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Short Communication

Method Development and Validation of Cariprazine Hydrochloride in Bulk by UV Spectrophotometric Method

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ABSTRACT

The goal is to develop and validate a simple, sensitive, precise, fast, and cost-effective method for estimating Cariprazine Hydrochloride in bulk in compliance with ICH guidelines. Linearity, Precision, Repeatability, Limit of Detection (LOD), Limit of Quantification (LOQ), Accuracy, Robustness, and Ruggedness of a simple double beam UV Spectrophotometric method have all been developed and validated. The absorbance of cariprazine hydrochoride in methanol is 252 nm. The LOD and LOQ were determined to be 1.63g/ml and 4.94g/ml, respectively, in the concentration range of 10-50 g/ml, supporting Beer's law. The proposed approach is precise, accurate, and repeatable, and it may be used to analyse Cariprazine hydrochloride in bulk on a routine basis.

INTRODUCTION

Cariprazine is a Gedeon Richter-developed oral atypical antipsychotic. It's a partial agonist for the dopamine D3 and D2 receptors that preferentially binds to the D3 receptor. Cariprazine binds to serotonin 5-HT1A receptors and acts as a partial agonist. Cariprazine was approved for the first time in the United States in September 2015, for the treatment of schizophrenia and the acute treatment of manic or mixed episodes associated with bipolar I disorder [1].

The chemical name (IUPAC) of Cariprazine hydrochloride is N′-[trans-4-[2-[4-(2,3-Dichlorophenyl)-1piperazinyl]ethyl]cyclohexyl]-N,N-dimethyl-urea with molecular formula C21H32Cl2N4O•HCl (Fig. 1) [2].

It is white to off white crystalline solid. It's soluble in a variety of organic solvents (methanol, dimethyl sulfoxide), but not in water. It is an Allergan Pharma product, marketed under the name Vraylar®, which was discovered and co-developed by Gedeon Richter [3].

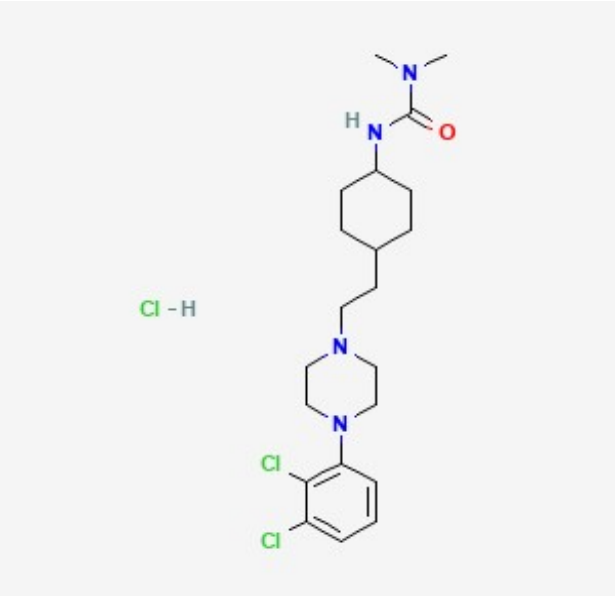

Figure 1: Chemical Structure of Cariprazine hydrochloride.

According to the literature review, no UV-Spectroscopic technique or Liquid Chromatography analysis for bulk and pharmaceutical dosage form has been reported for cariprazine hydrochloride.

The aim and objective of the present work was to develop and validate a simple, precise, sensitive spectroscopy method for Cariprazine hydrochloride in bulk.

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METHOD AND MATERIALS

Instrument

UV-Spectrophotometer of Shimadzu make and 1900 model having UV probe software were used for analysis. An electronic analytical weighing balance (Sartorius make) and a sonicator (RC Systems) were used in this study.

Chemicals and Reagents

Gift sample of Cariprazine hydrochloride was obtained from MSN Laboratories, Hyderabad. HPLC grade Methanol was purchased from Merck Company, Mumbai, and Water was obtained from in house Millipore water system.

Selection of Wavelength [4]

Methanol was chosen throughout the study because cariprazine hydrochloride is soluble in organic solvents such as Methanol and Dimethyl sulfoxide (DMSO). Cariprazine hydrochloride 10 µg/ml of working standard solution was scanned in between 200 nm to 400 nm and showed maximum absorption at 252nm by UV spectrophotometer (Fig. 2). To confirm the following analysis, an overlay spectrum using different concentrations was plotted (Fig. 3).

