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Research Article

STABILITY INDICATING RP-HPLC METHOD FOR THE ESTIMATION OF QUETIAPINE FUMARATE IN BULK AND TABLET DOSAGE FORM

PRAGATI TALUSANI AND LAKSHMI SIVASUBRAMANIAN*

Department of Pharmaceutical Analysis, Bharat Institute of Technology, Mangalpally (V), Ibrahimpatnam (M), RR Dist, Hyderabad 501510, Andhra Pradesh. Email: lakshmiss@hotmail.com

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ABSTRACT

A new simple, sensitive, precise and accurate high performance liquid chromatography method has been established and validated for analysis of Quetiapine fumarate in bulk and tablet dosage form.

Objective: To develop and validate high performance liquid chromatographic method for estimation of Quetiapine fumarate from bulk and tablet dosage form.

Method: The separation was achieved on a C18 column using a mixture of phosphate buffer, acetonitrile and methanol in the ratio 50:40:10v/v/v with a flow rate of 1ml/min and detection wavelength at 245nm. The method was validated for linearity, accuracy, precision and specificity as per ICH guidelines. The developed and validated method was successfully used for the quantitative analysis of commercially available dosage form.

Results: The retention time of Quetiapine fumarate was found to be at 5.08 min. Linearity of the method was found to be in the concentration range of 10-80 µg/ml with correlation coefficient of 0.999. The method was validated for accuracy, precision and recovery studies. Limit of detection (LOD) and limit of Quantification (LOQ) for Quetiapine were found to be 18.815 and 57.016 µg/ml respectively.

Conclusion: The high percentage of recovery and low percentage of relative standard deviation confirm the suitability of the method for the estimation of Quetiapine in bulk and tablet dosage form.

Keywords: Quetiapine fumarate, RP-HPLC, Stability indicating

INTRODUCTION

Quetiapine Fumarate (QUE) is an antipsychotic drug used to treat psychosis associated with Parkinson's disease and chronic schizophrenia. Literature review revealed that few methods were reported for quantitative analysis of QUE using UV visible spectrophotometer, HPLC and HPTLC [1-12]. An attempt has been made to develop and validate the stability indicating RP-HPLC method for the analysis of QUE which is highly sensitive, specific and reproducible. Various validation parameters such as accuracy, precision and recovery studies were carried out as per ICH guidelines [13, 14]. The developed method can be successfully applied to quality control and for other analytical purpose.

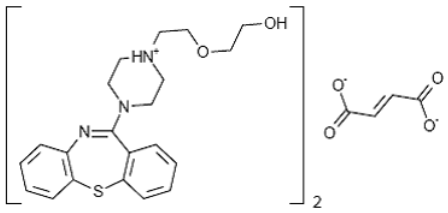

Fig. 1: Structure of Quetiapine fumarate

Chemicals and Reagents

Quetiapine fumarate reference substance with claimed purity of 99.6% was obtained from Sun Pharma, Sikkim as a gift sample. Acetonitrile (HPLC grade), methanol (HPLC grade) and other chemicals of analytical grade were purchased from Merck (Mumbai, India). HPLC grade water used was prepared in the laboratory using Milli-Q system (Millipore, USA).

Apparatus and Chromatographic conditions

HPLC apparatus consisting of Waters 2487 system equipped with dual 515 pump, dual wavelength absorbance detector, an Empower 2 software and rheodyne injection valve with a 20 µl loop was used for development and evaluation of this method. A Spherisorb C18 column (250 × 4.6mm id, 5µm particle size) was operated at ambient temperature. The mobile phase composed of a mixture of phosphate buffer, acetonitrile and water in the ratio 50:40:10 v/v/v was delivered isocratically at a flow rate of 1 ml/min. Absorption maximum was detected by scanning standard solution of drug over 200-400nm in Shimadzu model 1700 double beam UV spectrophotometer with a pair of 10 mm matched quartz cells. Measurements were made at 245nm using UV detector.

Preparation of Standard Solution

A stock solution of QUE was prepared at about 1 mg/ml in mobile phase.

Linearity

Linearity of the proposed method was checked by analyzing eight solutions in the range of 10-80 µg/ml for QUE. Each level was prepared in triplicate.

Accuracy

Method accuracy was performed by adding known amount of QUE to the Pre-analysed sample solution and then comparing the added concentration with the found concentration. Three levels of solutions were made which correspond to 50, 100 and 150% of the nominal concentration (30 µg/ml of QUE). Each level was prepared in triplicate.

Accuracy of the proposed method

Drug	Level (%)	n	Added Concentration (µg/ml)	Found Concentration (µg/ml)	% Recovery	% RSD
QUE	50	3	0	30.04	99.98	0.49
	100	3	10	39.79	97.65	0.61
	150	3	20	47.90	98.59	0.54

n = number of observations

Selectivity

The selectivity of the proposed method was checked by comparing the chromatogram of sample with the chromatogram of the reference standard. The amount of tablet formulation equivalent to 100 mg of QUE formulation was accurately weighed and transferred into a 100 ml volumetric flask. The mixture was shaken well with 70ml mobile phase and then the volume was made with mobile phase & filtered. About 1 ml of the filtrate was transferred into 10 ml volumetric flask and the volume was made up to 10 ml with mobile phase. Further dilution was made to obtain a final concentration of 20 µg/ml of QUE.

