ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Simple and Validated Ultraviolet Spectrophotometric Method for the Estimation of Lurasidone in Bulk Form

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ABSTRACT

A simple, sensitive, precise, accurate and economical spectrophotometric method of analysis for lurasidone in bulk form was developed and validated. The method employed acetonitrile as solvent and the drug shows maximum absorbance at 263 nm. The absorbance was found to increase linearly with increasing concentration of lurasidone, which is corroborated by the calculated correlation coefficient value (r^2 = 0.999). The linear regression analysis data for the calibration plot showed good linear relationship with in the concentration range of 10 – 60 µg/ml. The limit of detection and limit of quantitation were found to be 1.25316 µg/ ml and 3.797468 µg /ml respectively. This method was tested and validated for various parameters according to ICH guidelines. The results demonstrated that the procedure is accurate, precise and reproducible (R.S.D. < 2 %).
Keywords: Lurasidone, Validation, Estimation, UV spectrophotometry, Acetonitrile.

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ISSN: 0975-8585

INTRODUCTION

Chemically lurasidone is [(3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl]cyclohexylmethyl}hexahydro-4,7-methano-2*H*-isoindole-1,3-dione hydrochloride and it is an azapirone derivative [1]. The chemical structure of lurasidone hydrochloride (SM-13496) with its six chiral centers is shown in Fig. 1.

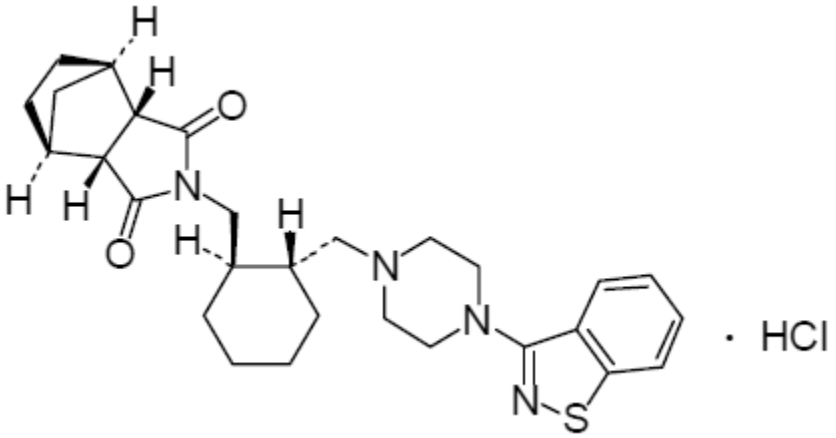

Fig. 1: Chemical structure of Lurasidone

lurasidone hydrochloride appears as a white to light yellow crystalline powder and is stable upto thirty six months. It's molecular formula is $C_{28}H_{36}N_4O_2S{\cdot}HCl$ and molecular weight is 529.14 [2]. In chloroform and acetonitrile, it is sparingly soluble; in ethanol it is slightly soluble; in water and acetone it is very slightly soluble, where as in toluene and 0.1 N HCl it is insoluble. It has an aqueous solubility of 0.224 mg/ml in water with maximum solubility of 0.349 mg/ml in pH 3.5 buffer. The melting range and density are 198–205^{0}C, 1.273 g/cc respectively [3].

Lurasidone is atypical antipsychotic and antischizophrenia drug. Boxed warning alerting prescribers are present in lurasidone in similar to any other atypical antipsychotics, which helps to treat dementia-related psychosis in older people [4]. Lurasidone was developed by Dainippon Sumitomo Pharma [2]. On 28th October, 2010, U.S. Food and Drug Administration (FDA) approved lurasidone for the treatment of schizophrenia by reviewing Phase III clinical trials [5]. Out of the four reviewed trials, it was found that two trails supported efficacy, marginal efficacy was observed in third trial where as last one was not interpretable due to high dropout rates [5].

