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RESEARCH ARTICLE

STABILITY INDICATING RP-HPLC METHOD FOR THE ESTIMATION OF QUETIAPINEFUMARATE IN BULK AS WELL AS IN PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

This study was designed to develop and validate a simple, sensitive, precise, and specific stability indicating reverse phase high-performance liquid chromatographic (HPLC) method for estimation of QuetiapineFumarate in bulk and its tablet dosage form. The HPLC separation was carried out by reverse phase chromatography on Thermo column Symmetry C18 (4.6 x 150mm, 5 µm) with a mobile phase composed Sodium dihydrogen phosphate and the pH was adjusted to 4.0 by Orthophosporic Acid & Methanol in the ratio of 35:65 v/v in isocratic mode at a flow rate of 1.0 ml/min. The run time was maintained for 6mins. The detection was monitored at 290 nm. The calibration curve for QuetiapineFumarate was linear from 20 to60 µg/ml. The inter-day and intra-day precision was found to be within the limits. The proposed method was adequate sensitivity, reproducibility, and specificity for the determination of QuetiapineFumarate in bulk and its tablet dosage forms. The limit of detection [LOD] and limit of quantification [LOQ] for QuetiapineFumarate were found to be 0.01 µg/ml and 0.03 µg /ml respectively. The Accuracy recoveries were 100.0-100.4% and reproducibility was found to be satisfactory.The bulk active pharmaceutical ingredient was subjected to thermal, photolytic, hydrolytic (acidic and basic) and oxidative stress conditions and stressed samples were analyzed by the proposed method. The method was validated in terms of linearity, precision, accuracy, specificity and robustness. All the validation was done as per ICH guidelines. The proposed method was simple, fast, accurate, and precise for the quantification ofQuetiapineFumarate in the dosage form, bulk drugs as well as for routine analysis in quality control.

Key-Words: QuetiapineFumarate, RP-HPLC, ICH, Stability Indicating Studies, LOD, LOQ.

INTRODUCTION

Quetiapine Fumarate is a white to off-white crystalline powder. Drug having efficacy in the treatment of schizophrenia and bipolar disorder is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonisms. An atypical antipsychotic, Quetiapine fumarate (2-[2-(4-dibenzo [*b, f*] [1, 4] thiazepin-11-yl-1-piperazinyl) ethoxy] ethanol fumarate (2:1 salt)) which has a unique receptor- binding profile belonging to a new chemical class, the dibenzothiazepine derivatives[1]. Quetiapine is an antagonist at a broad range of neurotransmitter receptors. Quetiapine is used in the treatment of schizophrenia or manic episodes associated with bipolar disorder. As a consequence, there is an increasing demand for new analytical methods for determination of same drug in most economical way. Several stability indicating HPLC methods were reported for the determination of Quetiapine[2], most of these require ultraviolet detection as Quetiapine is not electro active, some stability indicating, impurity characterizing, some they reported for determination of the drug in human plasma[3-5]. A HPTLC method was also developed and reported in the literature[6]. However none of these methods is sensitive enough for determination of the expected drug levels and some of them are time consuming and require complex sample pretreatment or long run times. Some Gas Chromatography–High Performance Liquid Chromatography (GC–HPLC) methods were also employed[7]. Some UPLC–MS methods were published for determination of Quetiapine [8-9]. The goal of our work was to develop a Stability Indicating Reverse Phase HPLC method for determination of Quetiapine in solid dosage form and to use the results for analysis of drug in pharmaceuticals in most economic way, as rapid and effective ways for determination of drugs in simple manner by Chromatography method is desirable because such methods are not that much (analytical papers) available as per our knowledge for the quality control of pharmaceutical formulations containing Quetiapine by RP HPLC. The chemical structure for the drug was represented in Fig. no. 1. To the best of our knowledge, none of the currently available analytical methods can separate all the known related compounds and degradation impurities of Quetiapine dosage form.

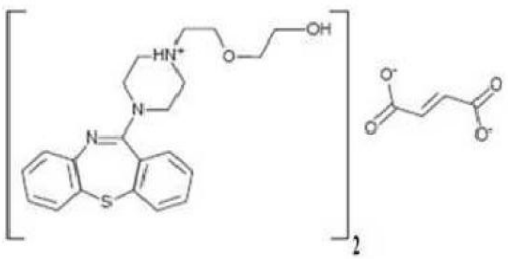

Figure 1: Chemical Structure of Quetiapine fumarate

Quetiapine pharmaceutical formulation is also not official in any pharmacopoeia yet. Furthermore, there is no less time-consuming and stability-indicating RP-RPLC method reported in the literature. Also the cost of the analysis using LCMS, GC/MSD and LC-MS-MS is very high and also very delicate instrument are needed compared to RP-HPLC with respect to routine quality control analysis.

Hence, we focused on developing a selective, fast, cost-effective and stability-indicating method using this advance technique (RP-HPLC) for the assay determination of Quetiapine in solid pharmaceutical dosage forms. Hence a reproducible stability-indicating RP-UPLC method was developed which is less time-consuming and more selective compared to the all present methods, which takes only about 5 min for a single run. Thereafter, this method was successfully validated according to the ICH guideline[10-11].

MATERIAL & METHOD [12]

Chemical and Reagent Used: The following chemicals were procured for the process Water [HPLC Grade], Quetiapine **[**Working Standards], Methanol [HPLC Grade], Ortho phosphoric acid all these chemicals were procured from STANDARD SOLUTIONS and HCL **[**LR Grade**]**procured from FINAR CHEMICAL LIMITED, NaOH [L R Grade]procured from S D FINE- CHEM LIMITED & H_2O_2 procured from ALPHA PHARMA LIMITED. The tablet [25mg Label Claim] was collected from the Local market and the manufacturer was Lupin Company. The brand name of the tablet is Placidine-25mg.

