottom flask. After time period the content was cooled to room temperature. Then 2 ml of 0.1 N NaOH solution was added. Then the volume was adjusted with diluent to get 10µg/ml for Lurasidone HCl. From the resultant solution (10µg/ml) 20µl was injected into the HPLC system, and the chromatogram was recorded to

assess the stability of the standard and sample.

II. Base degradation

Base decomposition studies were performed by refluxing 1 ml of stock solution (Standard and Sample). This was taken in a separate 10 ml of volumetric flask. 2 ml of 0.1 N NaOH solutions was added in each and mixed well and put for 7 hrs at 70 ºC in 250 ml Round bottom flask. After time period the content was cooled to room temperature. Then 2 ml of 0.1 N HCl solution was added. Then the volume was adjusted with diluent to get 10µg/ml for Lurasidone HCl. From the resultant solution (10µg/ml) 20µl was injected into the HPLC system, and the chromatogram was recorded to assess the stability of the standard and sample.

III. Oxidative degradation

Oxidation decomposition studies were performed by refluxing 1 ml of stock solution (Standard and Sample). This was taken in a separate 10 ml of volumetric flask. 2 ml of 3% H_2O_2 solutions was added and mixed well and put for 7 hrs at 70 ºC in 250 ml Round bottom flask. After time period the content was cooled to room temperature. Then the volume was adjusted with diluent to get 10µg/ml for Lurasidone HCl. From the resultant solution (10µg/ml) 20µl was injected into the HPLC system, and the chromatogram was recorded to assess the stability of the standard and sample.

IV. Photolytic degradation

1 ml of stock solution (Standard and Sample) was transferred in to 10 ml of volumetric flask. This solution was put in UV Chamber for 10 hrs. Then the volume was adjusted with diluent to get 10µg/ml for Lurasidone HCl. From the resultant solution (10µg/ml) 20µl was injected into the HPLC system, and the chromatogram was recorded to assess the stability of the standard and sample.

V. Thermal degradation

1 ml of stock solution (Standard and Sample) was transferred in to 10 ml of volumetric flask. This solution was put in Oven 110 ºC for 6 hrs. After time period the content was cooled to room temperature. Then the volume was adjusted with diluent to get 10µg/ml for Lurasidone HCl. From the resultant solution (10µg/ml), 20µl was injected into the HPLC system, and the chromatogram was recorded to assess the stability of the standard and sample**.**

Validation of RP-HPLC method

The proposed method was validated for specificity, linearity, accuracy, precision, limit of detection (LOD), limit of quantification (LOQ), robustness and system suitability as per international conference on harmonization (ICH) guidelines[14]

Specificity

Specificity is the ability of the analytical method to assess the analyte even in the presence of

components which may expect to be present in the sample. Blank, standard and sample solutions were prepared and injected into the HPLC system to check the interference and to establish specificity.

Linearity

The linearity for Lurasidone HCl was assessed in range of 5-15µg/ml for Lurasidone HCl. 0.5, 0.75, 1.0, 1.25, 1.5 ml solutions were pipette out from the Stock standard solution of Lurasidone HCl (100µg/ml) and transfer to 10 ml volumetric flask and make up with mobile phase to obtain 5, 7.5, 10, 12.5 and 15µg/ml for Lurasidone HCl. These solutions were analyzed by injecting 10µl into the HPLC system for 3 replicates. In term of slope, intercept and correlation co-efficient value, the graph of peak area obtained verses respective concentration was plotted.

Precision

Results should be expressed as Relative standard deviation (RSD) or coefficient of variance.

(A) Repeatability

Sample standard solution containing Lurasidone HCl (10µg/ml) was injected six times and areas of peaks were measured and %RSD was calculated.

(B) Intraday Precision

Sample standard solution containing Lurasidone HCl (5, 10, 15µg/ml) was injected three times in same day and areas of peaks were measured and %RSD was calculated.

(C) Interday Precision

Sample standard solution containing Lurasidone HCl (5, 10, 15µg/ml) was injected three times in different days and areas of peaks were measured and %RSD was calculated.

Accuracy

5µg/ml of drug solution was taken in three different flask label A, B and C. Spiked 80%, 100%, 120% of standard solution in it and diluted up to 10ml. The area of each solution peak was measured at 285 nm. The amount of Lurasidone HCl was calculated at each level and % recoveries were computed.

LOD and LOQ

The LOD & LOQ was estimated from 3 calibration curves used to determine linearity. For this, a series of solutions were injected, and the signal-to-noise ratio for each injection was calculated.