Robustness

Robustness of the method was performed by intentionally modifying the chromatographic conditions such as composition, flow rate and detection wavelength. The chromatographic parameters of each analyte such as retention time, tailing factor and number of theoretical plates were measured at each changed conditions.

Precision of the proposed method

Drug	Amount taken (µg/ml)	n	Within day precision		Between day precision	
			Mean (µg/ml)	% RSD	Mean (µg/ml)	% RSD
QUE	50	5	47.72	0.0471	43.68	0.1448

n = number of observations

Precision

For evaluating the with-in day precision, results of five replicate analyses of three different concentrations of samples were calculated on a single day. The between day precision was calculated from the samples analyzed on six different days.

LOD and LOQ

For calculating the LOD and LOQ values, solutions with known concentrations of analytes were injected into the HPLC system. The Limit of Detection (LOD) and Limit of Quantification (LOQ) were then measured by calculating the minimum level at which the analytes can be readily detected (signal to noise ratio of 3:1) and quantified (signal to noise ratio of 10:1) with accuracy respectively.

Forced Degradation Studies

Drugs were allowed to hydrolyze in base (0.1M NaOH), acid (0.1M HCl) and in different strengths of hydrogen peroxide (30%, 3%, 1%). Drug was also studied for its thermal degradation at 40^0C and 60^0C. An accurately weighed 50 mg of QUE was dissolved in methanol. To each flask 50 ml of respective acid and base were added and refluxed for 4 hrs. An accurately weighed quantity of sample was also kept in different strengths of hydrogen peroxide solution for specified period of time. The samples were withdrawn at different interval, allowed to cool to room temperature and treated as follows.

The acid and base samples were neutralized to pH 7. The samples stressed under thermal, light and H_2O_2 were used as such. All the samples were further diluted with mobile phase to get a concentration of 20 µg/ml of QUE. Blank was also treated in the same way.

RESULTS AND DISCUSSION

In this present work, conditions were optimized for the development and validation of a simple and accurate HPLC method for the determination of QUE in tablets. Method development was started with acetonitrile and phosphate buffer in the ratio 50:50 v/v. At this composition the component was eluted, but tailing factor was more. The acetonitrile content of the mobile phase was then reduced and replaced with methanol to give peak with good tailing factor. The most appropriate mobile phase composition was thus found to be a mixture of phosphate buffer, acetonitrile and methanol in the ratio 50:40:10 v/v/v .Under the desired experimental conditions, peak was obtained at the retention time of 5.08 minutes.

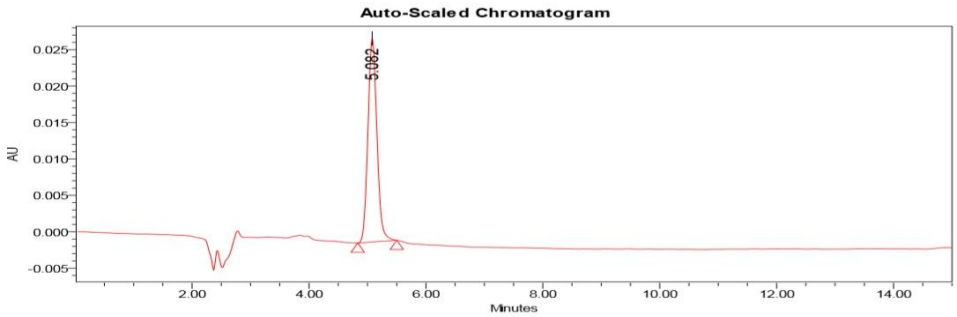

Fig. 2: The chromatogram of Quetiapine showing retention time at 5.08min

The developed chromatographic method was validated using ICH guidelines. Validation parameters performed include linearity, limit of detection and quantitation, selectivity, robustness, accuracy and repeatability. The calibration curve was linear over the concentration range of 10-80 µg/ml for QUE. The correlation coefficient was found to be greater than 0.996, which manifests a linear relationship between concentration and peak area. The linear regression equation was found to be Y = 27166 x + 48362 with correlation coefficient equal to 0.999. In this study, the LOD was found to be 18.815µg/ml and LOQ was found to be 57.016µg/ml for QUE.

The chromatogram of QUE in tablets is given in Figure 2 showing the selectivity of the proposed method. Robustness of the method was performed by intentionally modifying the chromatographic conditions. The results showed that the variance of the conditions had no appreciable effects to that of actual.