Apparatus and Chromatographic Conditions:

Equipment	:	High performance liquid chromatography equipped with Auto Sampler sand DAD or UV detector. (Waters, Alliance 2695 Separation Module with 2487 UV Vis Detector)
Column	:	Symmetry C18 (4.6 x 150mm, 5 µm Make: Thermo)
Flow rate	:	1.0mL per min
Wavelength	:	290 nm
Injection volume	:	20 µl
Temperature	:	Ambient
Run time	:	6.0 min
Detector	:	Photo diode array [For Force Degradation Studies]
Soft ware	:	Empower 2
Model No	:	2996
MFD by	:	WATERS

Preparation of Sodium Dihydrogen Phosphate buffer[13-15]: The Buffer Solution was prepared by weighing accurately and transferred 2.5mg of sodium dihydrogen phosphate into a 1000ml volumetric flask, dissolved and diluted to 1000ml with Water [HPLC grade]. The pH was adjusted to 4.0 with Orthophosphoric acid.

Preparation of mobile phase: The above mixture was taken [Buffer Solution] 350mL (35%) and 650 mL of Methanol HPLC (65%) mixed thoroughly and degassed in ultrasonic water bath for 5 minutes. Then it was filtered through 0.45 µ filter under vacuum filtration.

Diluent Preparation: The Mobile phase was used as diluent.

Preparation of the Quetiapine Standard & Sample Solution:

Standard Solution Preparation: The Standard Stock Solution was prepared by weighing accurately and transferred 10mg of Quetiapine [Working standard] into a 10 mL volumetric flask. About 7 mL of diluent was added and sonicated to dissolve it completely and the volume was made up to the mark with the same solvent. Further from the above Stock Solution pipette out 0.4 ml solution into a 10ml volumetric flask and diluted up to the mark with the diluent. The resultant solution was mixed well and then it was filtered through 0.45µm filter.

Sample Solution Preparation: The Sample Stock Solution was prepared by weighing accurately 5 Quetiapine Tablets and calculated the average weight. Further accurately weighed and transferred the sample equivalent to 10 mg of Quetiapine into a 10 mL volumetric flask. About 7 mL of the diluent was added and sonicated to dissolve it completely and the volume was made up to the mark with diluent. The resultant solution was mixed well and then it was filtered through 0.45µm filter. Further from the above Stock Solution pipette out 0.4 ml solution into a 10ml volumetric flask and diluted up to the mark with diluent. The resultant solution was mixed well and then it was filtered through 0.45µm filter.

Procedure for Injecting the Sample & Standards in the Chromatographic System[16-17]: About 20 µL of the standard and sample solutions were injected into the chromatographic system and measured the area for the Quetiapine peak and calculated the %Assay by using the suitable formulae.

System Suitability Results[18-19]: The Tailing factor for the peak due to Quetiapine in Standard solution should not be more than 2.0. The theoretical plates for the Quetiapine peak in Standard solution should not less than 2000.

Assay Calculation Formulae:

$$Assay\ \% = \frac{AT}{AS} \times \frac{WS}{DS} \times \frac{DT}{WT} \times \frac{P}{100} \times \frac{Avg.Wt.}{Label\ Claim} \times 100$$

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Where:

AT = Peak Area of Quetiapine obtained with test preparation

AS = Peak Area of Quetiapine obtained with standard preparation

WS = Weight of working standard taken in mg

WT = Weight of sample taken in mg

DS = Dilution of Standard solution

DT = Dilution of sample solution

P = Percentage purity of working standard

Results obtained for the Assay:

System Suitability Results:

1). The Tailing factor Obtained from the standard injection was 1.5.

2). The Theoretical Plates Obtained from the standard injection was 4324.4.

Assay Result Obtained:

Weight of 5 tablets: 0.5510 grams

Average Weight : 0.1030grams

$$\frac{1867403}{1875180}\times\frac{10}{10}\times\frac{0.4}{10}\times\frac{10}{10}\times\frac{10}{41.2}\times\frac{99.8}{100}\times\frac{103.0}{25}\times 100 = 99.4\%$$

VALIDATION DEVELOPMENT[20-22]

1. **Precision:** The precision of an analytical procedure expresses the closeness of measurements obtained from multiple sampling of the same homogenous sample under the prescribed conditions.

Table 1: The results for Precision

Injection	Area
Injection-1	1871423
Injection-2	1876279
Injection-3	1874529
Injection-4	1879273
Injection-5	1873436
Average	1874987.9
Standard Deviation	2973.1
%RSD	0.2

Acceptance Criteria: *The % RSD for the area of five standard injections results should not be more than 2%.*

Precision may be considered at three levels: repeatability, intermediate precision and reproducibility. The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements. The standard solutions were injected for five times and the area was measured for all five injections in HPLC. The %RSD for the area of five replicate injections was found to be within the specified limits. The data were represented in the Table no.1.

2. **Intermediate Precision:** To evaluate the intermediate precision (also known as Ruggedness) of the method, Precision was performed on different day by using different make column of same dimensions. The standard solutions were injected for five times and the area was measured for all five injections in HPLC. The %RSD for the area of five replicate injections was found to be within the specified limits. The Data were represented in Table no.2.

