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Research Article

A NOVEL VALIDATED RP-HPLC METHOD FOR THE DETERMINATION OF QUETIAPINE FUMARATE IN BULK AND PHARMACEUTICAL TABLET DOSAGE FORMS: APPLICATION TO DISSOLUTION STUDY

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ABSTRACT
A simple, specific, accurate, rapid, inexpensive isocratic Reversed Phase-High Performance Liquid Chromatography (RP-HPLC) method was developed and validated for the quantitative determination of Quetiapine Fumarate in pharmaceutical tablet dosage forms. RP-HPLC method was developed by using Welchrom C_{18}Column (4.6 X 250 mm, 5 µm), Shimadzu LC-20AT Prominence Liquid Chromatograph. The mobile phase composed of 10 mM Phosphate buffer (pH-3.0, adjusted with triethylamine): acetonitrile (50:50 v/v). The flow rate was set to 1.0 $mL.min^{-1}$ with the responses measured at 230 nm using Shimadzu SPD-20A Prominence UV-Vis detector. The retention time of Quetiapine Fumarate was found to be 3.260 minutes. Linearity was established for Quetiapine Fumarate in the range of 2-10 $\mu g.mL^{-1}$ with correlation coefficient 0.9999. The validation of the developed method was carried out for specificity, linearity, precision, accuracy, robustness, limit of detection, limit of quantitation. The developed method can be used for routine quality control analysis of Quetiapine Fumarate in pharmaceutical tablet dosage form.
Keywords: Quetiapine fumarate, Isocratic RP-HPLC, UV-Vis detector, Method Validation.

INTRODUCTION

Quetiapine Fumarate (Figure 1) Quetiapine fumarate (QTF) is chemically known as 2-(2-(4-dibenzo[b,f] [1, 4] thiazepine-11-yl-1- piperazinyl)ethoxy) ethanol fumaric acid (1 : 2 salt) (Figure 1). QTF was introduced in the clinic as a antipsychotic drug for the treatment of schizophrenia and other psychotic or schizoaffective disorders. QTF belongs to the same family as clozapine and olanzapine, which are classified as atypical antipsychotics and do not cause major extra pyramidal side effects. QTF is effective in the treatment of schizophrenia, treating both the positive and negative symptoms. Several analytical methods have been reported for the determination of QTF in biological fluids and pharmaceuticals. QTF was determined in biological materials by HPLC with UV [1-8], chemiluminescence [9], electrospray ionization MS [10-13], tandem MS / MS detection [14-17], UPLC with tandem MS detection [18,19], GC [20,21] and voltammetry [22]. Different techniques such as polarography [23], potentiometry [24], capillary zone electrophoresis [25,26], HPTLC [27-29], HPLC [30-33] and spectrophotometry [25,34-36] have earlier been used for the determination of QTF in pharmaceuticals. In fact there is a need for the development of a novel, simple, rapid, efficient RP-HPLC analytical method with reproducibility for determination of Quetiapine Fumarate in bulk and pharmaceutical dosage forms. The present study illustrates development and validation of a novel, simple, rapid and efficient RP-HPLC analytical method with reproducibility for determination of Quetiapine Fumarate in bulk and pharmaceutical tablet dosage form. The established method was validated with respect to specificity, linearity, precision, accuracy, robustness, LOD and LOQ according to ICH guidelines.

MATERIALS AND METHODS

Chemicals and Reagents

The reference sample of Quetiapine fumarate standard was kindly supplied as gift sample by Shasun pharmaceuticals, Pondicherry, India. All the chemicals were analytical grade. Potassium dihydrogen orthophosphate and phosphoric acid from Rankem Ltd., Mumbai, India, while acetonitrile (HPLC grade) and triethylamine (HPLC grade) from Merck Pharmaceuticals Private Ltd., Mumbai, India. Ortho phosphoric acid used was of HPLC grade and purchased from Merck Specialties Private Ltd., Mumbai, India. Commercial tablets of Quetiapine fumarate formulation was procured from local market. QUITIPIN-25 tablets are manufactured by Sun Pharma, Sikkim, India.

Instruments

Quantitative HPLC was performed on a isocratic high performance liquid chromatograph (Shimadzu LC-20AT Prominence Liquid Chromatograph) with a LC-20AT VP pump, manual injector with loop volume of 20 µL (Rheodyne), programmable variable wavelength Shimadzu SPD-20A Prominence UV-Vis detector and Welchrom C_{18} Column (4.6 X 250 mm, 5 µm particle size). The HPLC system was equipped with "Spinchrome" software. In addition an electronic balance (Shimadzu TX223L), digital pH meter (Systronics model 802), a sonicator (spectra lab, model UCB 40), UV-Visible Spectrophotometer (Systronics model-2203) were used in this study.