The LOD may be calculated as, LOD = 3.3 × (SD/Slope)

The LOQ may be calculated as, LOQ = 10 × (SD/Slope)

Where, SD= Standard deviation of Y-intercepts of 3 calibration curves.

Slope = Mean slope of the 3 calibration curves.

Robustness

Robustness was evaluated by making deliberate changes to the chromatographic parameters of

the method. Following parameters were changed one by one and their effect was observed on the same homogenous sample.

1. Flow rate of mobile phase was changed (± 0.1 ml/min) 0.9 ml/min and 1.1 ml/min.
2. Ratio of Mobile phase was changed (±2) Water: Methanol (08-92) and Water: Methanol (12- 88).

RESULTS AND DISCUSSION

Selection of wavelength

Standard solution of Lurasidone HCl (10µg/ml) was scanned between 200-400 nm using UV-visible spectrophotometer. The wavelength selected for determination of Lurasidone HCl was 285 nm (Figure 2).

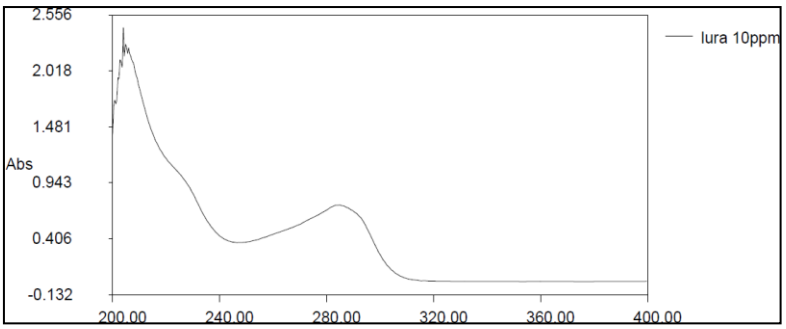

Figure 2: UV Spectra of Lurasidone HCl (10µg/ml) (Maximum Absorbance at 285 nm)

Selection of Mobile phase for Lurasidone HCl

Trial contains various mobile phase which are considered of Methanol and Water in different proportions and different volumes at different flow rate were tried. On the basis of various trial the mixture of Water: Methanol (10:90) at 1 ml/min flow rate, proved to be better than the other mixture in terms of peak shape, theoretical plate and asymmetry (figure 3).

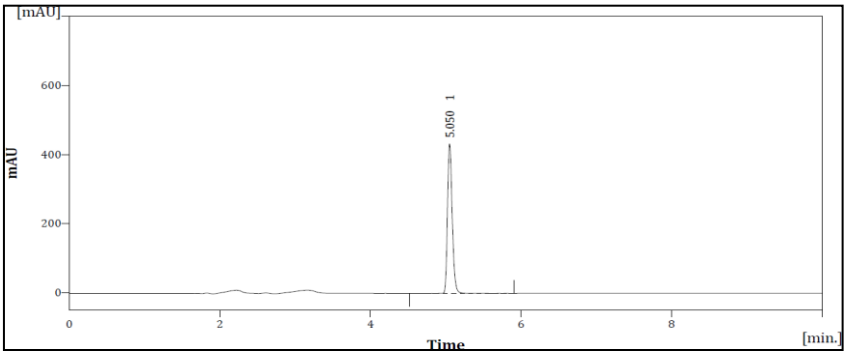

Figure 3: HPLC Chromatogram of Lurasidone HCl (10µg/ml) in Mobile phase Water: Methanol (10:90) (Flow rate 1.0 ml/min)

Forced degradation study of Lurasidone HCl by RP- HPLC

(I) Acid degradation

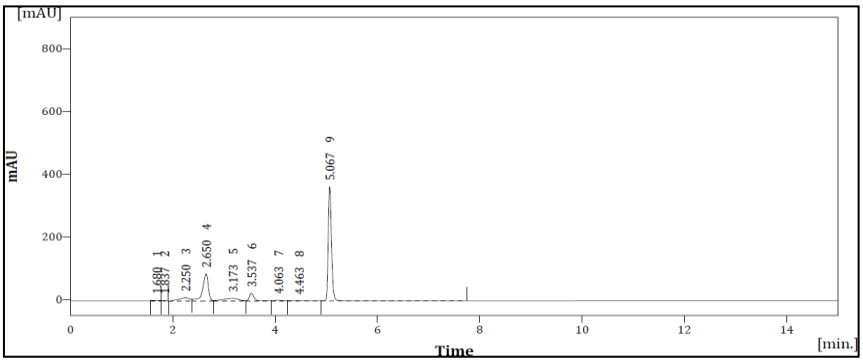

Figure 4: Acid Degradation sample (7 hrs at 70 ºC)