The System Suitability Data

Parameter	Drug
Retention time (min)	5.08
Tailing Factor	1.0
No: of theoretical Plates / meter	3577

Robustness Study of Quetiapine

Factor	Level	Rt (min)	Area
Flow rate (ml/min)			
1.1	+1	4.576	1508419
1.0	0	5.085	1716656
0.9	-1	5.940	2014075
Organic Phase Ratio (ml)			
55	+5	4.576	1508419
50	0	5.085	1716656
45	-5	5.940	2014075
Wavelength (nm)			
247	+2	4.576	1508419
245	0	5.085	1716656
243	-2	5.940	2014075

During the study it was observed that upon treatment of the drug with base (0.1M NaOH), acid (0.1M HCl) and hydrogen peroxide (30%, 3% and 1%), no degradation was observed. The percentage recovery of the drug under various stress conditions are indicated in the table. Figure 3a to 3d shows the chromatograms of force degraded samples. The drug was found to be stable under different stressed conditions.

Results of Forced Degradation Studies

S. No.	Type of Degradation	% Recovery
1	Alkali (0.1M NaOH, 60^{0}C, 4h)	102.05
2	Acid (0.1M HCl, 60^{0}C, 4h)	108.61
3	Oxidation (30%, 3%, 1% H_2O_2, 25^{0}C, 4h)	115.24
4	Oven (40^{0}C, 60^{0}C, 4h)	109.96

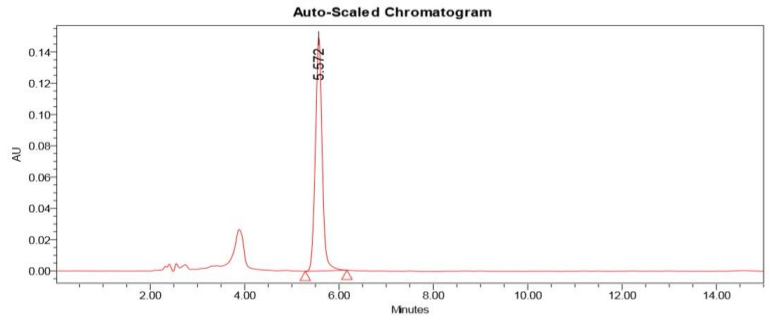

Fig. 3a: Chromatogram showing acid hydrolysis peak

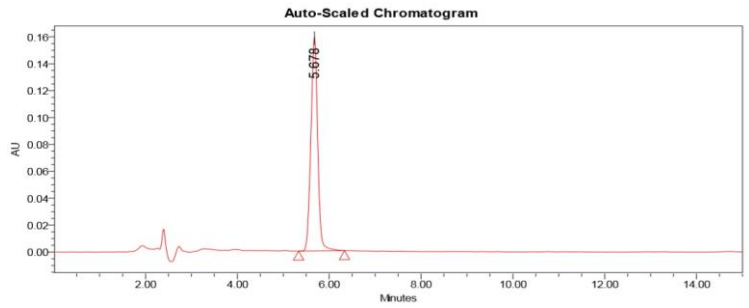

Fig. 3b: Chromatogram showing alkali hydrolysis peak

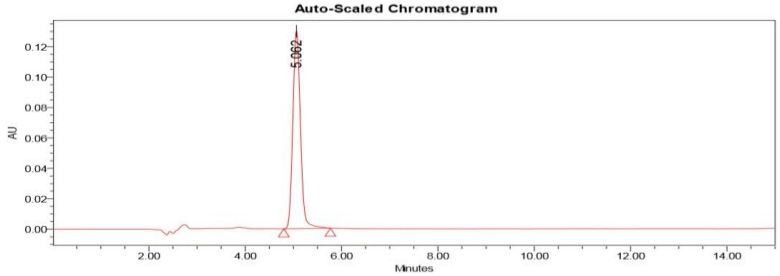

Fig. 3c: Chromatogram showing oxidation peak

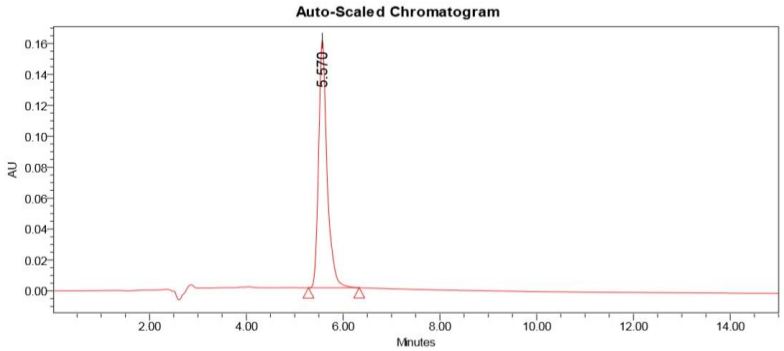

Fig. 3d: Chromatogram showing Dry heat stability of Quetiapine

CONCLUSION

A simple and accurate reverse phase HPLC method has been developed for the determination of Quetiapine fumarate. The method was validated by testing its linearity, accuracy, precision, limits of detection, quantitation, selectivity and robustness. The run time of less than 10 minutes allows its application for the routine determination of Quetiapine fumarate. Further, the proposed RP-HPLC method has excellent sensitivity, precision and reproducibility. The proposed method can be used as a stability indicating method for assay of Quetiapine fumarate in dosage form.

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