Chromatographic Conditions

Quetiapine fumarate was analyzed by various reversed phase columns like C_8 and C_{18} columns. Among C_8 and C_{18} columns, C_{18} (250 mm X 4.6 mm, 5 µm) column was selected. Various combinations of acetonitrile, phosphate buffer and methanol with triethylamine as column modifier

were tested. The mixture of 10 mM Phosphate buffer (pH adjusted to 3.0 using triethylamine) and Acetonitrile in ratio of 50:50 v/v was selected as mobile phase and UV detection wavelength was 230 nm with a flow rate of 1 $mL.min^{-1}$. Injection volume was 20 µL, with ambient temperature, run time was 6 minutes and retention time was 3.260 minutes. The resulting HPLC chromatogram was shown in Figure 3.

Preparation of Mobile Phase

A 10 mM Phosphate buffer was prepared by dissolving 6.056 g of potassium dihydrogen orthophosphate in 445 mL of HPLC grade water. To this 55 mL of 0.1 M phosphoric acid was added and pH was adjusted to 3.0 with triethylamine. The above prepared buffer and acetonitrile were mixed in the proportion of 50:50 v/v and was filtered through 0.45 µm nylon membrane filter and degassed by sonication.

Preparation of Standard Solution

About 100 mg of pure Quetiapine fumarate was accurately weighed and dissolved in 100 mL of mobile phase to get 1 $mg.mL^{-1}$ stock solution. Working standard solution of Quetiapine fumarate was prepared with mobile phase. The final volume was made with the mobile phase. The standard solution was filtered through 0.45 µm nylon membrane filter and degassed by sonication.

Preparation of Sample Solution

The content of 20 tablets of Quetiapine fumarate (QUITIPIN-25) were accurately weighed and transferred into a mortar and ground to a fine powder. From this, tablet powder which is equivalent to 100 mg of Quetiapine fumarate was taken and the drug was extracted in 100 mL of mobile phase. The resulting solution was filtered using Whatman Grade No.1 filter paper and degassed by sonication. This solution was further suitably diluted for chromatography.

Selection of Detection Wavelength

The UV spectra of various diluted solutions of Quetiapine fumarate in mobile phase were recorded using UV spectrophotometer. The peak of maximum absorbance was observed at 230 nm. This wavelength was used for detection of Quetiapine fumarate.

Calibration Curve for Quetiapine Fumarate

Replicates of each calibration standard solutions (2, 4, 6, 8, 10 $\mu g.mL^{-1}$) were injected using a 20 µL fixed loop system and the chromatograms were recorded. Calibration curves were constructed by plotting concentration of Quetiapine fumarate on X-axis and peak areas of standard Quetiapine fumarate on Y-axis and regression equations were computed for Quetiapine fumarate. The calibration data is presented in Table 2.

***In vitro* dissolution studies**

In vitro dissolution of six tablets containing Quetiapine fumarate was performed using 900 mL volume distilled water as the dissolution media at 50 rpm using an USP Apparatus II. The dissolution study was carried out in a 900 mL volume of distilled water as the dissolution media at 37°C (± 0.5) using the paddle method. 5 mL sample aliquots were withdrawn at 10, 20, 30, 45, 60 and 75 minutes using micropipettes and immediately replaced with equal volumes of fresh medium at the same temperature to maintain constant total volume during the test. All samples were filtered through 0.45 µm membrane filters. The concentrations of Quetiapine fumarate in samples were determined by the proposed HPLC method.

Validation of the Proposed Method

The developed method of analysis was validated as per the ICH for the parameters like system suitability, specificity, linearity, precision, accuracy, robustness and system suitability, limit of detection (LOD) and limit of quantitation (LOQ).

System Suitability

System suitability tests are an integral part of chromatographic method which was used to verify reproducibility of the chromatographic system. To ascertain its effectiveness, certain system suitability test parameters were checked by repetitively injecting the drug solution at the concentration level 10 $\mu g\ mL^{-1}$ for Quetiapine fumarate to check the reproducibility of the system. At first the HPLC system was stabilized for 40 minutes. One blank followed by six replicates of a single calibration standard solution of Quetiapine fumarate was injected to check the system suitability. To ascertain the systems suitability for the proposed method, the parameters such as theoretical plates, peak asymmetry, retention time and parameters were taken and results were presented in Table 1.

