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Method Development and Validation of Reverse Phase HPLC for Quetiapine Fumarate in Pharmaceutical Dosage

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ABSTRACT

A rapid, specific and accurate isocratic HPLC method was developed and validated for the assay of Quetiapine Fumarate in pharmaceutical dosage forms. The assay involved an isocratic – elution of Quetiapine Fumarate in ODS - C18 column using mobile phase composition consists of (50:50, v/v) of acetonitrile and sodium acetate with 0.1 % ortho phosphoric acid respectively. The wavelength of detection is 294nm. The method showed good linearity in the range of 2.01 to 50.20 µg mL^{-1}. The runtime of the method is 8 min. The proposed method can be used for routine quality control samples in industry in bulk and in finished dosage forms. In present study, a rapid specific precise and validated HPLC method for the quantitative estimation of Quetiapine Fumarate in pharmaceutical dosage forms has been reported. The developed method can be applied to directly and easily to the analysis of the pharmaceutical tablet preparations. The percentage recoveries were near 100% for given methods. The method was completely validated and proven to be rugged. The excipients did not interfere in the analysis. The results showed that this method can be used for rapid determination of venlafaxine in pharmaceutical tablet with precision, accuracy and specificity.

Keywords: Quetiapine Fumarate, Assay, reverse phase, HPLC.

INTRODUCTION

Quetiapine fumarate [Figure-1] commonly known as 2-(2-(4-dibenzo [1, 4] thiazepine-11-yl-1-piperazinyl) ethoxy ethanol fumaric acid (1:2 salt; formula $C_{29}H_{33}N_3O_{10}S$) molecular weight: 615.66 a dibenzothiazepine-compound, is one of the newly discovered anti-psychotic medication [1,2]. An oral anti-psychotic medicine behaves as an antagonist of multiple neurotransmitters and is used as a medication of schizophrenia. It is a selective antagonist with high affinity for the serotonin and dopamine receptors. Quetiapine fumarate belongs to the same family as clozapine and olanzapine, which are classified as a typical anti-psychotic and do not cause any major side effects. The generic name of Quetiapine fumarate is Seroquel, it is used for the medication of schizophrenia, a mental disturbance with symptoms like delusions, hallucinations, disruptive thinking and loss of contact with real world. It is also used for the short term treatment of disbelief associated with bipolar disorder. Seroquel is the first in a new class of anti-psychotic medications [3-5].

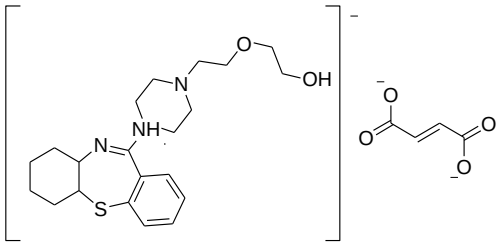

Figure 1: Molecular Structure of Quetiapine Fumarate

Several methods have been published for the quantitative determination of Quetiapine in bulk, and pharmaceutical and biological samples. These methods include UV- Visible spectrophotometry [10-12], UV derivative and extraction free methods [13], HPTLC[14] , capillary zone electrophoretic method [15], high performance liquid chromatographic (HPLC)-UV-detector [16-20], HPLC with solid phase extraction [21], UPLC with Mass- spectrophotometer-detector [22], HPLC with column switching method [23], Gas-Chromatography-Mass spectrophotometry [24] and hyphenated to techniques such as- LC-MS [25],HPLC-electro-spray-mass-ionization-spectrophometry[26],HPLC-Tandem-mass spectrophotometry [27], HPLC-MS-MS method [28].

MATERIALS AND METHODS

Chemicals and Reagents: Quetiapine fumarate (99.92%) is used as drug of analytical interest and Lamotrigine is used as internal standard. Acetonitrile, methanol and tetrahydrofuran, n-propanol (HPLC grade) was obtained from Qualigens®. Milli-Q® water was purchased from Ranbaxy® fine chemicals limited (RFCL). All other chemicals such as potassium dihydrogen orthophosphate, disodium hydrogen orthophosphate, Ammonium acetate, sodium acetate, ammonium dihydrogen orthophosphate, ortho phosphoric acid, acetic acid and all other chemicals used were of HPLC grade.