(II) Base degradation

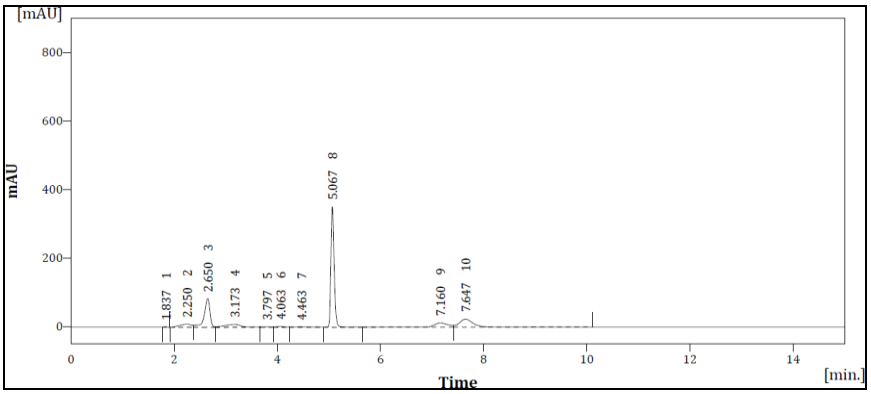

Figure 5: Base Degradation sample (7 hrs at 70 ºC)

(III) Oxidative degradation

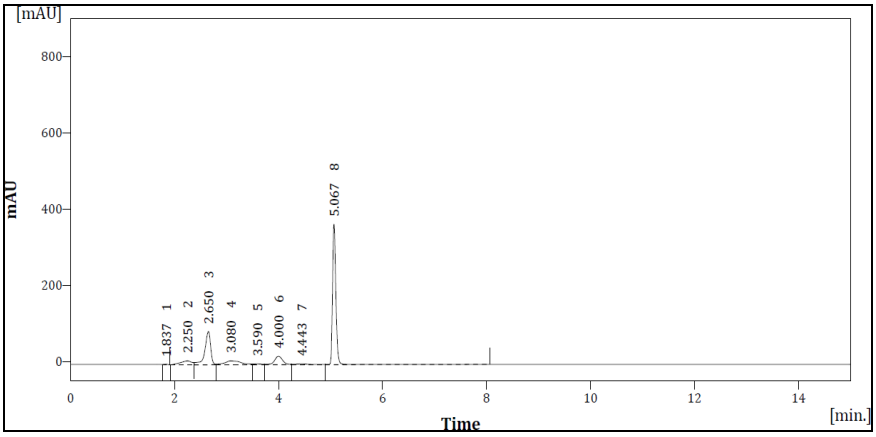

Figure 6: Oxidation Degradation sample (7 hrs at 70 ºC)

(IV) Photolytic degradation

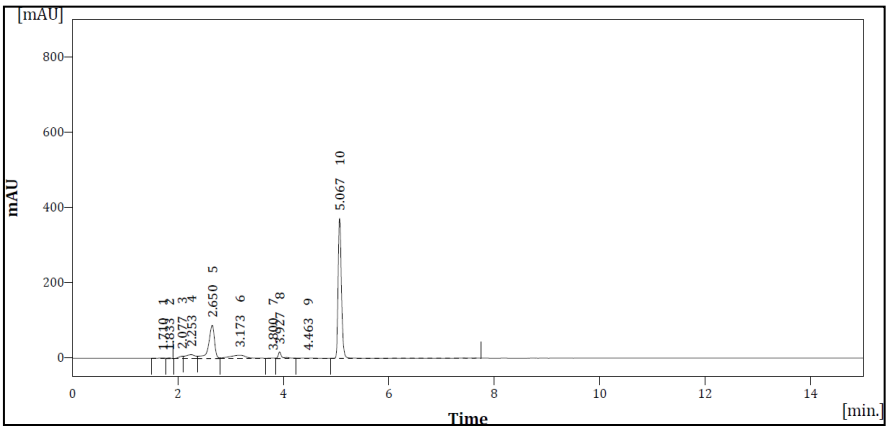

Figure 7: Photo Degradation sample (UV light_10 hrs RT)