Specificity

The effect of wide range of excipients and other additives usually present in the formulations of Quetiapine fumarate in the determinations under optimum conditions was investigated. The specificity of the RP-HPLC method was established by injecting the mobile phase and placebo solution in triplicate and recording the chromatograms. The common excipients such as lactose anhydrous, microcrystalline cellulose and magnesium stearate have been added to the placebo solution and injected and tested. The representative chromatogram of placebo was shown in Figure 2. The specificity results were presented in Table 5.

Linearity

The linearity graphs for the proposed assay methods were obtained over the concentration range of 2-10 $\mu g.mL^{-1}$ of Quetiapine fumarate. Method of least square analysis was carried out for getting the slope, intercept and correlation coefficient, regression data values and the results were presented in Table 2 and Table 3. The representative chromatograms indicating the Quetiapine fumarate were shown in Figure 5 to 9. A calibration curve was plotted between concentration and area response and statistical analysis of the calibration curve is shown in Figure 10.

Precision

Intraday and interday precision study of Quetiapine fumarate was carried out by estimating corresponding responses 3 times on the same day and on 3 different days for the concentration of 10 µg. The percent relative standard deviation (% RSD) was calculated which is within the acceptable criteria of not more than 2.0. The results for intraday and interday precision were presented in Table 6 and Table 7 respectively.

Accuracy (Recovery studies)

The accuracy of the method was determined by calculating recovery of Quetiapine fumarate by the method of addition. Known amount of Quetiapine fumarate at 80 %, 100 % and

120 % was added to a pre quantified sample solution. The recovery studies were carried out in the tablet in triplicate each in the presence of placebo. The mean percentage recovery of Quetiapine fumarate at each level was not less than 96 % and not more than 101 %. The results were presented in Table 8.

Robustness

The Robustness was evaluated by the analysis of Quetiapine fumarate under different experimental conditions such as making small changes in flow rate (± 0.2 ml / min), detection wavelength (± 5 nm), Mobile phase composition (± 5 %). The results were presented in Table 9.

LOD and LOQ

Limit of Detection is the lowest concentration in a sample that can be detected, but not necessarily quantified under the stated experimental conditions. The limit of quantitation is the lowest concentration of analyte in a sample that can be determined with acceptable precision and accuracy. Limit of Detection and Limit of Quantitation were calculated using following formula

LOD = 3.3(SD)/S and LOQ= 10 (SD)/S,
Where SD = standard deviation of response (peak area) and S = slope of the calibration curve.

The LOD and LOQ values are presented in Table 10.

***In vitro* dissolution studies**

The average percentage drug released within 75 minutes as detected by the proposed HPLC method after *in vitro* dissolution of tablets containing drug product are depicted in Figure 14. The dissolution pattern complies with the FDA standards, indicating suitability of the proposed method for the dissolution study of the drug. According to the FDA Guidance (Qui, Xu 2007) no less than 85 % of the active ingredients of the labeled claim should be dissolved within 30 minutes. Dissolution values are presented in Table 11. The representative chromatograms of dissolution are shown in Figure 11 to Figure 16**.**

Table 1: Optimized Chromatographic Conditions and System Suitability Parameters for Proposed HPLC Method for Quetiapine Fumarate

Parameter	Chromatographic conditions
Instrument	SHIMADZU LC-20AT prominence liquid chromatograph
Column	WELCHROM C_{18} Column (4.6 X 250 mm, 5 µm)
Detector	SHIMADZU SPD-20A prominence UV-Vis detector
Diluents	10mM Phosphate Buffer (pH-3): Acetonitrile (50 : 50 v/v)
Mobile phase	10mM Phosphate Buffer (pH-3): Acetonitrile (50 : 50 v/v)
Flow rate	1 $mL.min^{-1}$.
Detection wave length	By UV at 230 nm.
Run time	6 minutes
Column back pressure	128-130($kg.cm^{-2}$)
Temperature	Ambient temperature(25°C)
Volume of injection loop	20 µL
Retention time (R_t)	3.260 minutes
Theoretical plates [th.pl] (Efficiency)	4866
Theoretical plates per meter [t.p / m]	97317
Tailing factor (asymmetry factor)	0.735

Table 2: Linear Regression Data of the Proposed HPLC Method of Quetiapine Fumarate

