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Research Article

DEVELOPMENT AND VALIDATION OF RP-HPLC METHOD FOR ESTIMATION OF LURASIDONE HYDROCHLORIDE IN BULK AND PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

A simple, selective and rapid reverse phase high performance liquid chromatographic (RP-HPLC)method for the analysis of LurasidoneHCl in bulk and in tablet dosage form has been developed and validated. The method involves use of Indapamide as internal standard. Sample was resolved on a HiQSil C18 HS (250mm X 4.6 mm i.d., particle size 5µ) column. The mobile phase consisted of Methanol and Phosphate Buffer (0.01M, pH 3) in the ratio of 80:20 *v/v* which was sonicated to degas and delivered at a flow rate of 1ml/min at ambient temperature. The retention time of LurasidoneHCl was 5.3±0.05 minutes. Studies were performed using an HPLC system equipped with a PDA detector; the response was monitored at 231nm. The method is specific to Lurasidone and able to resolve the drug peak from internal standard and formulation excipients. The calibration curve was linear over the concentration range of 5-25 µg/ml (r^2=0.996). The limit of detection for Lurasidone was found to be 0.62µg/ml and the quantification limit was about 1.82µg/ml. The accuracy of the method was established based on the recovery studies. The proposed method can be applied to the routine analysis of LurasidoneHCl in bulk and in tablet dosage form.

Keywords: Lurasidone Hydrochloride, Indapamide, ICH, Validation.

INTRODUCTION

Lurasidone is an atypical antipsychotic drug approved by the U.S. Food and Drug Administration (FDA) for treatment of Schizophrenia on October 28, 2010[1].

Lurasidone Hydrochloride, chemically is (3aR,4S ,7R,7aS) – {(1R,2R) –2 -[4 -(1,2 - benzisothiazol-3-yl) piperazin –1– ylmethyl] cyclohexylmethyl } hexahydro - 4, 7- methano -2Hisoindole – 1,3 - dione hydrochloride (Fig.1)[2]. The efficacy of Lurasidone Hydrochloride in schizophrenia is mediated through a combination of central dopamine Type 2 (D2) and serotonin Type 2 (5HT2A) receptor antagonism and it givesantipsychotic activity.Lurasidone is metabolized in the liver via the enzyme CYP3A44. This means that its plasma concentrations may be increased when combined with CYP3A4 inhibitors like ketoconazole or grape fruit juice, possibly leading to more side effects. As with other atypical neuroleptics, Lurasidone should not be used in elderly patients because it puts them at an increased risk for a stroke or transient ischemic attack[3,4].

Literature search reveals following methods reported viz., simple spectrophotometric method for the estimation of Lurasidone in tablet dosage form[5,6] , Simple RP-HPLC method for quantitative analysis of Lurasidone[7,8]and LCMS method for quantification of Lurasidone in rat plasma and its application in pharmacokinetic studies[9].

There is a need for developing simple and economicmethods in HPLC, so we proceeded withHPLC and validated as per the ICHguidelines[10]. The present analytical workcomprises of economic simple, precise, rapid, sensitiveand accurate method for the estimation ofLurasidone Hydrochloride bulk and dosage form.

EXPERIMENTAL

MATERIALS AND METHODS

Chemicals and Reagents

LurasidoneHCl was provided as a gift sample by Wokhardt Pharmaceuticals, Aurangabad and Indapamide by Mylan Laboratories Ltd, Hyderabad. Both were used as such, without any further purification. Methanol (HPLC grade) was purchased from S. D. fine chemical Laboratories, Mumbai, India, Water (HPLC grade).

Instruments

Jasco Model V-550 UV-Visible Double beam spectrophotometer, ElgaLabwater (PURELAB UHQ-II) HPLC water purification system, Shimdazu Model AY-120 Balance and Jasco HPLC system comprising: Model PU 2080 Plus pump, Rheodyne sample injection port, HiQSiL C_{18} Columns, MD 2010 PDA detector, Borwin- PDA software (version 1.5)was used.

Chromatographic Conditions

The mobile phase consisting of methanol: 0.01MKH_2PO_4 buffer (adjust the pH 3 with o-phosphoric acid) in the ratio of 80:20 *v/v*, was filteredthrough 0.45µ membrane filter, sonicated and was pumped from the solvent reservoir. The flow rate of mobile phase was maintained at 1ml/min and the response was monitored at 231nm with a run timeof 10min. The volume of injection loop was 20µl.The column and the HPLC systems were kept at ambient temperature.