Instrumentation: The HPLC system consisted of a Shimadzu® Class VP Binary pump LC-10Atvp, SIL-10Dvp auto sampler, CTO-10Avp column temperature oven, PDA-UV detector. All the components of the system are controlled using SCL-10Avp System Controller. Data acquisitions were done using LC-solution software. All the glassware used is of class-A certified The chromatographic separation of Quetiapine fumarate (drug) and Lamotrogine (ISTD) was carried out using Grace Genesis™ C18 column (50 x 4.6 mm ID, 3µm). The other important instruments used which includes Shimadzu® micro balance (Model No: CPA225D), water bath (Life-scan®), centrifuge (Remi®) and ultrasonicator is make of Systronics® (Model No 289-A), and Eppendorf™ Micro-pipette of capacity range of 100 to 1000 µL) and Hamilton® syringe of 10µL is employed for sample injection in these experiments. UV-Visible spectrophotometer and lab-oven of make Lab-India®. PH-meter of Elico® make and graphite mortar for grinding was also used.

Preparation of Solutions

Drug stock Solution and Internal Standard: Two different stock solutions of Quetiapine fumarate working standard and Lamotrigine (internal standard) was prepared by dissolving accurately weighed 10 mg of drug in 10 mL of acetonitrile, so that final concentration is 1 mg mL^{-1}. The prepared stock solution is stored in 4^0C protected from light. Suitable dilution of drug and internal standard were prepared by using (50:50, v/v) methanol and 0.1 % ortho phosphoric acid as diluent. Dilution of internal standard is prepared to obtain a final concentration of 600 µg mL^{-1}.

Calibration Standards and Quality Control Samples: An eight point linear calibration curve standards were prepared using diluents solutions in the concentration range of 2.01 to 50.20 µg mL^{-1}. Calibration standards were prepared at the concentration of 2.01, 5.12, 10.04, 15.06, 25.10, 40.16, 45.18, 50.20 µg

mL^{-1} from first standard stock solution. 950 µL of the linear calibration standard and 50 µL of Internal standard dilution and transferred into the auto sampler for analysis. Three quality control samples at the concentrations of 5.12, 15.06 and 40.16 µg mL^{-1} representing low, medium and high quality control solutions were also prepared respectively. The quality control samples were prepared from second standard stock solution. For the preparation of linearity curve calibration standards 950 µg mL^{-1} is mixed with 50 µg mL^{-1} of internal standard and transferred into auto sampler for analysis.

Sample Preparation: Commercially available tablets of Quetiapine fumarate are taken from two different brands and tested for assay [Table 1]. Twenty tablets of each brand are taken and crushed to powder. A powder equivalent to 50 mg of Quetiapine fumarate is taken and transferred into a stoppered conical flask to which 25 mL of methanol is added. The contents are transferred into a stoppered flask and shaken for 20 min to extract the drug. Contents are carefully transferred into a centrifuge tube and centrifuged for 4000 rpm for 20 min. The supernatant liquid is taken and diluted with diluents, to obtain approximately final concentration of 25 µg mL^{-1}. This sample is analyzed in triplicate. The accuracy and concentration is determined using regression equation

Regression equation: $y = 25.10x - 1.186$

Method Validation

System Suitability: The system suitability was assessed by six replicate analysis of the drug at a concentration of 15.06 µg mL^{-1}. The acceptance criterion is ± 1% for the per cent coefficient of the variation for the peak area and retention times for the drug.

Table 1. List of Important Brand Names of Quetiapine Fumarate Available in Indian Market