Parameter	Method
Detection wavelength (λ max)	By UV at 230 nm
Linearity range (µg / ml)	2-10 $\mu g.mL^{-1}$
Regression equation (Y = a + bx)	Y = 115.5x + 10.67
Slope (b)	115.5
Intercept (a)	10.67
Standard deviation of slope (S_b)	0.953
Standard deviation of intercept (S_a)	1.073
Standard error of estimation (Se)	7.977
Correlation coefficient (r^2)	0.999

Table 3: Calibration Data of the Proposed HPLC Method of Quetiapine Fumarate

Concentration, $\mu g.mL^{-1}$.	Peak area, mV.s.
0	0
2	249.801
4	480.882
6	703.553
8	933.651
10	1163.024

Table 4: Assay Results of Quetiapine Fumarate Formulation

Formulation	Labeled amount	Amount found	% Assay ± RSD*
QUITIPIN-25	25 mg	24.577 mg	98.311 ± 1.621

* Average of 6 determinations

Table 5: Specificity Study

Name of the solution	Retention time (R_t) minutes
Mobile phase	No peaks
Placebo	No peaks
Quetiapine fumarate 10 $\mu g.mL^{-1}$	3.260 minutes

Table 6: Results of Precision Study (Intraday)

Sample	Concentration (µg.mL^{-1})	Injection no.	Peak area	% RSD (acceptance criteria < 2.0)
Quetiapine fumarate	25	1	2849.408	0.201
		2	2843.841	
		3	2850.739	
		4	2837.593	
		5	2853.734	
		6	2846.765	

Table 7: Results of Precision Study (Interday)

Sample	Concentration (µg.mL^{-1})	Injection no.	Peak area	% RSD (acceptance criteria < 2.0)
Quetiapine fumarate	25	1	2839.408	0.312
		2	2833.841	
		3	2840.739	
		4	2847.593	
		5	2833.734	
		6	2856.765	

Table 8: Recovery Data of the Proposed Quetiapine Fumarate by RP-HPLC Method

S. No	Concentration level	Amount added (µg.mL^{-1})	Amount found (µg.mL^{-1})	Mean % Recovery ± SD*	% RSD #
	80 %	8	7.949	98.639 ± 0.682	0.692
1		8	7.840		
		8	7.883		
	100 %	10	9.605	96.178 ± 0.233	0.242
2		10	9.602		
		10	9.644		
	120 %	12	11.889	97.856 ± 1.256	1.283
3		12	11.750		
		12	11.588		

*SD is standard deviation # % RSD is percentage of relative standard deviation.

Table 9: Robustness Results of Quetiapine Fumarate

S. No	Parameter	Optimized	Used	Retention time (R_t), min	Peak asymmetry
1.	Flow rate (± 0.2 mL.min^{-1})	1.0 mL.min^{-1}	0.8 mL.min^{-1}	3.836	1.300
			1.0 mL.min^{-1}	3.260	1.368
			1.2 mL.min^{-1}	3.024	1.250
2.	Detection wavelength (± 5 nm)	230 nm	225 nm	3.112	1.118
			230 nm	3.260	1.176
			235 nm	3.451	1.235
3.	Mobile phase composition (± 5 %)	50:50 v/v	55:45 v/v	3.418	1.118
			50:50 v/v	3.260	1.038
			45:55 v/v	3.109	1.474

Table 10: Limit of Detection (LOD) and Limit of Quantitation (LOQ)

Limit of Detection (LOD)	0.227 µg.mL^{-1}
Limit of Quantitation (LOQ)	0.690 µg.mL^{-1}

