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# STABILITY INDICATING RP-HPLC METHOD FOR DETERMINATION AND VALIDATION OF LURASIDONE HCL IN BULK AND PHARMACEUTICAL DOSAGE FORMS

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## ABSTRACT

**Objective:** To develop and validate a simple, selective, rapid and stability indicating reverse phase high performance liquid chromatographic (RP-HPLC) method for the analysis of Lurasidone HCl in bulk and its tablet dosage forms.

**Method:** Several trials were made by changing the mobile phase composition and finally the drug was resolved on a Thermo ODS, C18, (150 X 4.6 mm, 5µ) column, using the mobile phase consisting of sodium dihydrogen ortho phosphate buffer (pH 6.5) and acetonitrile in 60 : 40 ratio and pumped at a flow rate of 0.8 ml/min at ambient temperature. Studies were performed on Waters HPLC system equipped with PDA detector, the response was monitored at 230 nm. The developed method was validated as per ICH guidelines.

**Results:** The retention time of Lurasidone HCl was found to be 3.33±0.02 minutes. The calibration curve was linear over the concentration range of 10-60 µg/ml ($r^2$=0.9999). The limit of detection for Lurasidone HCl was found to be 0.25 µg/ml and the quantification limit was about 0.75 µg/ml. The accuracy of the method was established based on the recovery studies and the percentage recovery was in the range of 99.95 to 100.01. The drug was degraded in all the conditions like acid, alkali, oxidative, thermal and photolytic conditions by proposed RP-HPLC method.

**Research Value**: The proposed method can be applied for the routine analysis of Lurasidone HCl in bulk and its pharmaceutical dosage forms in quality control laboratory.

**Keywords**: *RP- HPLC; Lurasidone HCl; ICH; Validation.*

## INTRODUCTION

Lurasidone[1] is an atypical antipsychotic drug approved by the U.S. Food and Drug Administration (FDA) for treatment of Schizophrenia on October 28, 2010. Lurasidone HCl, IUPAC name (3aR,4S,7R,7aS)-2-[((1R,2R)-2-{[4-(1,2-benzisothiazol-3-yl)-piperazin-1-yl]methyl}cyclohexyl)methyl]hexahydro-1*H*-4,7-methanisoindol-1,3-dione hydrochloride (Fig.1). The efficacy of Lurasidone HCl in schizophrenia is mediated through a combination of central dopamine Type 2 (D2) and serotonin Type 2 (5HT2A) receptor antagonism and it gives antipsychotic activity. Literature search reveals following methods were reported viz., LC-MS in rat plasma[2], UV Spectrophotometry[3-5] and HPLC[6,7] in tablets. There is a need for developing simple, fast and economic method for the estimation of Lurasidone HCl in pharmaceutical dosage form. Hence the authors made an attempt to develop simple stability indicating RP-HPLC method for quantification of Lurasidone HCl in bulk and its pharmaceutical dosage form.

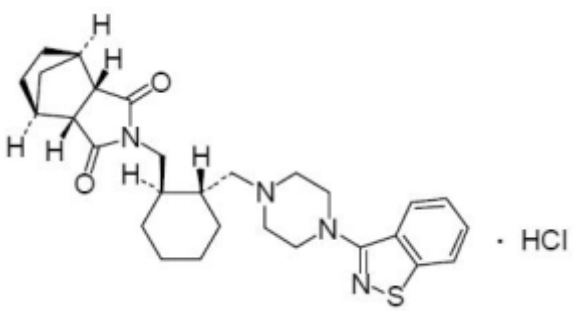


***Fig. 1:*** *Structure of lurasidone hydrochloride*

## MATERIALS AND METHODS

### *Chemicals and Reagents*

Lurasidone HCl was provided as a gift sample by Richard Pharmaceuticals, Hyderabad. Tablets were procured from the local market; HPLC grade methanol, water were purchased from S. D. Fine chemical Laboratories, Mumbai, India. Sodium dihydrogen ortho phosphate and acetonitrile were procured from Bioleo Labs, Hyderabad, India.