Brand name	Formulation/Combination	Dosage strength	Dosage form	Name of the manufacturer
Q Pin™	Quetiapine fumarate	25/50 mg	Tablet	Consern® Pharma Pvt Ltd.
Psyquit™	Quetiapine fumarate	25/100 mg	Tablet	Micro® labs ltd
Q-Win™	Quetiapine fumarate	25 mg	Tablet	Aronex® sciences pvt ltd.
Seroquin-FC™	Quetiapine fumarate	25 mg	Tablet	Cipla® ltd
Seroquin™	Quetiapine fumarate	25 mg	Tablet	Elite® pharma pvt
Quetic™	Quetiapine fumarate	25 mg	Tablet	IPCA® laboratories
Quel™	Quetiapine fumarate	25/50/100 mg	Tablet	Lupin® ltd
Placidin™	Quetiapine fumarate	25/100 mg	Tablet	Abbott® health care Ltd
Sizoquit™	Quetiapine fumarate	25 mg	Tablet	La® pharmaceuticals ltd
Qutace™	Quetiapine fumarate	25 mg	Tablet	Piramal® Health care
Adequet™	Quetiapine fumarate	25 mg	Tablet	Solus® (Ranbaxy)
Socalm™	Quetiapine fumarate	25 mg	Tablet	Pscho® remedies
Quiticool™	Quetiapine fumarate	25/50/100 mg	Tablet	Crescent® therapeutics ltd
Conquest™	Quetiapine fumarate	25/50/100 mg	Tablet	Torrent pvt labs
Q mind™	Quetiapine fumarate	50 mg	Tablet	Alkem® labs ltd
Quticool™	Quetiapine fumarate	200 /400 mg	Tablet	Pschco® remedies
Quticool -SR™]	Quetiapine fumarate	200 /400 mg	Tablet	Torrent® labs
Qutan-SR™	Quetiapine fumarate	400 mg	Tablet	Sun® Pharmaceuticals Ltd

Detection and Quantization Limits (Sensitivity): Limits of detection (LOD) (Fig 2) and quantization (LOQ) (Fig 3) were estimated from both linearity calibration curve method and signal to noise ratio method. The detection limit was defined as the lowest concentration level resulting in a peak area of three times the baseline noise. The quantization limit was defined as the lowest concentration level that provided a peak area with signal to noise ratio higher than 10, with precision (%CV) and accuracy with (±) 10%

Linearity (Calibration Curve): The calibration curve was constructed with eight concentrations ranging from 2.01 to 50.20 µg mL^{-1}. The linearity was evaluated by linear regression analysis, which was calculated by least square method. It is depicted in (Fig 4).

Accuracy and Precision: Accuracy of assay method was determined for both intra-day and inter-day variations using triplicate analysis of the QC samples. Precision of the assay was determined by repeatability (intra-day) and intermediate precision (inter-day). Repeatability refers to the use of the analytical procedure within the laboratory over the shorter period of the time that was evaluated by assaying the QC samples during the same day. Intermediate precision was assessed by comparing the assays on different days (3 days).

Stability: The stability of the drug is determined by using QC samples for the short term stability by keeping at room temperature up to 12 h and then analyzing them. Further, auto-sampler stability for up to 24 h was studied and established.

RESULTS AND DISCUSSION

Method Development and Validation: The HPLC procedure was optimized with a view to develop a stability indicating assay method. Different permutations and combinations, at different pH values ranging from pH 3.0 to pH 11.0 using various columns like Hypersil-BDS-C18, Symmetry C18, Ymc-pack