Table 11: Dissolution data for Quetiapine Fumarate

Time (minutes)	% Dissolved
10	56.91
20	75.83
30	87.27
45	93.91
60	95.97
75	97.95

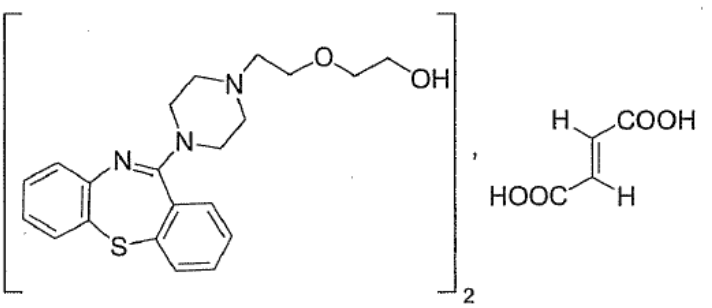

Figure 1: Structure of Quetiapine Fumarate

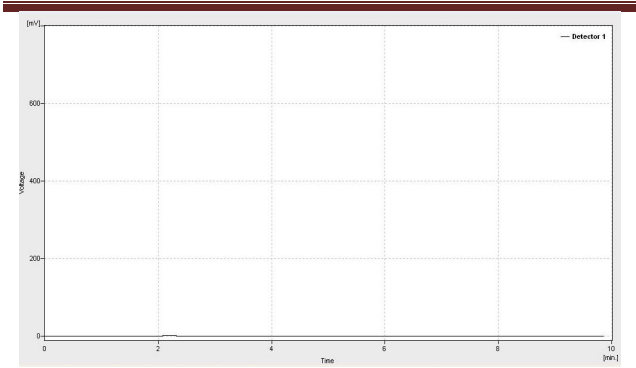

Figure 2: Chromatogram of Placebo

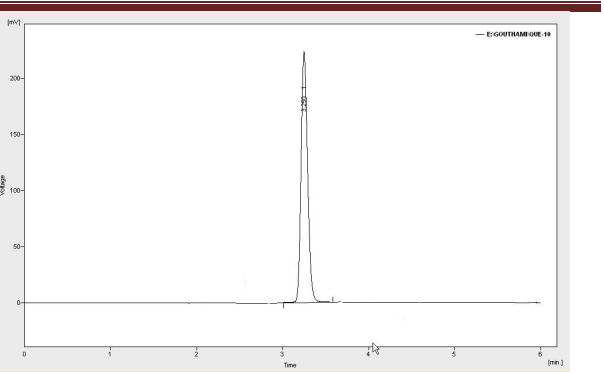

Figure 3: A Typical Chromatogram of Quetiapine Fumarate Standard

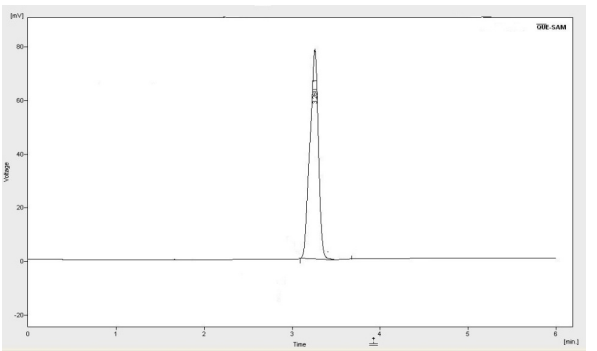

Figure 4: Chromatogram of Market Formulation (Quitipin-25 tablets) of Quetiapine Fumarate

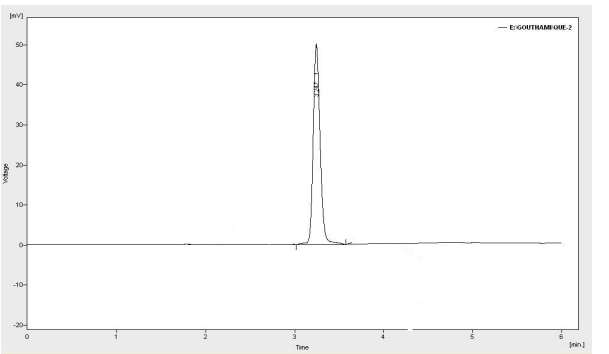

Figure 5: Standard Chromatogram of Quetiapine Fumarate (2 µg.ml^{-1})

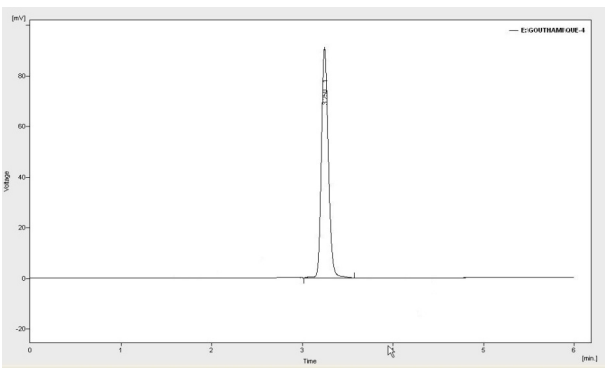

Figure 6: Standard Chromatogram of Quetiapine Fumarate (4 µg.mL^{-1})