(V) Thermal degradation

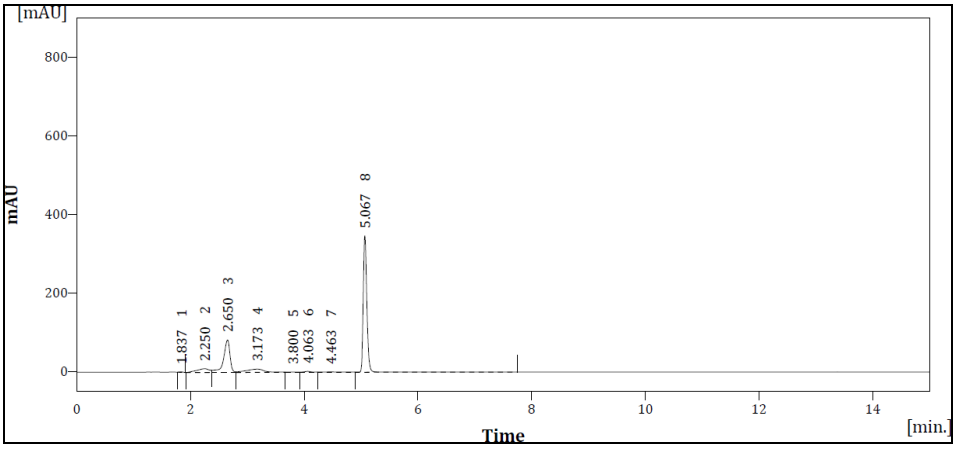

Figure 8: Thermal Degradation sample (110 ºC for 6 hrs)

Table I: % Degradation of Lurasidone HCl in standard and sample

Condition	Area	%Degradation Standard	Area	%Degradation Sample
Acid	1660.205	12.27	1637.808	13.45
Base	1603.944	15.24	1568.398	17.12
Oxidation	1699.170	10.21	1671.527	11.67
Photo	1696.974	10.32	1669.024	11.80
Thermal	1552.432	17.96	1562.549	17.43

Validation of stability indicating RP-HPLC method:

Specificity:

From the chromatogram of Blank, standard and sample solutions, it was observed that there is no interference of any substances which may likely to be present in sample when it is compared with

retention time of standard (Table II).

Table II: Specificity data for Lurasidone HCl

Test	Retention time
Standard	5.057 min
Sample	5.063 min

Linearity:

Correlation co-efficient for calibration curve Lurasidone HCl was found to be 0.999.

The regression line equation for Lurasidone HCl is as following: y = 190.31x - 8.6338. (figure 9).

Table III: Linearity data for Lurasidone HCl

Sr. No.	Concentration (µg/ml)	Area
1	5	957.125
2	7.5	1395.775
3	10	1911.274
4	12.5	2348.839
5	15	2859.518

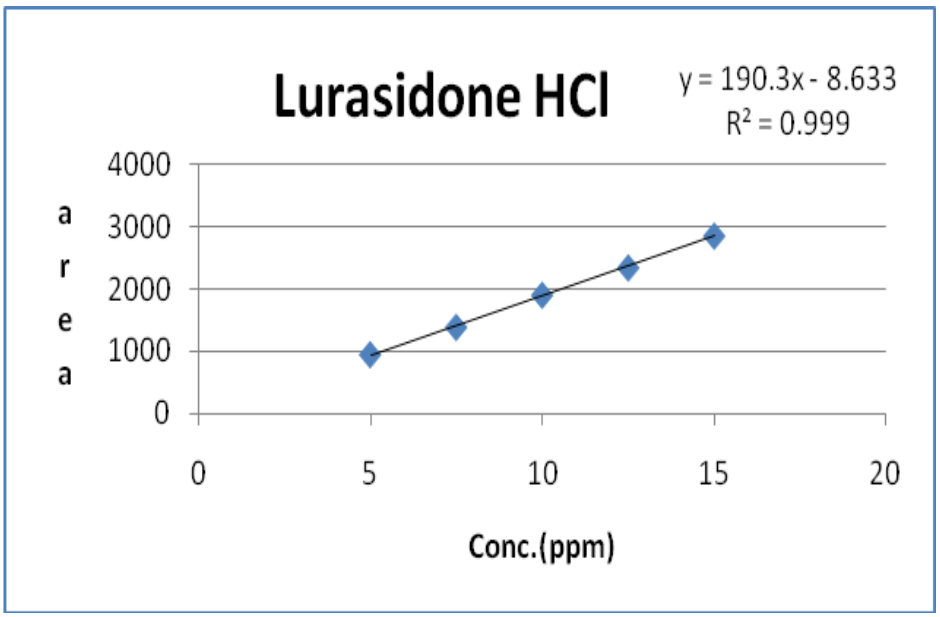

Figure 10: Calibration Curve of Lurasidone HCl (5-15 µg/ml)

Precision

(I) Repeatability

The % RSD for Lurasidone HCl (10µg/ml) was found to be 0.376 (Table IV).