Preparation of Standard Solution of LurasidoneHCl

Stock solution of LurasidoneHCl was prepared by dissolving accurately weighed 10 mg of drug initially in methanol in 10ml volumetric flask and further dilutions were made by dilution of appropriate volume of stock solution with mobile phase.(The final concentrationis 10µg/ml).

Preparation of stock solution of IS

Stock solution of Indapamide was prepared by dissolving accurately weighed 10 mg of Indapamide initially in methanol in 10ml volumetric flask and further dilutions were made with mobile phase to get (5µg/ml) concentration.

RESULTS

This optimized method led to the retention time of 5.3±0.1 min. for LurasidoneHCl and 3.6 min. for Indapamide. The system suitability parameters were within limits.

METHOD VALIDATION

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

Specificity

The specificity of the method was ascertained by peak purity profiling studies. The peak purity values were found to be more than 0.997, indicating the non interference of any other peak of degradation product, formulation excipients or impurity.

Linearity and Range

Linearity was tested for the range of concentrations 5-25µg/ml. Each sample in five replicates was analyzed and peak areas were recorded. Response factor was calculated by taking the ratio of mean peak area of Lurasidone and Indapamide. Table 2 represents the response factor of LurasidoneHCl. The response factors were plotted against the corresponding concentrations to obtain the calibration curve. Figure 3 and 4 represents the chromatogram of linearity and calibration curve for LurasidoneHCl respectively.

Accuracy

To check accuracy of the method, recovery studies were carried out by preparing sample solution at three different levels 80, 100 and 120 %. Basic concentration of sample chosen was 10µg/ml of LurasidoneHCl standard solution. These solutions were injected to obtain the chromatogram. The drug concentrations were calculated by using linearity equation of LurasidoneHCl. The results obtained are shown in Table 3

PrecisionThe intra-day precision study of LurasidoneHCl was carried out by estimating the peak responses six times on the same day with15µg/ml concentration and inter-day precision study of LurasidoneHCl was carried out by estimating the peak responses six times on different days with 15µg/ml concentration and % RSD value obtained was calculated to determine method precision Table no.4

Limit of detection and quantification (LOD and LOQ)

From the linearity data the limit of detection and Quantitation was calculated, using the following formula.

$$\mathbf{LOD = 3.3\ \sigma / S \quad and \quad LOQ = 10\ \sigma / S}$$

σ = standard deviation of the response

S = slope of the calibration curve of the analyte.

Robustness

The robustness of an analytical method was determined by analysis of aliquots from homogenous lots by differing physical parameters like flow rate, mobile phase composition and pH and its impact on peak area was studied. The resultsaregiven in Table 5

DISCUSSION

The analytical method was developed by studying different parameters. First of all, maximum absorbance was found to be at 231nm and the peak purity was excellent.Injection volume was selected to be 20µl which gave a good peak area (figure 2). The columnused for study on LurasidoneHCl, HiQSiL C18, 250,5µm was chosen that resulted in symmetric peak shape. Ambienttemperature was found to be suitable for theanalysis. The flow rate was fixed at 1ml/min because of satisfactory retention time. Different pHand ratios of mobile phase constituents were studied,mobile phase with Methanol: Phosphate buffer in the ratio of 80:20 *v/v*was optimized due to goodsymmetrical peak. Run time was selected to be 10min because analyteelutes at around 5.3 min.The percent recovery was found to be 98.53-100.19.Both Intraday and Interday precision wasfound to be well within range. Inspecificity study, there was no interference bydegradant, impurity andexcipients. Detection limit was found to be 0.62µg/ml. The analytical method was foundlinear over the range of 5-25µg/ml.