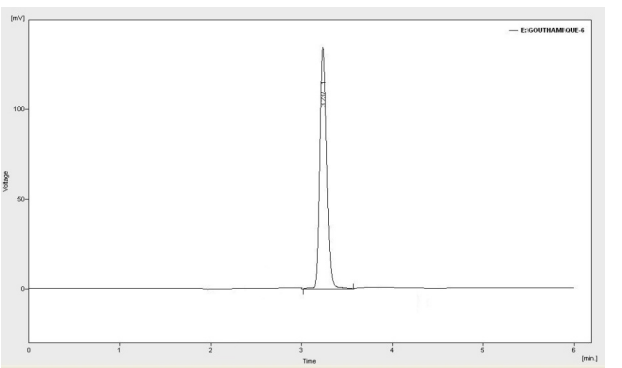

Figure 7: Standard Chromatogram of Quetiapine Fumarate (6 µg.mL^{-1})

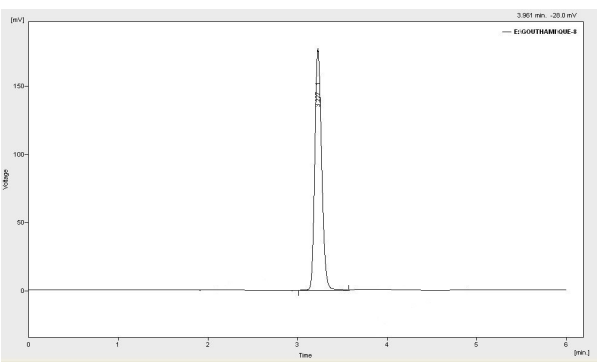

Figure 8: Standard Chromatogram of Quetiapine Fumarate (8 µg.mL^{-1})

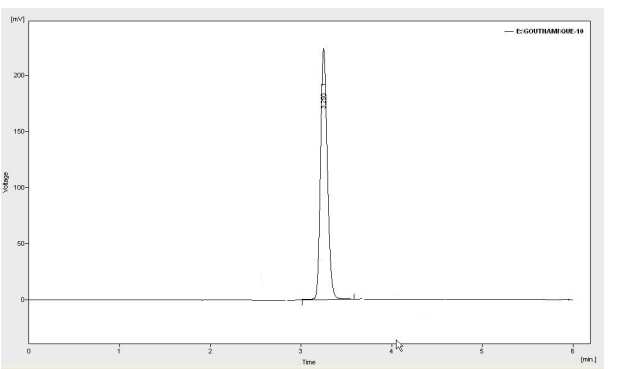

Figure 9: Standard Chromatogram of Quetiapine Fumarate (10 µg.mL^{-1})

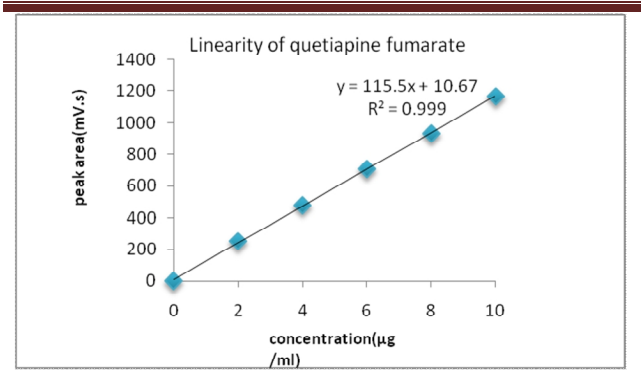

Figure 10: Calibration Plot of Quetiapine Fumarate

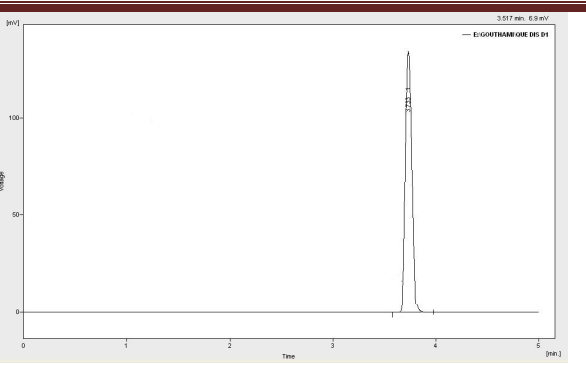

Figure 11: Chromatogram for *In Vitro* Dissolution of Quetiapine Fumarate at 10 minutes