Table 2: The results for Intermediate Precision (Ruggedness)

Injection	Area
Injection-1	1869365
Injection-2	1868938
Injection-3	1861814
Injection-4	1867522
Injection-5	1866552
Average	1866837.9
Standard Deviation	3023.9
%RSD	0.2

Acceptance Criteria: *The % RSD for the area of five standard injections results should not be more than 2%.*

3. **Accuracy:** The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and value found. The standard solution with Accuracy -50%, Accuracy -100% and Accuracy -150% solutions were injected to the chromatographic system. The amount found was calculated and amount added for the drug [Quetiapine] was calculated and calculated the individual recovery and mean recovery values. The data were represented in Table no. 3.

Table 3: The results for Accuracy

%Concentration (at specification Level)	Area	Amount Added (mg)	Amount Found (mg)	% Recovery	Mean Recovery
50%	2006872	5.0	5.0	100.0%	100.5%
100%	4014113	10.0	10.0	100.0%	
150%	6104804	15.0	15.2	101.4%	

Acceptance Criteria: *The % Recovery for each level should be between 98.0 to 102.0%.*

4. **Linearity:** The linearity of the analytical procedure is its ability (within a given range) to obtain the test results which are directly proportional to the concentration (amount) of analyte in the sample. Different levels were prepared and injected each level into the chromatographic system and the peak area was measured. Plotted a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peak area) and calculated the correlation coefficient. The data were represented in Table no.4.

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Table 4: The results for Linearity

Sl. No.	Linearity Level	Concentration	Area
1	I	20µg/ml	1121401
2	II	30µg/ml	1529276
3	III	40µg/ml	1879755
4	IV	50µg/ml	2344717
5	V	60µg/ml	2766815
Correlation Coefficient			0.999

Acceptance Criteria: *The Correlation coefficient should be not less than 0.999.*

5. **Limit of Detection:** The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantities as an exact value. Several approaches for determining the detection limit are possible, depending on whether the procedure is a non instrumental or instrumental.

Calculation of S/N Ratio:

Average Baseline Noise obtained from Blank

Signal Obtained from LOD solution (0.25% of target assay concentration)

S/N = 152/51= 2.98

Acceptance Criteria: The S/N Ratio value should be 3 for LOD solution.

6. **Limit of Quantification:** The Quantification limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The Quantification limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/ or degradation products. Several approaches for determining the Quantification limit are possible, depending on whether the procedure is a non- instrumental or instrumental.

Calculation of S/N Ratio:

Average Baseline Noise obtained from Blank

Signal Obtained from LOD solution (0.75% of target assay concentration)

S/N = 509/51 = 9.98

Acceptance Criteria: The S/N Ratio value should be 10 for LOQ solution.

7. **Robustness:** The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameter and provides an indication of its reliability during normal usage. As part of the Robustness, deliberate change in the Flow rate, Mobile Phase composition, Temperature Variation was made to evaluate the impact on the method. As part of the Robustness, deliberate change in the Flow rate, Mobile Phase composition, Temperature Variation was made to evaluate the impact on the method.

a) The flow rate was varied at 0.7 to0.9 ml/min. The Standard solution 40 µg/ml was prepared and analysed using the varied flow rates along with method developed flow rate. On evaluation of the above results, it was concluded that the variation in flow rate does not affected the method significantly. Hence it indicated that the method was robust even by change in the flow rate ±10%.

b) The Organic composition in the Mobile phase was varied from70% to 50%. The Standard solution 40 µg/ml was prepared and analysed using the varied Mobile phase composition along with the actual mobile phase composition. On evaluation of the above results, it was concluded that the variation in 10% Organic composition in the mobile phase does not affected the method significantly. Hence it was indicated that the method was robust even by change in the Mobile phase ±10%. The data were represented in Table no. 5 & 6.

Table 5: The results for the Robustness with change in the Flow Rate.

Sl. No.	Flow Rate (ml/min)	System Suitability Results	
		USP Plate Count	USP Tailing
1	0.7	4486	1.5
2	0.8	4324.4	1.5
3	0.9	4306	1.4

Table 6: The results for Robustness with change in the Organic Composition in the Mobile Phase

Sl. No.	Change in Organic Composition in the Mobile Phase	System Suitability Results	
		USP Plate Count	USP Tailing
1	10% less	4758	1.5
2	*Actual	4324.4	1.5
3	10% more	3807	1.5

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8. Degradation studies[23]: The International Conference on Harmonization (ICH) guideline entitled stability testing of new drug substances and products requires that stress testing be carried out to elucidate the inherent stability characteristics of the active substance. The aim of this work was to perform the stress degradation studies on the Quetiapine Fumarate using the proposed method.

a. Hydrolytic degradation under acidic condition: 0.4 ml of stock solution (1000 µg/ml) of the drug [Quetiapine Fumarate] was prepared and taken in a 10 volumetric flask in which 3 ml of 0.1N HCl was added. Then the volumetric flask was kept at normal condition for 90 minutes and then it was neutralized with 0.1 N NaOH and the volume was made up to [10ml] with the diluent. The resultant solution was filtered with 0.45 microns syringe filter and placed in the vial.

b. Hydrolytic degradation under alkaline condition: 0.4 ml of stock solution (1000 µg/ml) of the drug [Quetiapine Fumarate] was prepared and taken in a 10 ml volumetric flask in which 3 ml of 0.1N NaOH was added. Then the volumetric flask was kept at normal condition for 90 minutes and then it was neutralized with 0.1 N HCL and the volume was made up to mark [10ml] with the diluent. The resultant solution was filtered with 0.45 microns syringe filter and placed in the vial.