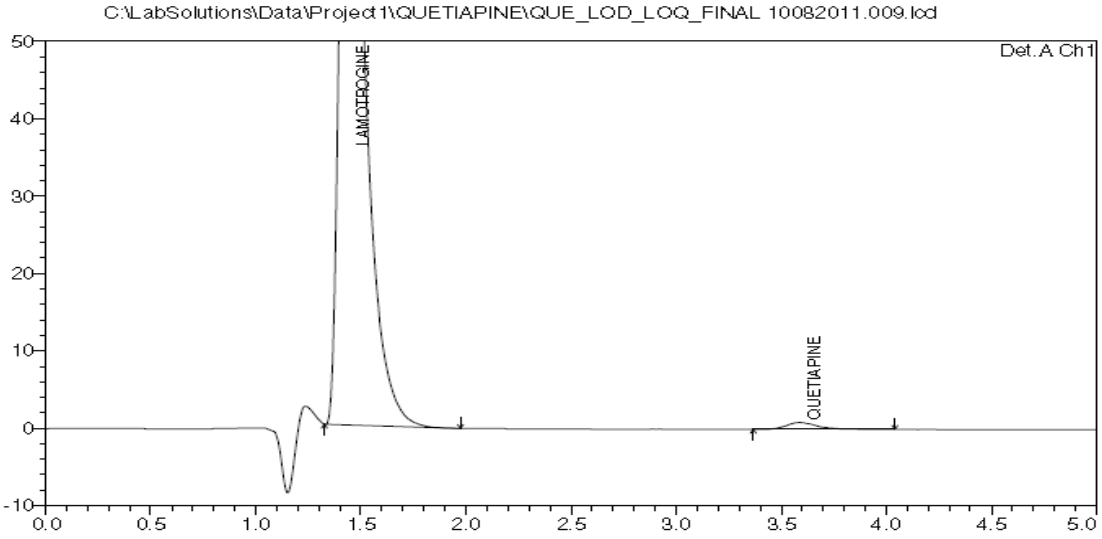

Figure 2. Representative Chromatogram of LOD Injection

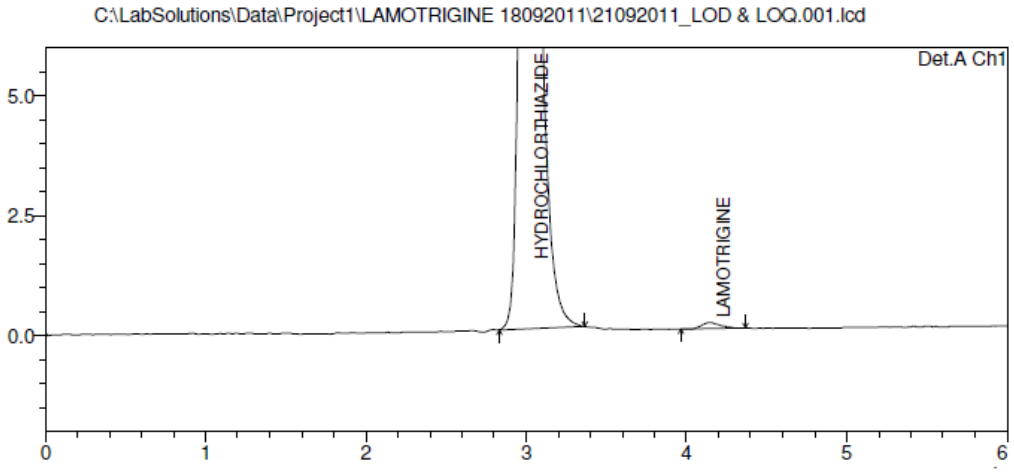

Figure 3. Representative Chromatogram of LOQ Injection

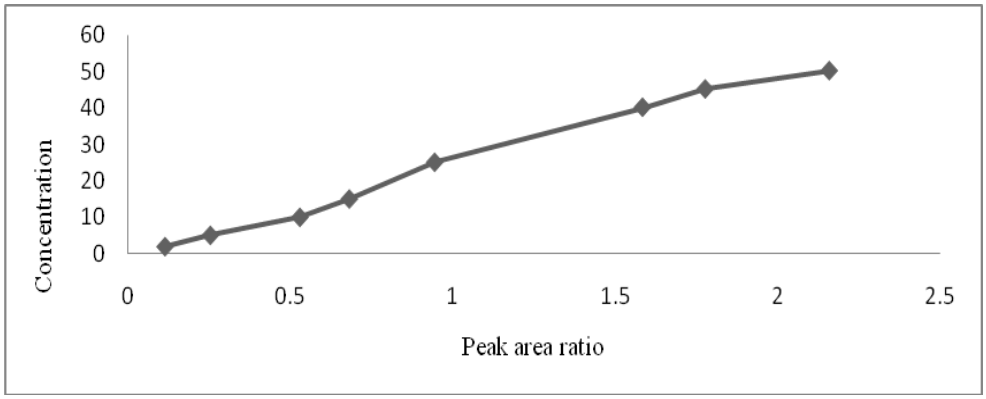

Figure 4. Graph Representing Concentration and Peak-Area Ratio

C18, Ymc-pack pro, Sperisorb C18, Phenomenox C18 have been tried with different buffer salts such ammonium acetate, ortho phosphoric acid, di-potassium hydrogen orthophosphate, in combination with acetonitrile, methanol and tetrahydrofuran. However good resolution, less tailing and high theoretical plates are obtained with ODS column C18 50 X 4.6 cm 5µ. Mobile phase composition consists of (50:50 v/v) of acetonitrile and 0.1 % ortho phosphoric acid respectively operated on isocratic mode The flow rate of the method is 1.0 mL min^{-1}. Diluents are prepared in the same way as mobile phase which consist of (50:50) methanol and 0.1% orthophosphoric acid. The wavelength of detection is 294nm. The column temperature is maintained at 25^0 C. At the reported flow rate peak shape was excellent, however increasing or decreasing the flow rate increased the tailing factor and resulting in poor peak shape and also resolution between the drug and internal standard also decreased. Hence 1.0 mL min^{-1} was optimized flow rate decreasing the consumption of the mobile phase, which in turn proves to be cost effective for long term routine quality control analysis. There was no interference in the drug and internal standard, from the blank. The peak shape and symmetry were found to be good when the mobile phase composition of 50:50 v/v was used with better resolution of the drug and internal standard.

Method Validation

System Suitability: The system suitability was assessed by six replicate analysis of the drug at a concentration of 15.06 µg mL^{-1}. The other parameters which are of interest are United States Chromatography The acceptance criteria are ± 1 % for the percent coefficient of the variation for the peak area and retention times for the both drug and internal (USP) theoretical plates, USP tailing factor and USP