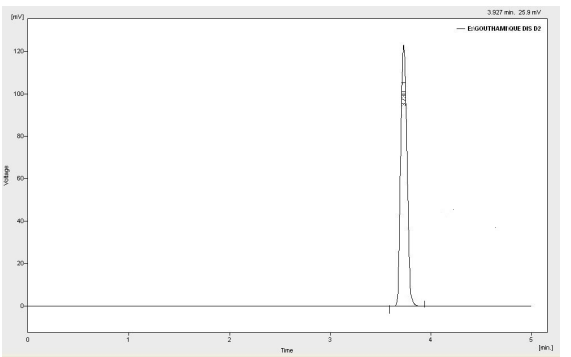

Figure 12: Chromatogram for *In Vitro* Dissolution of Quetiapine Fumarate at 20 minutes

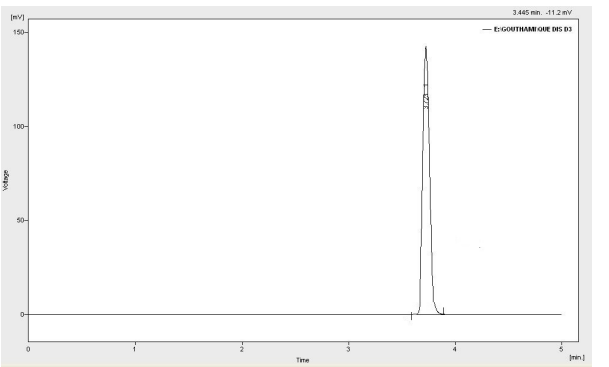

Figure 13: Chromatogram for *In Vitro* Dissolution of Quetiapine Fumarate at 30 minutes

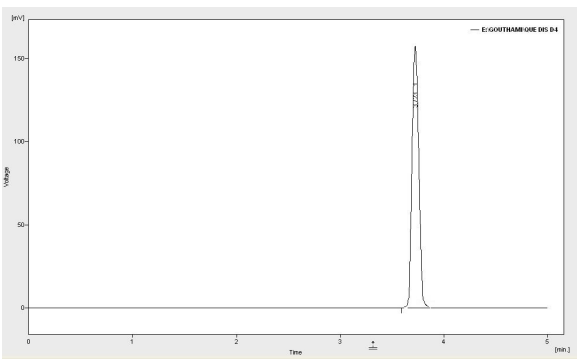

Figure 14: Chromatogram for *In Vitro* Dissolution of Quetiapine Fumarate at 45 minutes

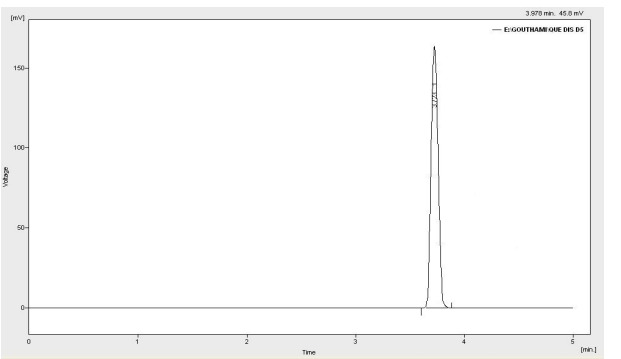

Figure 15: Chromatogram for *In Vitro* Dissolution of Quetiapine Fumarate at 60 minutes

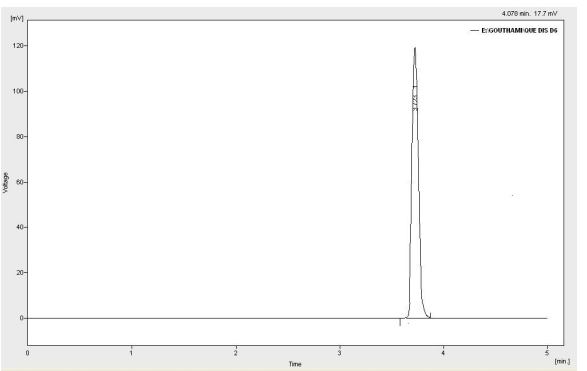

Figure 16: Chromatogram for *In Vitro* Dissolution of Quetiapine Fumarate at 75 minutes