### *Instrumentation*

Waters HPLC Quaternary gradient 2695 series, equipped with auto sampler, temperature control, auto injector with capacity to inject 5 µL to 500 µL and PDA detector. Thermostat column compartment connected

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that has a capacity to maintain 5°C to 60°C column temperature. Waters HPLC System is equipped with Empower-2 software.

***Experimental Conditions***

The HPLC system was operated isocratically at flow rate of 0.8 ml/min at 30°C ±0.5°C for 30 min. The mobile phase found to be most suitable for analysis was sodium dihydrogen orthophosphate buffer (pH6.5) and acetonitrile in 60:40%v/v and detection was carried out at 230 nm.

***Preparation of Mobile phase***

About 60 ml of phosphate buffer pH adjusted to 6.5 with diluted orthophosphoric acid solution) and 40 ml of acetonitrile taken in a 100 ml volumetric flask was used as mobile phase which was filtered through a 0.45 µ membrane filter.

***Diluent*:** Mobile phase.

***Preparation of standard solution of Lurasidone***

Stock solution of Lurasidone HCl was prepared by dissolving accurately weighed 40 mg of standard drug transferred initially in 50 ml diluent taken in 100 ml volumetric flask (400 µg/ml) and further made up to the mark with mobile phase. From this about 1 ml of standard stock solution was transferred into 10 ml volumetric flask and diluted to volume with diluent to get final concentration of 40 µg/ml.

***Preparation of sample solution of Lurasidone***

Accurately weighed and finely powdered not fewer than 20 tablets. Accurately weighed and transferred the powder equivalent to 40 mg of Lurasidone HCl into a 100 ml volumetric flask and 50 ml of diluent was added, and sonicated for 30 minutes with intermittent shaking at controlled temperature and diluted to volume with mobile phase. The solution was filtered through 0.45 µ membrane filter. Transferred 1 ml of the above solution into a 10 ml volumetric flask and made up to the mark with diluent.

## RESULTS

**Method development and optimization**

Some important parameters like pH of the mobile phase, concentration of the acid or buffer solution, etc., were tested for a good chromatographic separation. Trials showed that an acidic mobile phase with reverse phase C18 column gives symmetric and sharp peaks. Mobile phase composition of sodium dihydrogen orthophosphate buffer (pH 6.5) and acetonitrile in 60:40 (v/v) at a flow rate of 0.8 ml/min showed good resolution. For the quantitative analytical purposes the wavelength was set at 230 nm. For the quantitative determination of Lurasidone HCl in formulations, initially standard solution was injected into the column five times and the retention time of Lurasidone HCl was found to be 3.33±0.02 min (Fig.2). Then the sample solution was injected into the system and the resulting chromatogram was recorded (Fig.3) for quantification of Lurasidone HCl in capsules. The % assay was found to be 99.99%.

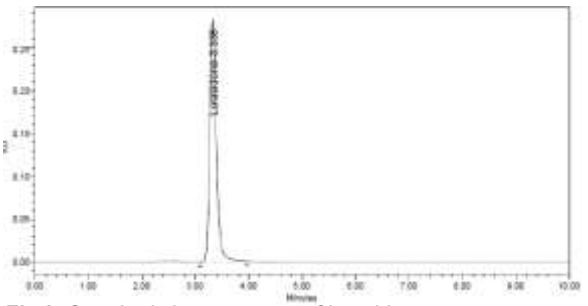

***Fig.2:*** *Standard chromatogram of lurasidone*

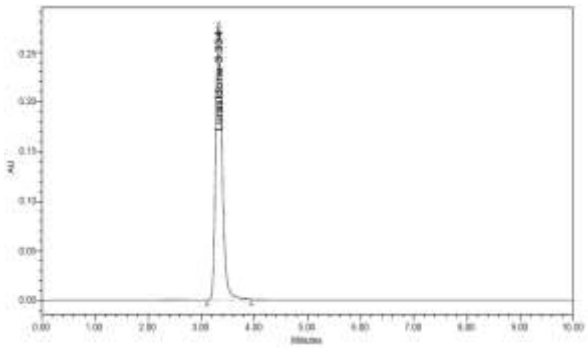

***Fig.3:*** *Chromatogram of lurasidone HCl sample solution*

## METHOD VALIDATION[8-10]

The developed method was validated as per ICH Q2 (R1) guidelines.