resolution between the internal standard and drug. The % RSD of the peak area and the retention time for both drug and internal standard are calculated and found to be within the acceptable the range [Table 2]. The overlay chromatogram of six injections is represented in [Figure 5]. A representative chromatogram of drug and internal standard is represented in **[**Figure 6].

Determination and Quantization Limits (Sensitivity): Limits of detection (LOD) [Figure 2] and quantization (LOQ) [Figure 3] were estimated from both linearity calibration curve method and signal to noise ratio method. The detection limit was defined as the lowest concentration level resulting in a peak area of three times the baseline noise. The quantization limit was defined as the lowest concentration level that provided a peak area with signal to noise ratio higher than 10, with good precision (% CV) and accuracy with (±) 10 % for LOD and 33 % for LOQ. [Figure 2] and [Figure 3] represent the six replicate injections of the limit of detection and limit of quantification. The method is found to be sensitive which can be determined from the data obtained from the [Table 3] and [Table 4].

Table 2. System Suitability Study

	Area		Theoretical plates	Tailing	Resolution	P/A ratio	Retention time	
	ISTD	Drug					ISTD	Drug
Inj-01	802777	557601	5485	1.25	10.21	0.695	1.45	3.62
Inj-02	796543	564024	5449	1.25	10.23	0.708	1.45	3.63
Inj-03	788450	542945	5566	1.25	10.37	0.689	1.44	3.63
Inj-04	773744	545361	5619	1.25	10.43	0.705	1.44	3.62
Inj-05	787322	543398	5587	1.25	10.32	0.690	1.44	3.62
Inj-06	791033	551887	5457	1.25	10.28	0.698	1.44	3.62
Mean	789978	550869	5527	1.25	10.3067	0.697334	1.443	3.623
SD	9807.74	8583.17	72.57	0.00	0.0841	0.00783	0.005	0.005
RSD	1.24	1.56	1.31	0.00	0.8156	1.122889	0.358	0.143

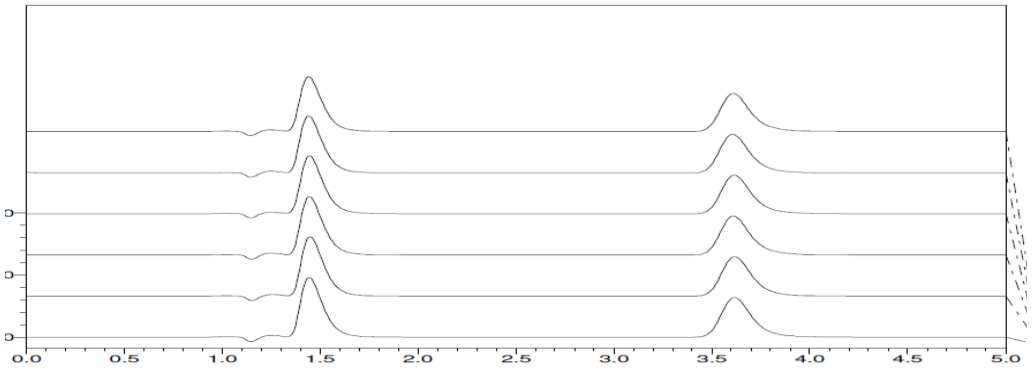

Figure 5. Overlay Chromatogram Representing Replicate Injections (N=6) of System Suitability Solution