c. Thermal induced degradation: 0.4 ml of stock solution (1000 µg/ml) of the drug [Quetiapine Fumarate] was prepared and taken in a 10 ml volumetric flask in which 3 ml of diluent was added. Then the volumetric flask was kept at reflex condition for 60 minutes and the volume was made up to [10ml] with the diluent. The resultant solution was filtered with 0.45 microns syringe filter and placed in the vial.

d. Oxidative degradation: 0.4 ml of the stock solution of the drug [Quetiapine Fumarate] (1000 µg/ml) was prepared and taken in 10 ml volumetric flask in which 1 ml of 3 % w/v of hydrogen peroxide was added and the volume was made up to the mark [10ml] with the diluent. The volumetric flask was then kept at room temperature for 15 min. The resultant solution was filtered with 0.45 microns syringe filter and placed in the vial.

e. Photolytic degradation: The sample of the drug [Quetiapine Fumarate] was exposed to near ultra violet lamp in Photostablity Chamber providing illumination for 1hr-5hr. 10 mg of the sample was dissolved in distilled water [HPLC grade] and the volume was made up to mark [10 ml]. From the above solution dilutions were carried out to achieve the appropriate concentration to make 30µg/ml and the solution was taken in the vial.

Table 7: Represented the following results were observed from the degradation studies

Sl. No.	Degradation Studies	Retention Time	Area	Height	USP Plate Count	USP Tailing Factor	Purity Angle	Purity Threshold
1	Hydrolytic degradation under acidic condition	3.262	2006753	264504	4492.6	1.52	0.53	0.63
2	Hydrolytic degradation under alkaline condition	3.263	1963597	258816	4496.5	1.51	0.32	0.45
3	Thermal induced degradation	3.260	1920441	253128	4526.9	1.51	0.41	0.53
4	Oxidative degradation	3.262	1834129	241751	4863.9	1.51	0.26	0.32
5	Photolytic degradation	3.264	1898863	250283	4321.5	1.51	0.19	0.21

RESULT & DISCUSSION

The present study was carried out to develop a sensitive, precised and accurate stability indicating RP-HPLC method for the estimation of Quetiapine Fumarate in bulk as well in pharmaceutical dosage form. In order to develop the method under isocratic conditions, mixtures of Sodium Dihydrogen Phosphate Buffer [with different pH] and Methanol [HPLC grade] in different combinations were tested as mobile phase on a Symmetry C18 (4.6 x 150mm, 5 µm, Make: Thermo) column. A binary mixture of Sodium Dihydrogen Phosphate Buffer [pH 4.0 adjusted with Orthophosphoric acid] and Methanol [HPLC Grade] in 35:65 v/v proportion was proved to be the most suitable of all combinations since the chromatographic peaks were better defined and resolved and almost free from tailing. The retention times obtained for the drug [Quetiapine Fumarate] was around 2.854 min. A model chromatogram was shown in Fig. no.2.

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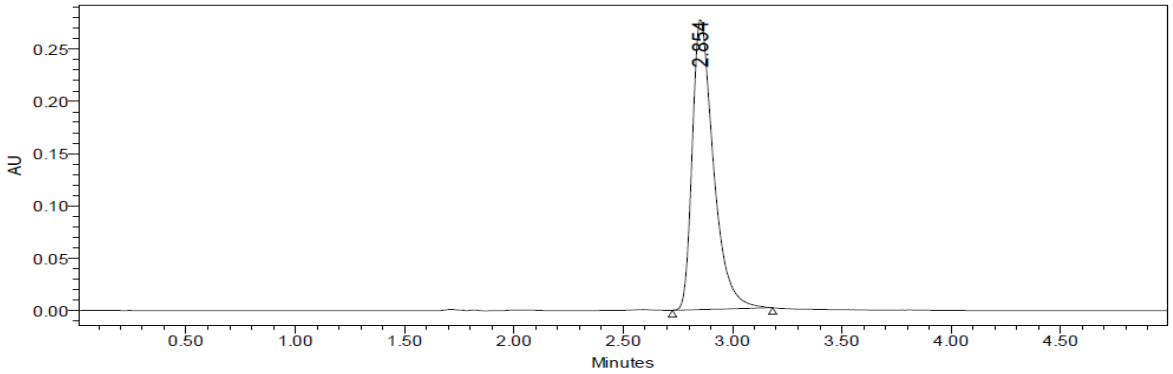

Figure 2: A model Chromatograph for the Drug Quetiapine Fumarate

The Precision data was represented in Table no. 1. When Quetiapine was analyzed by the proposed method in the intra and inter-day (Ruggedness) variation results, a low coefficient of variation was observed and it was represented in Table no. 2. This shows that the present HPLC method was highly precised and it was represented in Fig no. 3.