The improvement of memory impairment due to MK-801 induction was found to be higher in lurasidone compared to other antipsychotics [6] and hence proved to be a clinically useful drug for cognitive impairments in treatment of schizophrenia [7]. Positive symptoms (viz., delusions, hallucinations) as well as negative symptoms (viz., emotional withdrawal, apathy) of schizophrenia were alleviated by lurasidone in the clinical studies carried out by Nakamura *et al.,*[8] and except akathisia no extra pyramidal side effects were induced in spite

of its effective D2 antagonistic actions [9]. The enzyme CYP_3A_4 helps the metabolization of lurasidone in the liver [10].

For the assay of lurasidone in tablet dosage form, an RP-HPLC method was developed and validated by using a mobile phase comprising a mixture of acetonitrile, methonal and acetic acid in the volume ratio of 35, 40 and 25 respectively [11]. An LC/MS/MS (liquid chromatography–tandem mass spectrometric) method was developed by Tae-Sung *et al.,* [12] for pharmacokinetic study of lurasidone in rats, in which the mobile phase was acetonitrile with 0.1% formic acid and into the column of octadecylsilica with 0.1% formic acid (5µm, 2.0×50mm), the diluted supernatant of a mixture of acetonitrile, internal standard (Ziprasidone) and plasma samples were directly injected.

Since, literature review shows that only two methods are available for quantitative determination of lurasidone, it is felt worthwhile to develop a simple and rapid UV method which will be accurate, precise and economical for determination of lurasidone in bulk forms by conducting systematic trials.

MATERIALS AND METHODS

The spectrophotometric measurements were carried out using a double beam LABINDIA UV – Visible spectrophotometer (UV – 3092) connected to computer and loaded with PMT detector UV – WIN 5 software. The instrument has an automatic wavelength accuracy of 0.1 nm and matched quartz cells of 10 mm (1.0 cm) cell path length. Shimadzu AUX-220 balance was used for weighing the samples. All the reagents used were of analytical grade.

Scanning and determination of maximum wavelength (λ_{max})

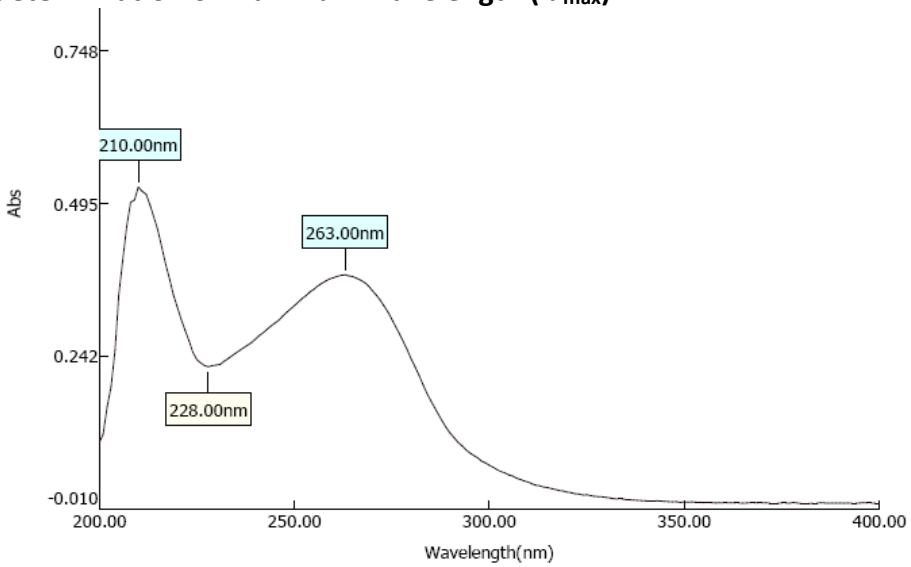

Fig. 2: UV spectrum of Lurasidone.

ISSN: 0975-8585

In order to ascertain the wavelength of maximum absorption (λ_{max}) of the drug, qualitative solution of the drug was prepared in acetonitrile and scanned by using UV spectrophotometer within the wavelength region of 230 – 380 nm against acetonitrile as blank. The calibration curve was constructed for absorbance versus concentration of lurasidone. The resulting spectrum was shown in Fig. 2, and the absorption curve showed characteristic absorption maxima at 263 nm for lurasidone.