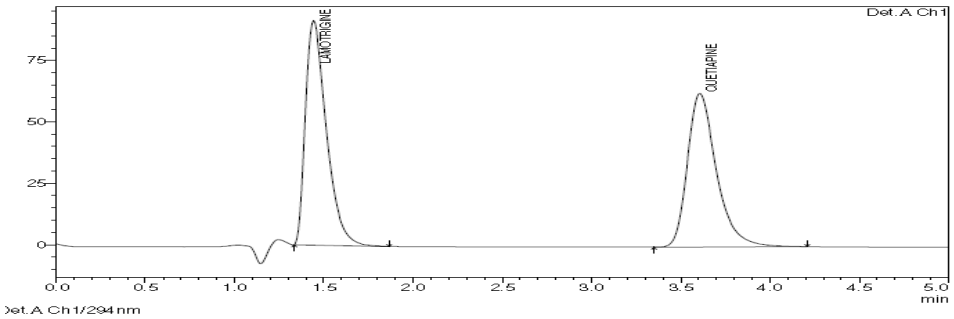

Figure 6. Representative Chromatogram Containing Both Internal Standard and Drug Linearity

Table 3. Limit of Detection

Injection no	Area	Peak area ratio	Theoretical plates	Tailing factor	Resolution
01	4103	0.0049	6609	1.20	11.17
02	4186	0.0051	6845	1.23	11.28
03	4241	0.0051	6787	1.26	11.03
04	4360	0.0052	6912	1.15	11.32
05	4238	0.0050	6974	1.22	11.3
06	4263	0.0051	6874	1.20	11.27
Mean	4231.83	0.0051	6833.5	1.21	11.22833
S.D	85.11	0.0001	126.6787	0.036878	0.110167
RSD	2.01	2.08	1.85	3.05	0.98

Linearity (calibration curve): The calibration curve was constructed with eight concentrations ranging from 2.01 to 50.20 µg mL noise. The quantization limit was defined as the lowest concentration level that provided a peak area with signal to noise ratio higher than 10, with good precision (% CV) and accuracy with (±) 10 % for LOD and 33 % for LOQ. [Figure 2] and [Figure 3] represent the six replicate injections of the limit of detection and limit of quantification. The method is found to be sensitive which can be determined from the data obtained from the [Table 3] and [Table 4]. The peak area ratio of the drug to the internal standard was evaluated by linearity graph. The linearity was evaluated by linear regression analysis, which was calculated by least square method is depicted in [Figure 7].

Table 4. Limit of Quantification

Injection no	Area	Peak area ratio	Theoretical plates	Tailing factor	Resolution
01	8421	0.0096	6395	1.26	11.06
02	8909	0.0103	6345	1.37	11.09
03	8790	0.0102	6388	1.23	11.06
04	8438	0.0098	6609	1.32	11.09

05	8220	0.0095	6506	1.23	11.08
06	8492	0.0099	6323	1.23	11
Mean	8545	0.0099	6427.667	1.273333	11.06333
SD	256.04	0.0003	109.0388	0.058878	0.033862
RSD	3.00	3.11	1.70	4.62	0.31

The calibration curve constructed was evaluated by its correlation coefficient. The peak area ratio of the drug and internal standard was linear, and the range, is 2.01 and 50.20 µg mL noise. The quantization limit was defined as the lowest concentration level that provided a peak area with signal to noise ratio higher than 10, with good precision (% CV) and accuracy with (±) 10 % for LOD and 33 % for LOQ. [Figure 2] and [Figure 3] represent the six replicate injections of the limit of detection and limit of quantification. The method is found to be sensitive which can be determined from the data obtained from the [Table 3] and [Table 4]. The linearity was determined in three sets, the correlation coefficient (r^2) was consistently greater than 0.999 [Table 5].