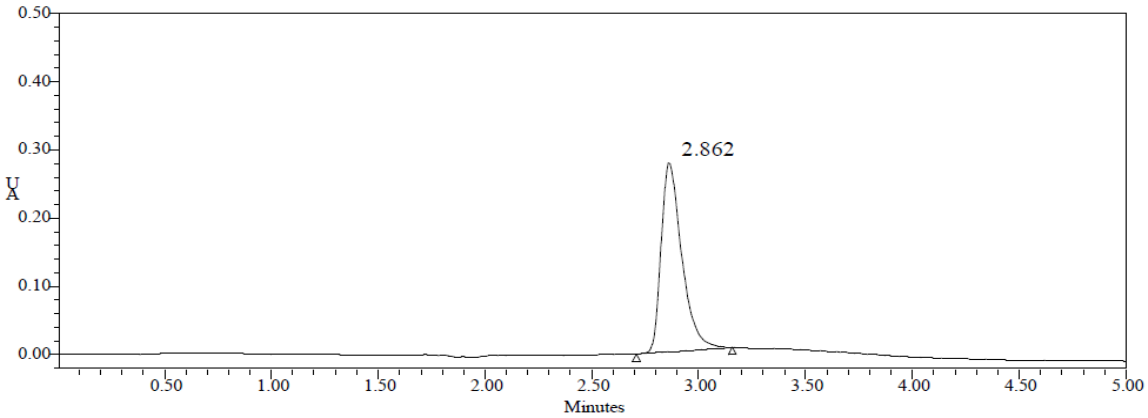

Figure 3: A Model Chromatograph represents the Ruggedness

The Accuracy recoveries were found to be 100.0-100.4% and reproducibility was found to be satisfactory. The Accuracy data were summarized in Table no. 3. In order to test the linearity of the method, five dilutions of the working standard solutions of the drug in the range of 20 to 60µg per mL were prepared. The data was represented in Table no. 4. Each of the dilutions was injected into the column and the Linearity Curve was represented in Fig no. 4.

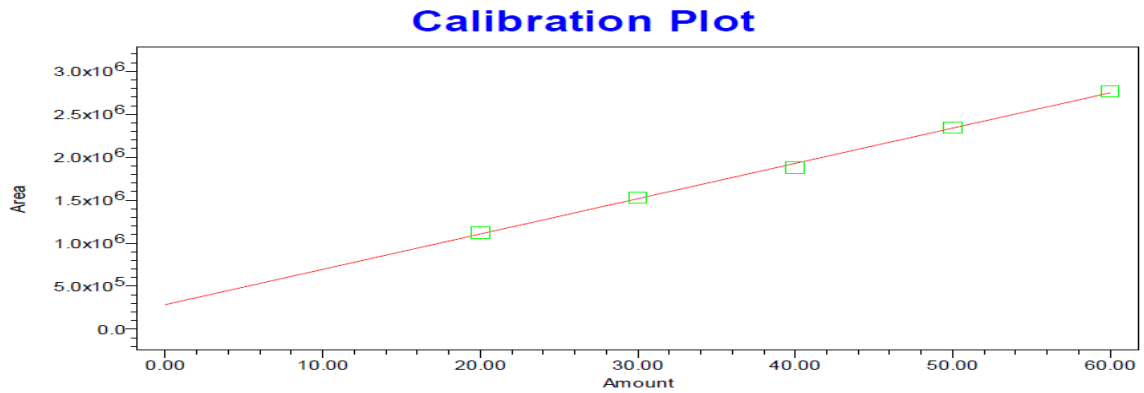

Figure 4: Calibration Curve or Linearity Curve for the Drug QuetiapineFumarate

The method was duly validated by evaluation of the required parameters. Robustness of the method was found out by testing the effect of small deliberate changes in the chromatographic conditions in the chromatographic conditions and the corresponding peak areas. The factors selected for this purpose was flow rate and percentage composition variation in organic phase [Methanol]. The method was found to be robust enough that the peak area was not apparently affected by small variation in the chromatographic conditions. The Fig.no.5, 6, 7 & 8 were represented the Robust nature of the chromatograph.

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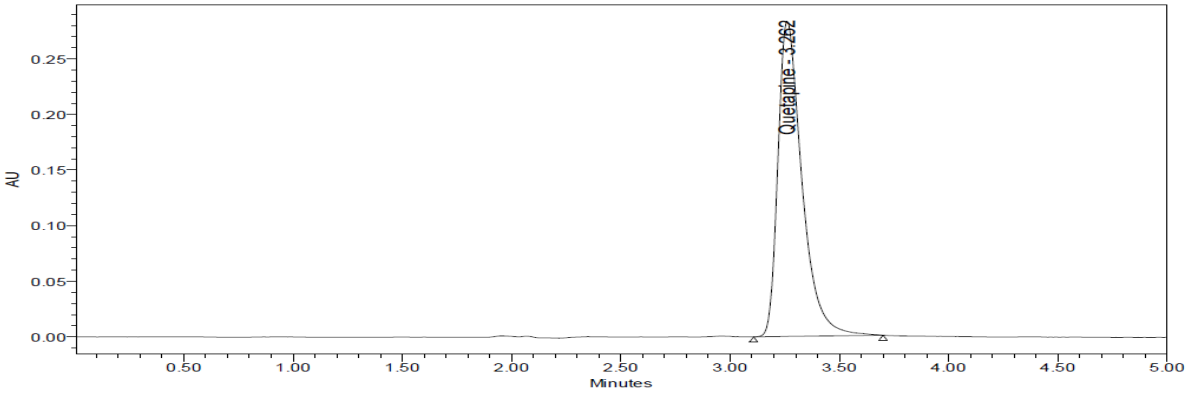