Preparation of Standard Stock Solutions

Standard stock solution (primary) was prepared by dissolving 10 mg of lurasidone in 10 ml of acetonitrile to get concentration of 1mg/ml (1000µg/ml) and was stored at + 4ºC during the study. Secondary stock solution was prepared daily by diluting 1ml of the primary stock solution to final volume of 10 ml using acetonitrile to get concentration of 0.1mg/ml (100µg/ml).

Preparation of calibration standard solutions

Suitable aliquots of the secondary standard solution of lurasidone (10 – 60 ml) were transferred to a series of calibrated 100 ml standard volumetric flasks and the volume was made up to the mark with acetonitrile.

RESULTS AND DISCUSSIONS

Method Validation

Validation is one of the most important steps in method development for analytical determinations. The main validation parameters such as linearity and range, accuracy and precision, recovery, ruggedness, limit of detection (LOD) and limit of quantitation (LOQ) were evaluated in developed method [13 – 16].

Linearity and range

Table 1. Calibration values of Lurasidone.

Concentration (µg/ml)	Absorbance*
0	0
10	0.158
20	0.333
30	0.476
40	0.634
50	0.793
60	0.951

* Average of three determinations.

ISSN: 0975-8585

The absorbance values for different standard solutions (10, 20, 30, 40, 50 and 60 µg/ml) of lurasidone were measured at λ_{max} 263 nm, against acetonitrile as blank. Each point of the calibration graph corresponded to the mean value obtained from three independent measurements (Table 1). The calibration graph (Fig. 3) was constructed by plotting absorbance versus concentration of lurasidone. The calibration graph of the absorbance versus concentration was found to be linear over the range of 10 – 60 µg/ml for the proposed method. The linear regression equation obtained was y = 0.0158x + 0.003, where y is the absorbance and x is the concentration in µg/ml of pure drug solution. The summary of optical and regression parameters was shown in Table 2.

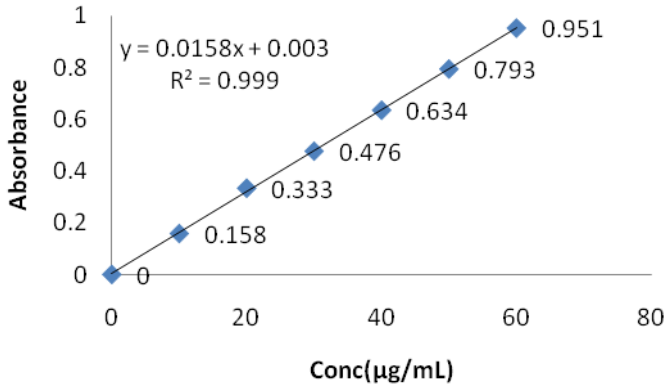

Fig. 3: Calibration graph of Lurasidone.

Table 2. Optical characteristics, statistical data of the regression equations and validation parameters for of Lurasidone.

S. No.	Parameter	Observation
Optical characteristics		
1.	Apparent molar absorptivity (l/mol.cm)	8455
2.	Sandell's sensitivity (µg/cm^2/A)	0.0626
Regression analysis		
1.	Slope	0.0158
2.	Intercept	0.003
3.	Regression coefficient (*r*)	0.999
Validation parameters		
1.	λ_{max} (nm)	276
2.	Specificity	No interference at analyte wave length
3.	Beer's Law Limit (Linearity, µg/ml)	10 – 60
4.	Limit of detection (µg/ml)	1.25316
5.	Limit of quantitation (µg/ml)	3.797468

Accuracy

To determine the accuracy of the proposed method, recovery studies were carried out by adding different amounts (50%, 100%, and 150%) of bulk samples of lurasidone to 20 µg/ml so that overall concentration will be within the linearity range. The accuracy was expressed in

ISSN: 0975-8585

terms of percent recovery. The mean of percentage recovery values was 93.48 – 100.88. The results were given in Table 3. The statistical analysis of data obtained for the estimation of lurasidone indicates a high level of accuracy for the proposed method as evidenced by the low values of standard deviation and relative standard deviation.

Table 3. Recovery of Lurasidone using the proposed UV method.