Table 5. Regression Analysis of Linearity Data of Quetiapine Fumarate*

	Mean ± S.D
Slope	25.10 ± 0.06
Intercept	1.186 ± 0.08
Correlation coefficient(R^2)	0.999 ± 0.0003

*Each mean value is a result of triplicate analysis (n=3)

[Figures 7, 8] shows the overlay chromatogram of linearity injections, correlation can be subject to mis-interpretation, since different datasets can yield identical regression statistics.

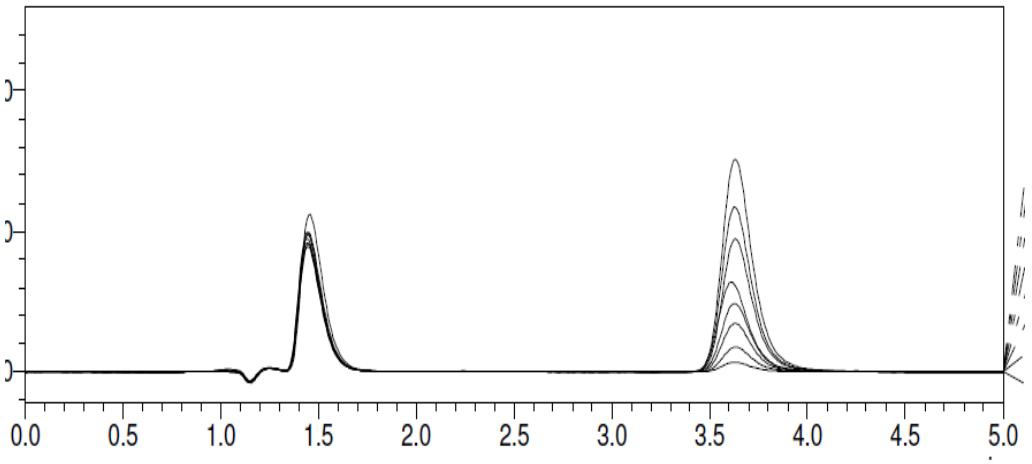

Figure 7. Overlay Chromatograms of Linearity Level Solutions of Quetiapine Fumarate

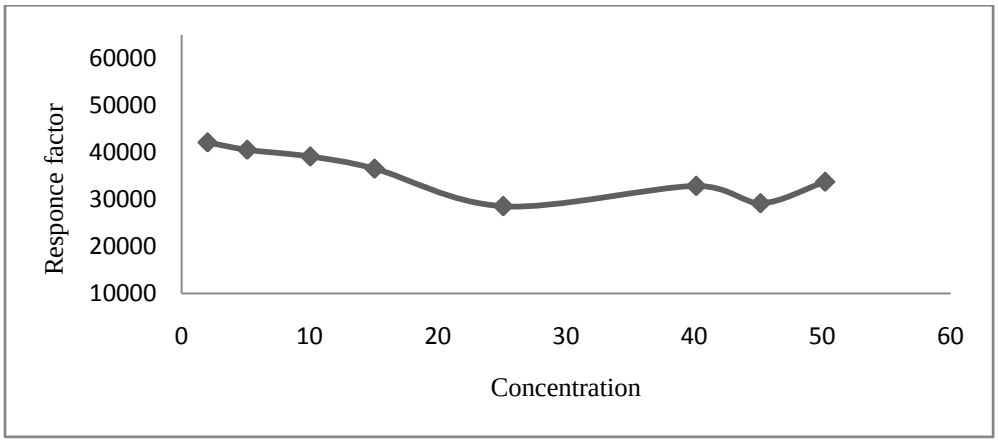

Fig 8. Graph Representing Response Factor and Concentration

Accuracy and Precision: Accuracy and precision calculated for the QC samples during the intra- and inter –day run are given the (Table 6). The intra-day (day-1) and inter-day accuracy ranged from 98.61 to 101.97 %. The results obtained from intermediate precision (inter-day) also indicated a good method precision .All the data were within the acceptance criteria.