Table 1: System suitability parameter

Name	RT (Min)	Concentration (µg/ml)	Area (µV.Sec)	Plates	Asymmetry	Resolution
Lurasidone	5.32	10	269421	3263	0.87	2.723
Indapamide	3.6	5	215300	3938	0.8	4.638

Table 2: Results of linearity of LurasidoneHCl

S.no.	Concentration (µg/ml)	Area of Lurasidone	Area of Indapamide	Response Factor
1	5	135808.8	203088.8	0.669
2	10	260660.2	209559.6	1.243
3	15	388119.8	211868.2	1.83
4	20	547423.2	215892	2.535
5	25	699296	211993	3.29
Correlation coefficient (r^2)		**0.996**		
y-intercept		**0.046**		
Slope		**0.130**		

Table 3: Recovery studies of LurasidoneHCl

Level (%)	Recovered Conc. (µg/ml)	Area of Lurasidone	Area of Indapamide	Response Factor	% Recovery
80	8	204828	209889	0.9758	98.53
100	10	261002	211829	1.232	98.54
120	12	321020	212018	1.5141	100.19

Table 4: Interday and Intraday precision study of LurasidoneHCl 15µg/ml

Replicate	Interday(Response Factor)	Intraday(Response Factor)
1	1.80	1.850
2	1.79	1.83
3	1.86	1.80
4	1.84	1.78
5	1.85	1.79
6	1.82	1.825
Mean of Response factor	**1.82**	**1.81**
Std. Dev.	**0.028**	**0.0267**
RSD	**0.0153**	**0.0147**
% RSD	**1.53**	**1.473**

Table 5: Robustness study

Drug	% RSD							
	pH (3)		Flow Rate ($1mLmin^{-1}$)		Wavelength (231nm)		Mobile phase ratio (80 : 20)	
	2.8	3.2	0.8	1.2	230	232	79: 21	81: 19
LurasidoneHCl	1.512	1.23	1.0840	1.3428	2.04	0.9644	0.6465	0.1984

Table 6: Summary of validation study

S.No.	Validation parameters	LurasidoneHCl
1.	Linearity Equation (r2) Range	Y=0.13x - 0.046 R^2 = 0.996 5- 25µg/ml
2.	Precision (% RSD) Interday Intraday	 1.53 1.473
3.	Accuracy	% Recovery
	80	*98.53*
	100	*98.54*
	120	*100.19*
4.	Limit of Detection	0.62 µg/ml
5.	Limit of Quantitation	1.89 µg/ml
6.	Specificity	Specific
7.	Robustness	Robust

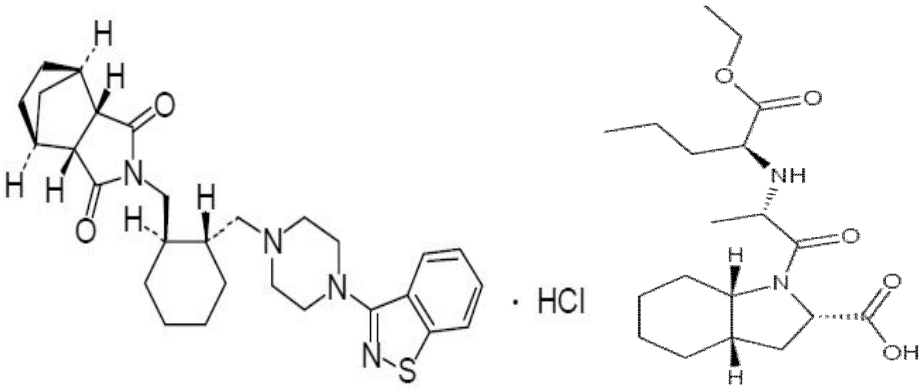

Fig. 1: Structure of Lurasidone Hydrochloride and Indapamide

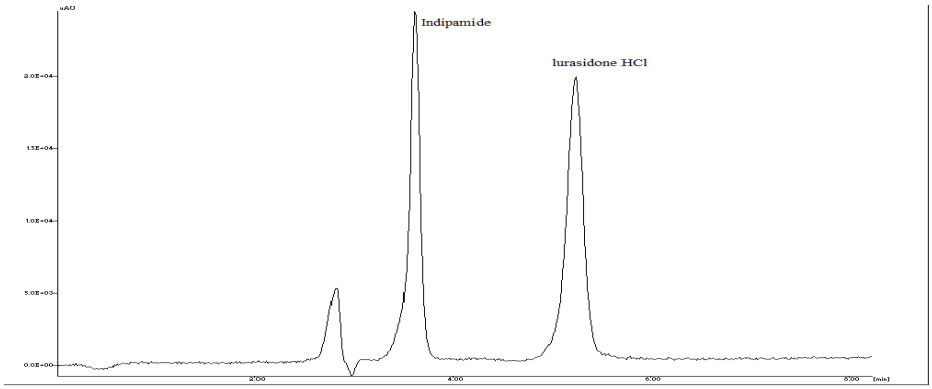

Fig. 2: Chromatogram of mixed standard solution of Indapamide (5µg/ml) andLurasidoneHCl (10 µg/ ml)