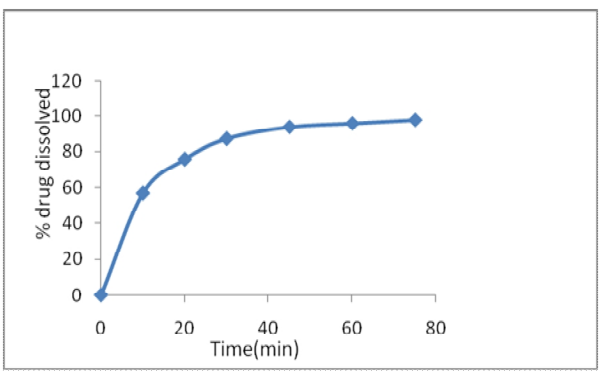

Figure 17: *In Vitro* Dissolution Profile of Quetiapine Fumarate

RESULTS AND DISCUSSION

The mobile phase consisting of 10 mM phosphate buffer (pH-3.0): acetonitrile (50:50 % v/v at1 $mL.min^{-1}$ flow rate was optimized which gave sharp peak, minimum tailing factor with short run time for Quetiapine fumarate. The retention time for Quetiapine fumarate was 3.260 min. UV spectra of Quetiapine fumarate showed that the drug absorbed maximum at 230 nm, so this wavelength was selected as the detection wavelength. System suitability parameters andoptimized chromatographic conditions are shown in Table 1. The calibration curve for Quetiapine fumarate was found to be linear over the range of 2-10 $\mu g.mL^{-1}$. The data of regression analysis of the calibration curve is shown in Table 2 and Table 3. The developed method was applied to the assay of Quetiapine fumarate tablets. The experimental results are given in Table 4. The results were very close to labeled value of commercial tablets. The representative standard and sample chromatograms of Quetiapine fumarate are shown in Figure 3 and 4 respectively. The regression equation was found to be $Y = 115.5x + 10.67$ with correlation coefficient is $r^2 = 0.9999$ which indicates this method has good linearity. The representative chromatograms indicating the Quetiapine fumarate are shown in Figure 5 to 9. The linearity of the graph is shown in Figure 10. The specificity was studied for the examination of the presence of interfering components, while the comparison of chromatograms there was no interference from placebo (Figure 2) with sample peak. They do not disturb the elution or quantification of Quetiapine Fumarate, furthermore the well-shaped peaks also indicate the specificity of the method. Therefore, it was concluded that the method is specific. The specificity results are summarized in Table 5. Precision was studied to find out intra and inter day variations in the test methods of Quetiapine Fumarate for the three times on the same day and different day. The intra-day and inter-day precision obtained was % RSD (< 2.0) indicates that the proposed method is quite precise and reproducible and results are shown in Tables 6 and 7. Recovery studies of the drug were carried out for the accuracy parameter at three different concentrations levels i.e., multiple level recovery studies. A known amount of Quetiapine Fumarate standard was added into pre-analyzed sample and subjected them to the proposed HPLC method. The % recovery was found to be within the limits as listed in Table 8. Generally the mean percentage recovery of Quetiapine fumarate at each level was not less than 96 % and not more than 101 %. In this case percentage recovery of Quetiapine fumarate was found to be in the range of 97.94 % to 99.09 %. The method precision was done and the low % RSD (0.130) values indicates that the proposed method which was in good agreement with precision. Robustness was done by small changes in the chromatographic conditions like mobile phase flow rate, temperature, mobile phase composition etc. It was observed that there were no marked changes in the chromatograms. In fact the parameters are within the limit which indicates that the method has robustness and suitable for routine use. The Robustness results are presented in Table 9. The limit of detection (LOD) and limit of quantitation (LOQ) was calculated based on the standard deviation (SD) of the response and the slope (S) of the calibration curve at levels approximating the LOD and LOQ. The limit of detection (LOD) was 0.227 $\mu g.mL^{-1}$ and the limit of quantitation (LOQ) was 0.690 µg / mL which show that this method is very sensitive. The results are presented in Table 10.

CONCLUSION

A New validated RP-HPLC method has been developed for the quantitative determination of Quetiapine fumarate in bulk and pharmaceutical tablet dosage forms. Statistical analysis of the results shows that the proposed procedure has good precision and accuracy. The method was completely validated shows satisfactory results for all the method validation parameters tested and method was free from interference of the other active ingredients and additives used in the formulation. In fact results of the study indicate that the developed method was found to be simple, reliable, accurate, linear, sensitive, economical and reproducible and have short run time which makes the method rapid. Hence it can be concluded that this method may be employed for the routine quality control analysis of Quetiapine fumarate in active pharmaceutical ingredient (API) and pharmaceutical preparations. The developed method can also be conveniently adopted for dissolution testing of tablets containing Quetiapine fumarate.

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