Table 6. Intra-Day, Inter-Day Precision and Accuracy of Quetiapine Fumarate*

	Nominal concentration		
	5.12µg mL^{-1}	**15.06 µg mL^{-1}**	**40.16 µg mL^{-1}**
Day=1			
Mean (n=3)	183638	502614	1297619
S.D	948.01	10442.68	1514.80
RSD	0.52	2.07	0.12
Recovery(%)	100.4907	100.11	99.49
Day=2			
Mean(n=3)	227511	523982	1310744
S.D	379.36	3262.83	21904
RSD	0.17	0.62	1.67
Recovery(%)	100.64	101.00	99.52
Day-3			
Mean (n=3)	199599	516802	1293679
S.D	1216.50	4041.45	1760.91
RSD	0.61	0.78	0.14
Recovery(%)	99.36	101.50	99.69

*Each mean value is a result of triplicate analysis (n=3)

Stability: The stability of the drug is determined by using QC samples for the short-term stability by keeping at room temperature up to 12 h and then analyzing them. Further, auto sampler stability for up to 24 hours and long term stability unto 3.0 days were also established. Stability studies at three different concentrations of low, medium, high QC levels conditions were utilized to establish the stability. The mobile phase is stable up to 72 h [Table 7, Table 8].

Robustness study: Robustness is the measure of method capacity to remain unaffected by deliberate small changes in the chromatographic conditions. The experimental conditions were deliberately altered to test and evaluate the robustness of the method. The impact of flow rate (0.6±0.1), column temperature (25 ± 5^0C) changes and effect of mobile phase composition (±10 %) was evaluated on the important system suitability factors such as retention time, theoretical plates, tailing factor, and resolution.

Table 7. Effect of Various Parameters in Assessment of Method

		Observed values			
Parameters	**Variation**	**Retention time**	**Theoretical plates**	**Tailing factor**	**Resolution**
Flow rate (mL/min)	0.5	3.63	5942	1.22	10.86
	0.7	3.62	5910	1.19	10.23
Column temperature (^{0}C)	20	3.62	6308	1.25	11.22
	30	3.75	6115	1.22	9.79
Mobile phase (% organic)	90	3.63	5960	1.23	10.79
	110	3.62	5840	1.25	9.29

Table 8. Short Term, Auto Sampler and Long Term Stability of Quetiapine Fumarate

	Nominal concentration		
	5.12µg mL^{-1}	**15.06 µg mL^{-1}**	**40.16 µg mL^{-1}**
Short term stability (12 hours)			
Mean (n=3)	185884	512701	1273781
S.D	1239.619	2388.92	2057.69
RSD	0.6669	0.47	0.16
Recovery (%)	100.38	100.77	98.52
Auto sampler stability(24 hours)			
Mean(n=3)	200490	5069977	1281959
S.D	813.61	3132.07	6885.33
RSD	0.41	0.62	0.54
Recovery (%)	100.00	100.19	98.31

APPLICATIONS

The HPLC method developed is sensitive and specific for the quantitative determination of Quetiapine fumarate. Quetiapine fumarate tablets of 200 mg, 300 mg strength from two different manufacturers [Table 2] were evaluated for the amount of Quetiapine fumarate. The amount of Quetiapine fumarate in Tablet 1 is 98.49 ± 0.36 and Tablet 2 is 98.59 ± 0.35. Sample preparation details have been discussed earlier. None of the tablets ingredients interferes with the analytic peak. The spectrum of Quetiapine fumarate is extracted from the tablets was matching with that of standard Quetiapine fumarate showing the purity of peak of Quetiapine fumarate in the tablets.

CONCLUSIONS

A rapid sensitive and specific method for the determination of Quetiapine fumarate in the pharmaceutical; formulations has been developed using Lamotrigine as the internal standard. The method gave accurate and precise results in the concentration range of 2.01 to 49.500 µg/mL. The mobile phase composition is (50**:**50, acetonitrile **:** 0.1% ortho phosphoric acid) at the flow rate of 0.6 ml/min. The retention times of internal standard and the drug are 1.45 ± 0.05 and 3.6 ± 0.05 respectively. The column is a 50 X 4.6 mm C_{18} column with the particle size of 3 µm. Quetiapine fumarate is tested for the stress conditions like photo stability, acid stability, alkaline, oxidation and thermal conditions for the 24hours. Quetiapine fumarate is stable and did not show any signs of degradation under stress conditions.

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