Figure 5: The Robustness chromatograph with decrease in the flow rate

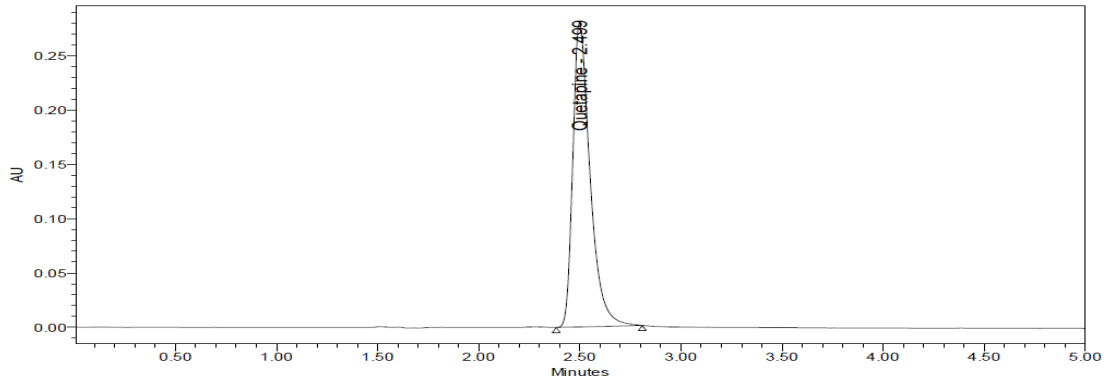

Figure 6: The Robustness Chromatograph with increase in the flow rate

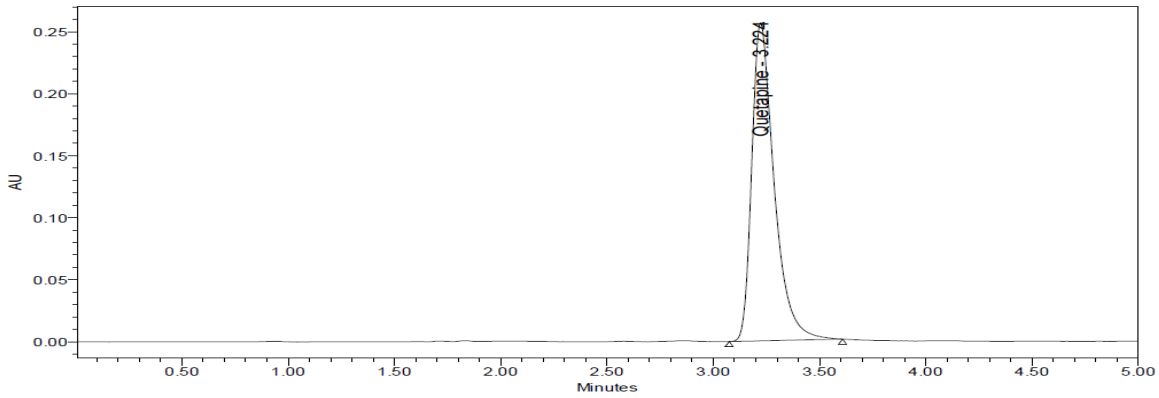

Figure 7: The Robustness chromatograph with less Mobile Phase composition

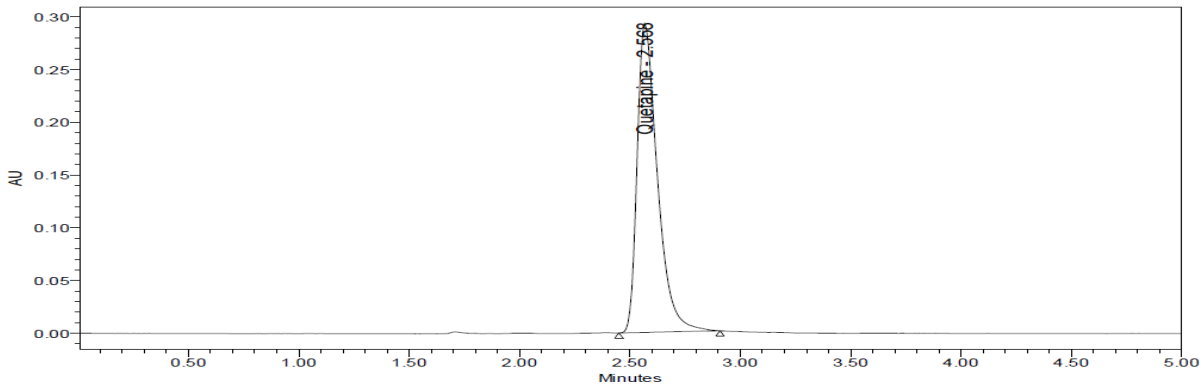

Figure 8: The Robustness chromatograph with more Mobile Phase Composition

The system suitability parameters were within the limits as shown in Table 5 and 6 for the drug. Limit of detection and limit of quantification of the method were calculated basing on standard deviation of the response and the slope (s) of the calibration curve at approximate levels of the limit of detection and limit of quantification. The LOD for

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the drug was found to be 0.01µg/ml and LOQ for the Drug was found to be 0.03µg/mL.

In order to evaluate the stability of Quetiapine Fumarate and ability of the method to separate Quetiapine Fumarate from its degradation products, Quetiapine Fumarate was subjected to various stress conditions such as Hydrolytic degradation under acidic condition (using 0.1N HCl & 0.1 N NaOH), Hydrolytic degradation under alkaline condition (using0.1N NaOH & 0.1N HCL), Thermal induced degradation (Reflex Condition for 60 mins), Oxidative degradation (by using 3 % w/v of hydrogen peroxide), Photolytic degradation (exposed to near ultra violet lamp in photostablity chamber providing illumination for 1hr, 5hr). The following chromatograph represents the degradation studies for the drug [Quetiapine Fumarate] which were represented in fig. no.9, 10, 11, 12 & 13.