***Accuracy***

The accuracy of the method was determined at three different concentration levels 80 %, 100 % &120 % by recovery experiments. The recovery studies were carried out in triplicate on composite blend collected from 20 tablets of Lurasidone HCl and analyzed as per the proposed method. The percentage recovery was found to be in the range of 99.95 % to 100.01 % which were within the limits. The results of accuracy (Table 1) revealed that the method was more accurate.

***Table 1:*** *Recovery studies of lurasidone*

| Sample | Level (%) | Amount added (µg/ml) | Amount Recovered (µg/ml\) | % * Mean Recovery |
|---|---|---|---|---|
| Lurasidone | 80 | 32 | 32.02 | 99.95 |
| | 100 | 40 | 40.05 | 99.97 |
| | 120 | 48 | 48.12 | 100.01 |

**Average of three determinations*

***Precision***

The intra-day precision study of Lurasidone HCl was carried out by estimating the peak responses for six determinations on the same day with15 µg/ml concentration and inter-day precision study of Lurasidone HCl was carried out by estimating the peak responses for six determinations on different days using 15 µg/ml of Lurasidone HCl solution and % RSD value was calculated. The results of precision (Table 2) revealed that the method was more precise.

***Table 2:*** *System and method precision of lurasidone*

| S. No | Peak area of lurasidone | |
|---|---|---|
| | System Precision | Method Precision |
| 1 | 2409109 | 2396552 |
| 2 | 2393725 | 2397645 |
| 3 | 2392514 | 2398812 |
| 4 | 2398451 | 2389856 |
| 5 | 2388914 | 2395545 |
| 6 | 2388585 | 2398832 |
| Avg | 2395216 | 2396207 |
| Std Dev | 7703.1153 | 3365.6192 |
| %RSD | 0.322 | 0.140 |

### *Linearity of detector response*

To establish linearity of the proposed method, six different sets of drug solution was prepared and analyzed. Standard curve was constructed in the concentration range of 10-60 µg/ml for lurasidone HCl (Fig. 4). Slope, intercept and the correlation coefficient were determined and the results are shown in Table 3.

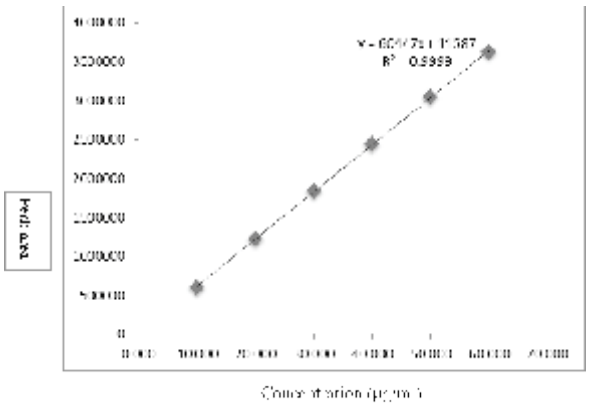

***Fig.4:*** *Calibration curve of lurasidone*

***Table 3:*** *System suitability parameters*

| Parameters | Lurasidone |
|---|---|
| Linearity Range | 10-60(µg/ml) |
| Regression coefficient($R_2$) | 0.9999 |
| System precision (% RSD ) | 0.332 |
| Method precision (% RSD ) | 0.140 |
| Accuracy | 99.95-100.01% |
| LOD | 0.25µg/ ml |
| LOQ | 0.75µg/ml |

### *Limit of detection (LOD) and Limit of quantization (LOQ)*

The limit of detection and limit of quantization for Lurasidone HCl were calculated from the linearity data using relative standard deviation of the response and slope of the calibration curve. The limit of detection of a compound is defined as the lowest concentration of analyte that can be detected. The limit of quantification is the lowest concentration of a compound that can be quantified with acceptable precision and accuracy. The LOD & LOQ values of Lurasidone HCl were found to be 0.25 µg/ml and 0.75 µg/ml respectively.