Preparation of Stock and Working Standard Solution

10 mg of Cariprazine hydrochloride was accurately weighed and taken in 100 ml clean and dry volumetric flask. Drug was dissolved and diluted up to the mark using methanol. This was considered as the standard stock solution (100µg/ml). 1 ml of the stock solution was pipette out and made up to 10 ml to get a concentration 10 µg/ml and was treated as the working standard [5].

Method Validation [6-8]

To validate newly developed method parameters as per the ICH guidelines was followed.

Specificity

UV spectrum of blank (Methanol) and solution containing Cariprazine Hydrochloride was scanned between range of 400-200 and observed for interference of any absorbance at 252 nm.

Linearity and Range

From this stock solution, appropriate dilutions were made to get final concentration of 10, 20, 30, 40, and 50µg/ml and absorbance was taken at λ_{max} 252 nm. (Table 1) Averages of such 5 sets of values were taken for standard calibration curve, and the calibration curve was plotted. The solutions were ready in triplicates and absorbance was measured at 252 nm.

Table 1: Absorbance at different aliquots

Concentration (µg/ml)	Absorbance
10	0.179
20	0.377
30	0.558
40	0.732
50	0.936
R^2=0.999	
y=0.018x-0.002	

Limit of Detection and Limit of Quantification

The LOD and LOQ were calculated based on the standard deviation of the response (y intercepts of regression lines) and the slope using 3 independent analytical curves, as defined by ICH. Cariprazine hydrochloride LOD and LOQ were calculated as 3.3 σ/S and 10 σ/S, respectively, where σ is the standard deviation of Y intercept (ICH guidelines) and S is the slope of the Cariprazine Hydrochloride calibration curve.

Precision

System Precision

Precision was measured in six replicates of solution containing cariprazine hydrochloride that was prepared and the absorbance was recorded at 252 nm on same day at different time intervals. On alternate days the obtained system precision, intraday precision and inter-day precision data and absorbance were measured and % RSD was calculated.

Method Precision

Method precision was determined by performing tests of:

(i) Repeatability (Intraday precision) (Table 3) and
(ii) Intermediate precision (Interday precision) (Table 4) performed during 2 consecutive days at different working concentrations.

Ruggedness

In order to determine the ruggedness normally six replicates of solutions containing cariprazine hydrochloride were prepared and absorbance of each replicate was measured by different analyst also by using different instruments and %RSD as calculated for absorbance.

Robustness

Robustness was determined by performing the same proposed method on different wavelengths. The analysis showed %RSD less than 2 and indicates that the method developed is robust.

Solution Stability

In order to check solution stability fresh stock was prepared and dilutions were made using fresh solvent, absorbance's of each dilutions containing cariprazine hydrochloride was compared with that of old stock dilutions that is after 24 and 36 hours and % RSD for absorbance's was calculated.

RESULT AND DISCUSSION

Method Development & Validation

Solvents were analysed including Ethanol, DMSO, and Methanol at 1 mg/ml concentration. However, cariprazine hydrochloride was found to be soluble and stable at room temperature using methanol. Therefore, this solvent was used for the determination of suitable detection wavelength and working concentration of standard. International Conference on Harmonization (ICH) has provided guidelines i.e. Q2 (R1) for validation of analytical method which defines this process as characteristic performance that is established by laboratory studies [6]. Also, this process meets the requirements for intended analytical application. UV spectrophotometric method developed was validated according to guidelines for validation of analytical procedures. The method was validated for the parameters like specificity, linearity, accuracy, system precision, intra-day precision, inter-day precision/ intermediate precision, ruggedness and robustness.

Specificity

There was no interference showed by the solvent spectrum at 252 nm. The UV spectrum of cariprazine Hydrochloride is represented in Fig. 2.

Linearity

Linearity and range was resolute by plotting standard calibration curve using concentration UV absorbance's obtained by linear dilution of cariprazine hydrochloride. The absorbance range was between the concentration of 10, 20, 30, 40, and 50µg/ml. The regression (r^2) of cariprazine hydrochloride was 0.999. Linearity data as signified in Table 1. Overlay spectrum of linearity of cariprazine hydrochloride is shown in Fig. 3 with standard calibration curve was presented in Fig. 4.