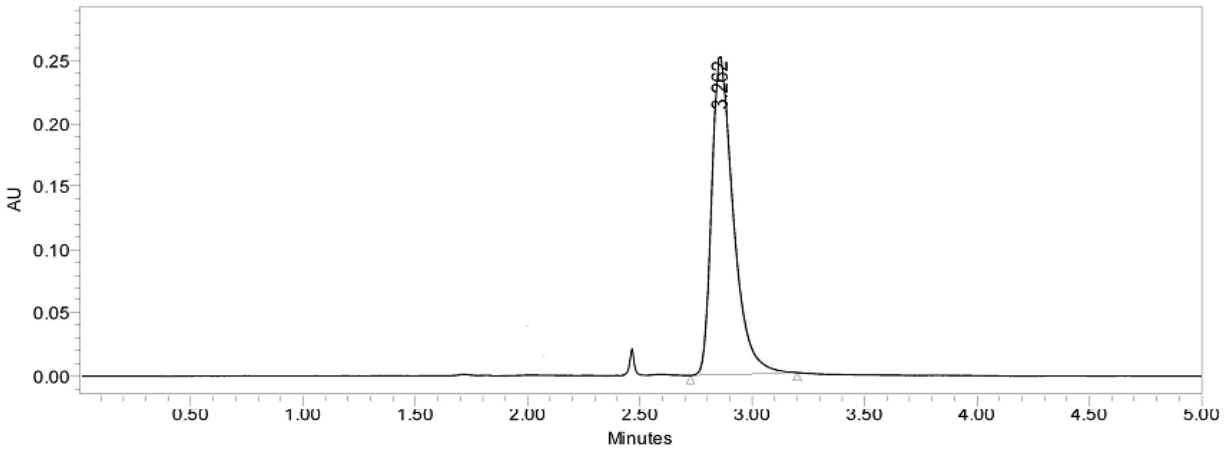

Figure 9: The chromatograph represents the Hydrolytic degradation under acidic condition

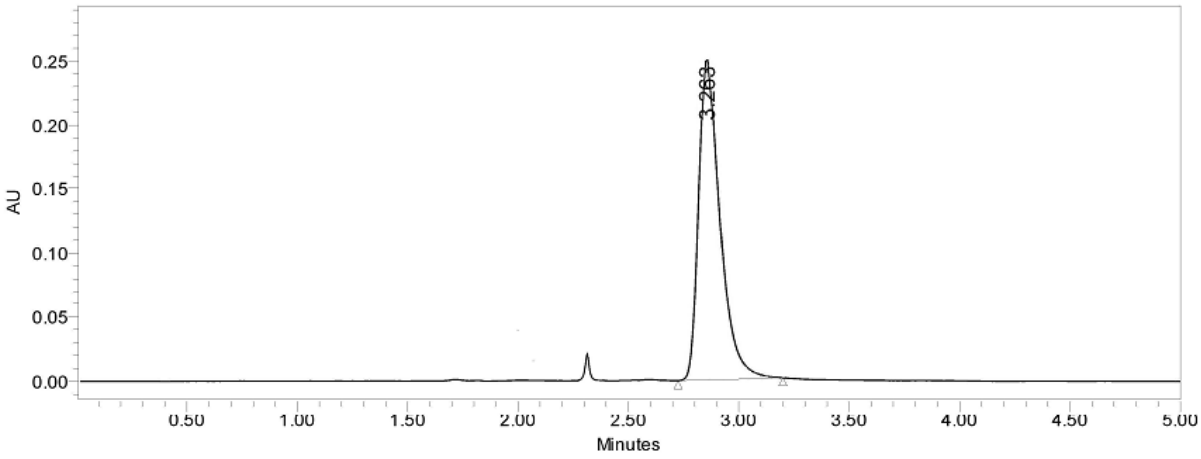

Figure 10: The chromatograph represents the Hydrolytic degradation under alkaline condition