### *Robustness*

The robustness of analytical method was determined by analysis of aliquots from homogenous lots by varying the chromatographic parameters like flow rate, mobile phase composition, pH and their impact on retention time and peak area were studied. The method was demonstrated to be robust over an acceptable working range of its HPLC operational parameters.

## FORCED DEGRADATION STUDIES

### *Acid degradation sample*

Weighed and finely powdered not fewer than 20 Tablets. Accurately weighed and transferred powder equivalent to 40 mg of Lurasidone HCl into a 200 ml round bottom flask containing 100 ml of freshly prepared 0.1N of HCl and sonicated for 30 minutes with intermittent shaking at controlled temperature. Then it was left aside for 12 hrs. After 12 hrs, filtered the solution through filter paper and neutralized the solution with suitable base. 1 ml of filtrate was diluted to 10 ml with mobile phase. The resulting solution was injected into HPLC and the resulting chromatogram is recorded (Fig. 5).

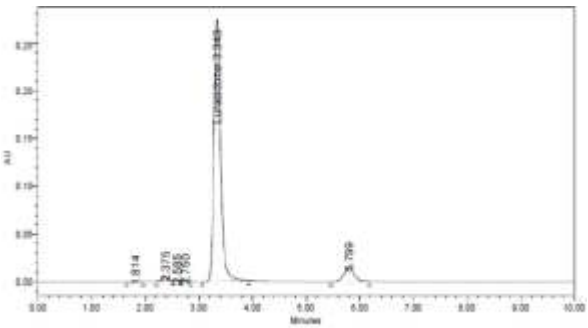

***Fig.5:*** *Chromatogram for lurasidone HCl - acid degradation*

### *Base degradation sample*

Weighed and finely powdered not fewer than 20 tablets. Accurately weighed and transferred powder equivalent to 40 mg of Lurasidone HCl into a 200 ml round bottomed flask and 100 ml of freshly prepared 0.1N NaOH was added, and sonicated for 30 minutes with intermittent shaking at controlled temperature. Then it was left aside for 12 hrs. After 12 hrs filtered the solution through filter paper and neutralized the solution with suitable acid. About 1 ml of filtrate was diluted to 10 ml with mobile phase then the resulting solution was injected into HPLC and the chromatogram was recorded (Fig. 6).

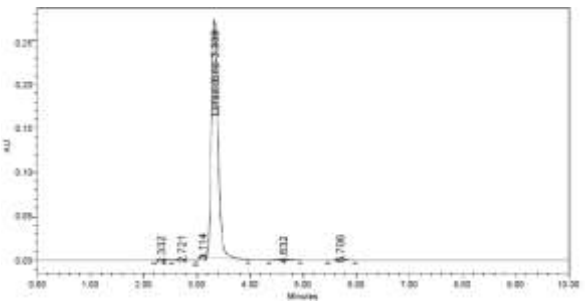

***Fig.6:*** *Chromatogram for lurasidone HCl - base degradation*

***Peroxide degradation sample***

Weighed and finely powdered not fewer than 20 Tablets. Accurately weighed and transferred powder equivalent to 40 mg of Lurasidone HCl into a 200 ml round bottomed flask and 50 ml of freshly prepared 10% hydrogen peroxide was added, and sonicated for 30 minutes with intermittent shaking at controlled temperature. It is left aside for 12 hrs. After 12 hrs, filtered the solution through filter paper. About 1 ml of filtrate was diluted to 10 ml with mobile phase (diluent). The resulting solution was injected to HPLC and the chromatogram was recorded (Fig. 7).