Level of recovery (%)	Nominal concentration used (µg/ml) (a)	Amount of drug spiked (µg/ml) (b)	Total amount of drug µg/ml (a + b) (µg/ml) (Theoretical)	Amount of drug recovered (µg/ml) (Practical)	Statistical evaluation	% Recovery = Practical / Theoretical x 100
50	20	9.80	29.80	27.79		93.27
				28.30		94.97
				27.48		92.21
					Mean	93.48
					SD	1.39
					RSD	1.49
100	20	20.10	40.10	39.95		99.21
				40.20		100.25
				41.21		102.77
					Mean	100.88
					SD	1.67
					RSD	1.66
150	20	30.20	50.20	47.73		95.08
				47.29		94.20
				47.60		94.83
					Mean	94.70
					SD	0.45
					RSD	0.48
					Grand Mean	95.95

Precision

The precision of a method is defined as the closeness of agreement between independent test results obtained under optimum conditions. Two different concentrations of lurasidone in the linear range (20 and 30 µg/ml) were analyzed in six independent series in the same day (intra-day precision) and in six consecutive days (inter-day precision) and results were given in Table 4.

Table 4. Intraday and Inter-day precision readings of the proposed method.

Concentration of Lurasidone (µg /ml)	Concentration (µg /ml)*			
	Intraday (Mean ± SD) (n=6)	% RSD	Inter-day (Mean ± SD (n = 6)	% RSD
30	28.56 ± 0.376	1.318	30.63 ± 0.007	1.142
40	28.59 ± 0.322	1.126	40.44 ± 0.545	1.357

***** Averages of six determinations

ISSN: 0975-8585

The RSD values of intra-day studies varied from 1.126 to 1.318 and inter-day studies varied from 1.142 to 1.357 showed that the precision of the method was satisfactory.

Ruggedness

The ruggedness of the proposed method was evaluated by applying the developed procedure for assay of 20 µg/ml and 30 µg/ml of lurasidone using the same instrument by two different analysts under the same optimized conditions at different days. The obtained results were found to be reproducible, since there was no significant difference between analysts. Thus, the proposed methods could be considered rugged (Table 5).

Table 5. Ruggedness data of Lurasidone by two analysts at different days.

S. No.	Test concentration (µg/ml)	Concentration (µg /ml)			
		Analyst 1		Analyst 2	
1	20		20.578		20.515
			20.832		20.832
			20.642		20.642
			20.452		20.452
			20.578		20.578
			20.389		20.389
		Mean	20.580	**Mean**	20.570
		SD	0.160	**SD**	0.160
		% RSD	0.753	**% RSD**	0.764
2	30		28.933		28.870
			28.047		28.300
			28.933		28.616
			28.806		28.553
			28.363		28.363
			28.300		28.616
		Mean	28.560	**Mean**	28.550
		SD	0.376	**SD**	0.204
		% RSD	1.318	**% RSD**	0.715

Detection of LOD and LOQ

For determination of sensitivity of the proposed method, LOD and LOQ were calculated. Based on the signal to noise ratio they were quantified. The lowest detectable concentration of the analyte by the method is LOD where as the minimum quantifiable concentration is LOQ. LOD and LOQ for lurasidone were calculated according to the ICH guidelines by using S (relative standard deviation of the response) and σ (slope of the calibration curve) and the results indicate that the proposed method is sensitive to detect and quantify.

LOD = 3.3 × σ /S = 1.25316 µg /ml and
LOQ = 10 × σ /S = 3.797468 µg /ml

ISSN: 0975-8585

CONCLUSIONS

In this study a simple, fast and reliable UV spectrophotometric method was developed and validated for the determination of lurasidone in bulk form. The proposed method can be used for the routine quality control analysis of lurasidone in bulk form. This method has the lowest LOD value and is more sensitive method. From the results obtained, we concluded that the suggested method showed high sensitivity, accuracy and precision.

ACKNOWLEDGEMENT

The authors are grateful to Chalapathi Institute of Pharmaceutical Sciences, Chalapathi Nagar, Lam, Guntur Dist, Andhra Pradesh, India for providing the necessary research facilities.

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