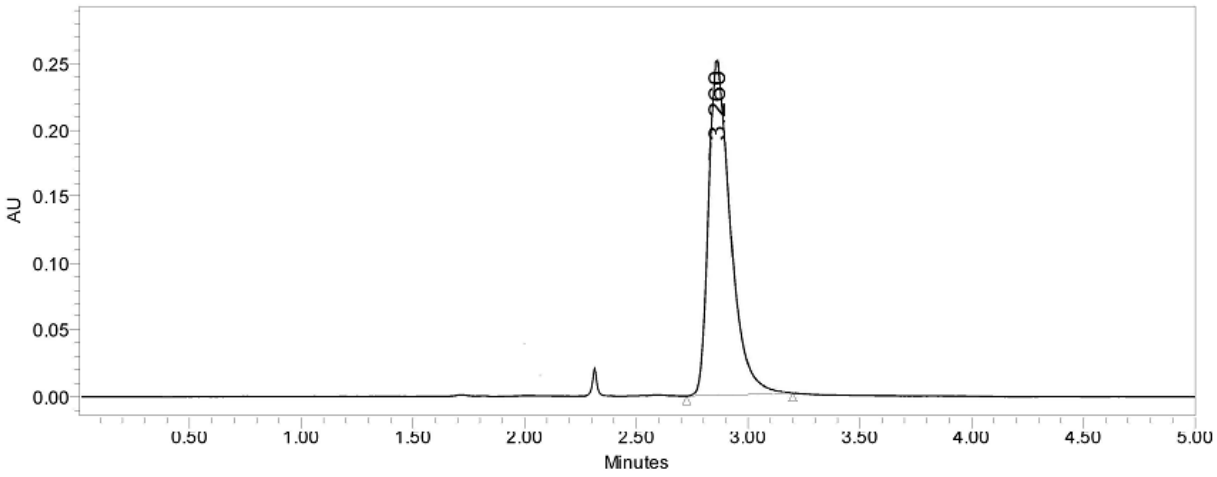

Figure 11: The chromatograph represents the Thermal induced degradation

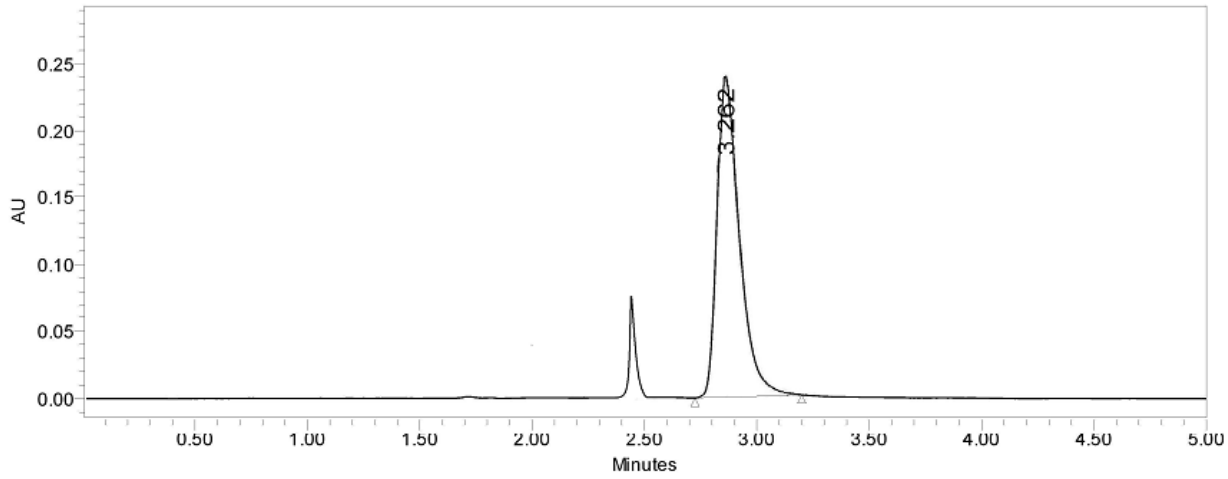

Figure 12: The chromatograph represents theOxidative degradation

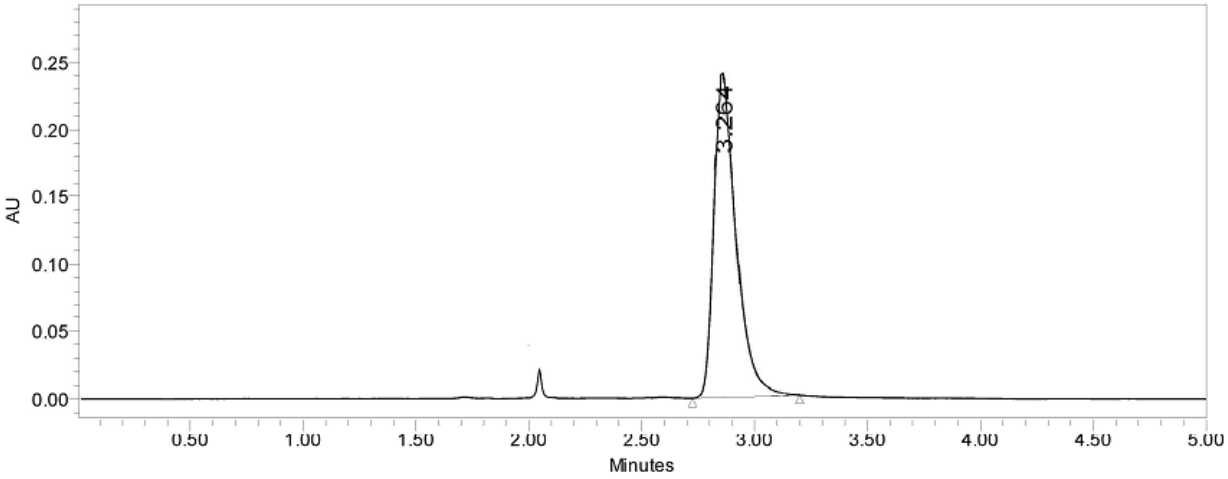

Figure 13: The chromatograph represents thePhotolytic degradation

The drug content formulations were quantified by using the proposed analytical method. The low coefficient of variation in the recovery data indicates the reproducibility of the method in dosage forms. It can be concluded that the proposed stability indicating HPLC method was sufficiently sensitive and reproducible for the analysis of Quetiapine in the Tablet formulation dosage forms within a short analysis time.

CONCLUSION

It can be concluded that the proposed stability indicating RP-HPLC method developed for the quantitative determination of Quetiapine Fumarate in bulk and in its formulations was simple, selective, sensitive, accurate, precise and rapid. The method was proved to be superior to most of the reported methods. The mobile phases was simple to prepare and economical. The sample recoveries in the formulation were in good agreement with their respective label claims and they suggested non-interference of formulation excipients in the estimation. Hence this method can easily be adopted as an alternative method to reported ones for the routine determination of Quetiapine Fumarate depending upon the availability of chemicals and nature of other ingredients present in the sample. The method also finds use in clinical, biological and pharmacokinetic studies of Quetiapine Fumarate. The method was validated as per ICH guidelines, and validation acceptance criteria were met in all cases. Application of this method for estimation of Quetiapine Fumarate from tablet dosage form and stressed samples showed that neither the degradation products nor the excipients interfered in the estimation of drug. Hence, this method was specific, stability-indicating and can be successfully used for the estimation of Quetiapine Fumarate in bulk and pharmaceutical dosage forms.

 ISSN: 2250-1177 CODEN (USA): JDDTAO

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 ISSN: 2250-1177 CODEN (USA): JDDTAO