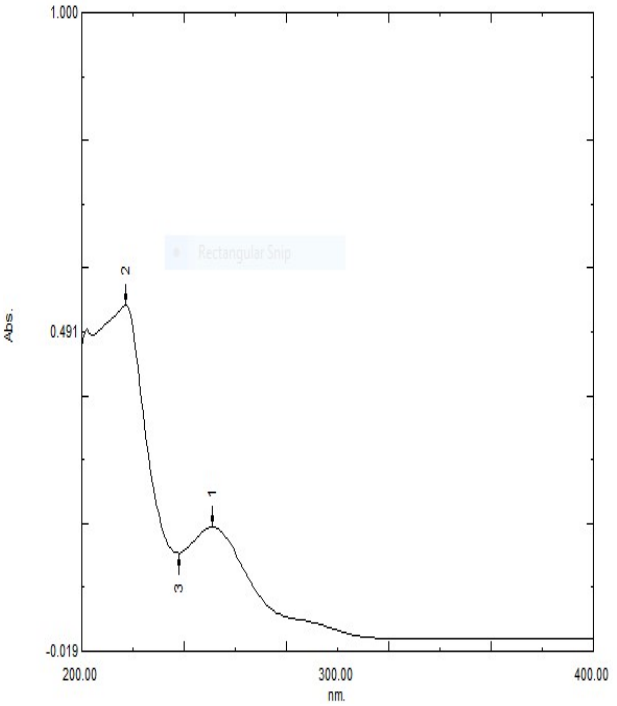

Figure 2: UV spectrum of the standard Cariprazine hydrochloride

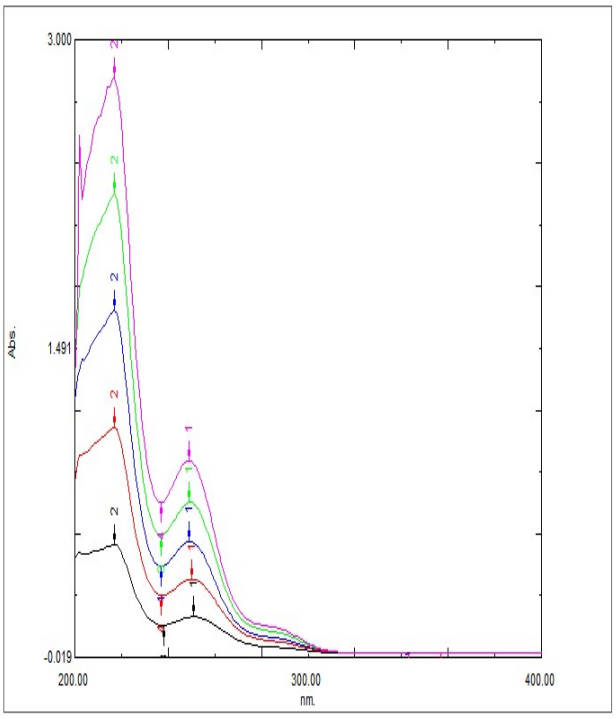

Figure 3: Overlay spectrum of the standard Cariprazine hydrochloride at different concentrations

Limit of Detection and Limit of Quantification

The LOD and LOQ were found 1.63 µg/ml and 4.94 µg/ml respectively.

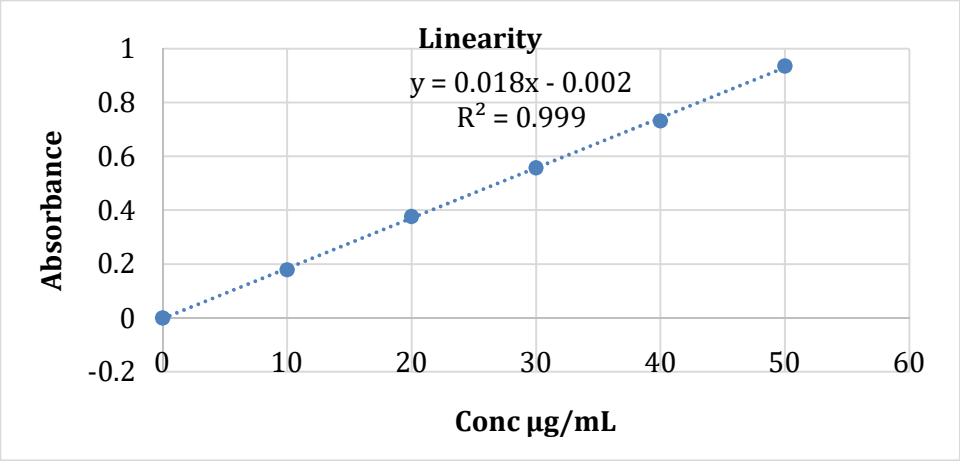

Figure 4: Linearity graph of Cariprazine hydrochloride.