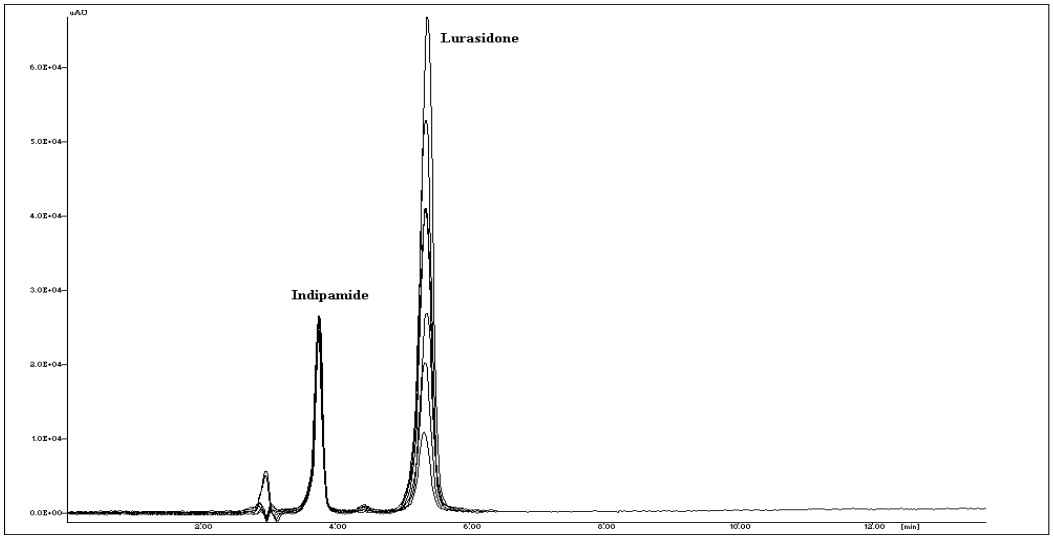

Fig. 3: Chromatogram of linearity of LurasidoneHCl (5-25 µg/ml)

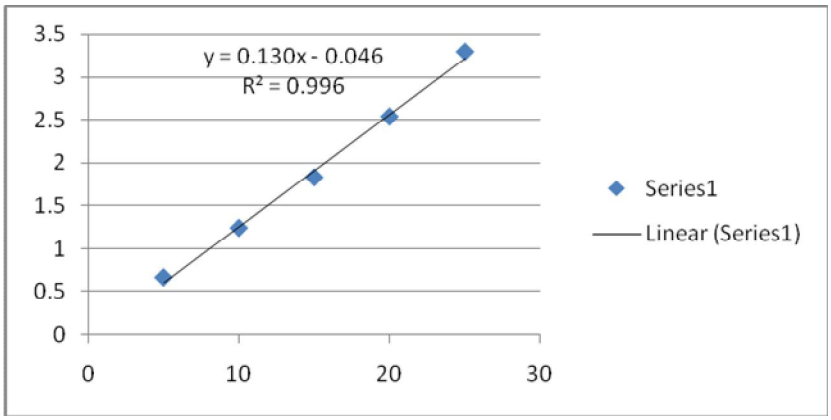

Fig. 4: Calibration curve for LurasidoneHCl

CONCLUSION

Proposed study describes new LC method for the estimation of LurasidoneHCl in tablet formulation. Only two HPLC methods have been reported that use acetonitrile in mobile phase which is costlier than methanol, in our method mobile phase is binary mixture of methanol and buffer and chromatographic run time of 10 min allows the analysis of a large number of samples in short period of time, so method is simple economic, sensitive, accurate and precise and has been validated as per the ICH guidelines. Therefore the proposed method can be used for routine analysis of Lurasidone Hydrochloride in its tablet formulation.

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