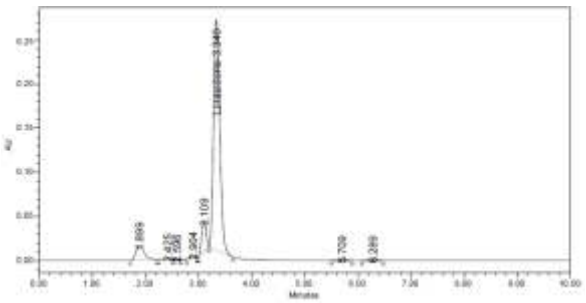

***Fig.7:*** *Chromatogram of $H_2O_2$ stressed sample*

***Thermal degradation sample***

Sample equivalent to 40 mg of Lurasidone HCl was quantitatively transferred into a clean and dry Petri dish and spread. Petri dish was placed in an oven which was maintained at 100°C for 12 hrs. After 12 hrs, contents were transferred into 100 ml volumetric flask which contained 50 ml of diluents, sonicated for 10 minutes and diluted to volume with diluent. Further the solution was filtered through filter paper. About 1 ml of filtrate was diluted to 10 ml with mobile phase. The resulting solution was injected into HPLC and the resulting chromatogram was recorded (Fig. 8).

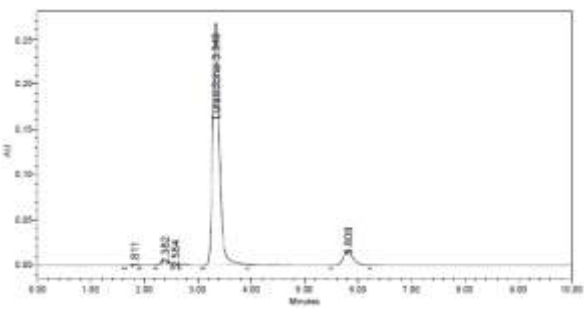

***Fig.8:*** *Chromatogram of UV stressed sample*

***Photolytic degradation***

Sample quantitatively equivalent to 40 mg of Lurasidone HCl was transferred into a clean and dry petri plate which was placed in UV chamber for 12 hrs. After 12 hrs contents were transferred to a 50 ml volumetric flask and 30 ml of diluent was added, sonicated for 10 minutes and diluted to volume with diluent. The solution was filtered through filter paper. From this 1 ml of filtrate was diluted to 10 ml with mobile phase. The resulting solution was injected into HPLC and the chromatogram was recorded (Fig. 9).

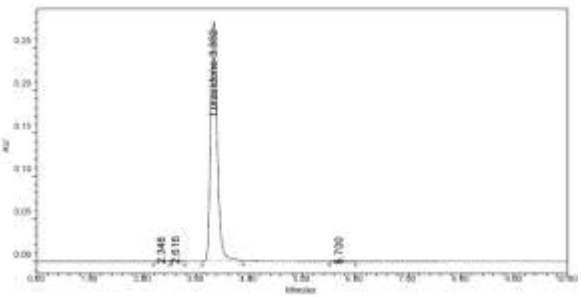

***Fig.9:*** *Chromatogram of thermal degradation*

The drug degraded in all the above conditions by proposed HPLC method and the results of stability testing are given in Table 4, which indicate a high degree of selectivity of the method.

***Table 4:*** *Forced degradation studies for lurasidone*

| Stressed Conditions | $R_t$ (min) | Peak area | %Purity | % Degradation |
|---|---|---|---|---|
| Standard drug | 3.33 | 2395925 | 100 | - |
| Acid degradation | 3.34 | 2265230 | 94.36 | 5.64 |
| Alkali degradation | 3.33 | 2281576 | 95.04 | 4.96 |
| Oxidative degradation | 3.34 | 2151776 | 89.63 | 10.37 |
| Photolytic degradation | 3.34 | 2307204 | 96.10 | 3.90 |
| Thermal degradation | 3.33 | 2299192 | 95.77 | 4.23 |

## CONCLUSION

The proposed method was found to be simple, fast, robust, more precise and highly accurate under the proposed experimental conditions. In the developed method, chromatographic run time was 10 min that allows the analysis of large samples in short period of time. Hence the developed method can be used for routine analysis for estimation of Lurasidone HCl in bulk and its pharmaceutical dosage forms.

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**CONFLICT OF INTEREST:** The authors report that there are no conflicts of interests.

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