Table IV: Repeatability data for Lurasidone HCl

Sr. No.	Concentration (µg/ml)	Area	Mean ± S.D (n=6)	% R.S.D
1	10	1898.016	1890.137±7.109	0.376
2		1886.558		
3		1882.782		
4		1897.839		
5		1882.638		
6		1892.992		

(II) Intraday precision

% RSD in Intraday precision for Lurasidone HCl was found in range of 0.178-0.490. (Table V).

Table V: Intraday precision data for Lurasidone HCl

Sr. No.	Concentration (µg/ml)	Mean ± S.D (n=3)	% R.S.D
1	5	958.395±2.215	0.231
2	10	1898.688±9.307	0.490
3	15	2874.191±5.109	0.178

(III) Interday precision

% RSD in Interday precision for Lurasidone HCl was found in range of 0.435-1.254 (Table VI).

Table VI: Interday data for Lurasidone HCl

Sr. No.	Concentration (µg/ml)	Mean ± S.D (n=3)	% R.S.D
1	5	947.144±11.874	1.254
2	10	1909.368±8.318	0.435
3	15	2845.380±13.112	0.461

Accuracy:

The percentage recovery and % RSD were calculated. The mean percentage recovery of lurasidone hydrochloride and % RSD were found to be within limits (table VII).

Table VII: Recovery data for Lurasidone HCl

Sr. No.	Conc. Level (%)	Sample amount (µg/ml)	Amount Added (µg/ml)	Amount recovered (µg/ml)	% Recovery	Average (% Recovery)	% RSD
1	80 %	5	4	4.014	100.354	98.509	1.754
2		5	4	3.877	96.927		
3		5	4	3.930	98.246		
4	100 %	5	5	5.035	100.698	101.427	1.576
5		5	5	5.134	102.689		
6		5	5	5.195	103.894		
7	120 %	5	6	6.036	100.606	99.638	0.843
8		5	6	5.951	99.181		
9		5	6	5.948	99.126		

LOD and LOQ:

Calibration curve was repeated for three times and the standard deviation (SD) of the intercepts was calculated. Then LOD and LOQ were calculated as follows (table VIII):

Table VIII: LOD and LOQ data for Lurasidone HCl

LOD	LOQ
LOD = 3.3 x (SD / Slope) = 3.3 x (70.35/190.31) =1.22µg/ml	LOQ = 10 x (SD / Slope) = 10x (70.35/190.31) =3.70µg/ml

Robustness:

The obtained results (table IX) indicated the minor changes in each condition did not affect the method and the system suitability parameters were found to be within limits.

Table IX: Robustness data for Lurasidone HCl

Sr. No.	Area at Flow rate (- 0.2 ml/min)	Area at Flow rate (+ 0.2 ml/min)	Area at Mobile phase (- 2 ml)	Area at Mobile phase (+2 ml)
1	1905.366	1891.976	1924.327	1848.856
2	1897.745	1903.750	1935.875	1859.972
3	1912.918	1898.630	1922.318	1846.951
% R.S.D	0.398	0.311	0.380	0.380

Assay of Marketed formulation:

Results for assay and %RSD of marketed formulation (Atlura 40) was found within limit (Table X).

Table X: Assay of Marketed formulation

Sr. No.	Label claim (mg)	Result (mg)	% Assay	average % Assay	SD	%RSD
1	40	38.526	96.314	96.007	0.409	0.426
2	40	38.217	95.542			
3	40	38.466	96.165			

CONCLUSION

RP-HPLC method was developed for Forced degradation study of Lurasidone HCl which includes Acid, Base, Oxidative, Photo and Thermal degradation. With proposed RP-HPLC method, separation of drug and its degradation products were achieved with good resolution. Proposed method used simple mobile phase i.e. Water: Methanol (10:90) which was very cost effective. Retention time of Lurasidone HCl was found to be 5.050 min with a flow rate of 1.0 ml/min. The proposed method was simple, rapid, accurate, economic and precise. Therefore proposed method can be used for routine analysis of Lurasidone HCl in tablets.

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