Precision

System precision -Six replicate recording of absorbance at 252 nm of 10 µg/ml concentration standard solution showed %RSD (Relative Standard Deviation) less than 2, which indicates acceptable reproducibility and thereby the precision of the system. System precision results are tabulated in Table 2.

Method precision results of (i) repeatability (Intraday precision) (ii) Intermediate precision (Interday precision) are tabulated in Table 3 and Table 4 respectively. Method was found to be precise as the %RSD calculated for cariprazine hydrochloride at each precision level was found to be less than 2%.

Table 2: Results of System Precision

N	Absorbance
1	0.175
2	0.179
3	0.170
4	0.172
5	0.171
6	0.173
Average	**0.173**
SD	**0.0032**
% RSD	**1.88**

Table 3: Results of Method Precision (Intraday)

Concentration (µg/ml)	Sample Absorbance	Mean Absorbance±S.D.	% RSD
10	0.175	0.173±0.002	1.42
	0.172		
	0.174		
	0.178		
	0.173		
	0.171		
30	0.510	0.507±0.002	0.46
	0.510		
	0.506		
	0.508		
	0.504		
	0.508		
50	0.924	0.922±0.003	0.43
	0.919		
	0.917		
	0.921		
	0.928		
	0.924		

Table 4: Results of Method Precision (Interday)

Concentration (µg/ml)	Sample Absorbance	Mean Absorbance±S.D.	% RSD
10	0.179	0.177±0.001	0.77
	0.179		
	0.178		
	0.177		
	0.176		
	0.176		
30	0.538	0.538±0.001	0.34
	0.540		
	0.542		
	0.538		
	0.537		
	0.538		
50	0.924	0.923±0.003	0.39
	0.922		
	0.918		
	0.921		
	0.926		
	0.928		

Ruggedness

The % RSD values calculated for cariprazine hydrochloride was found to be less than 2% which indicates that the method developed is rugged (Table 5).

Table 5: Results of Ruggedness

Analyst	Absorbance	Mean Absorbance ± S.D.	% RSD
Analyst 1	0.172	0.173±0.002	1.68
	0.179		
	0.171		
	0.172		
	0.174		
	0.175		
Analyst 2	0.179	0.176±0.002	1.55
	0.172		
	0.175		
	0.176		
	0.179		
	0.178		

Robustness

The analysis showed %RSD less than 2 and indicates that the method developed is robust (Table 6).

Table 6: Results of Robustness

Wavelength (in nm)	Sample Abs*	Standard Abs*	Mean Abs*	% RSD
251	0.168	0.179	0.169	1.14
	0.169			
	0.172			
	0.167			
	0.168			
	0.171			
253	0.175	0.179	0.173	0.92
	0.174			
	0.172			
	0.174			
	0.176			
	0.172			

***Abs=Absorbance**

Solution Stability

The solution stability for cariprazine hydrochloride was determined by the %RSD or absorbance was calculated from prepared fresh solution and after 24, 36 hours solution containing cariprazine hydrochloride. Results analyzed were found to be within the acceptance. Solution stability study was done for 36 hours and data have been displayed in (Table 7).

Table 7: Solution stability data of Cariprazine Hydrochloride

Concentration (µg/ml)	Abs* of fresh stock dilutions	Abs* after 24 hrs	Abs* after 36 hrs
10	0.179	0.186	0.188
10	0.179	0.186	0.189
10	0.172	0.184	0.184
10	0.174	0.183	0.188
10	0.178	0.188	0.190
10	0.175	0.183	0.186
SD	0.002	0.002	0.002
% RSD	1.66	1.08	1.15

***Abs=Absorbance**

CONCLUSION

The newly developed UV Spectrophotometric analytical method is specific for determination of Cariprazine hydrochloride in bulk. The method developed was found to be linear, simple, precise, robust, rugged, and economic for estimation of cariprazine.

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