ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR ESTIMATION OF QUETIAPINE FUMARATE IN BULK AND PHARMACEUTICAL DOSAGE FORM

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Abstract: An accurate, precise, and specific method developed for estimation of Quetiapine Fumarate in bulk. The API is used for the method development by UV spectroscopy with Ethanol: Water (50:50). The calibration curve method showed wavelength maxima for Quetiapine Fumarate at 295 nm with Ethanol: Water (50:50). This method obeys Beer's law in the concentration range of 5-50µg/ml with correlation coefficient 0.999 for Quetiapine Fumarate. The precision results are not more than 2%. The LOD and LOQ were found to be 0.552 and 1.6728 respectively. The percentage assay of Quetiapine Fumarate in pharmaceutical dosage form was found to be 99.89%. The results of analysis have been validated in order to verify linearity, precision, and accuracy for the goal intended and further implementation for the quantification analysis in the pharmaceutical dosage form. The newly developed spectroscopic method is used for the routine analysis for Quetiapine Fumarate in pharmaceutical dosage forms.

Keywords: Analytical Method, Quetiapine Fumarate, Validation, UV spectroscopy

1. INTRODUCTION

Quetiapine Fumarate (QTP) chemically is 2-[-2(4-Dibenzo [b,f] [1.4] thiazepin-11-yl-1-piperazinyl) ethoxy] ethanol fumarate salt (Figure 1). [1, 2 -5] is an atypical antipsychotic and has been approved by the FDA (Food and Drug Administration) for use in the treatment of schizophrenia, [6, 7-10] acute mania, [6, 11, 12] and bipolar depression [6, 13]. The preclinical profile of quetiapine is similar to the first atypical antipsychotic (clozapine) but it has a reduced tendency to cause motor disturbances. Quetiapine is a dibenzothiazepine derivative. [14-15] It produces antagonistic effect on serotonin 5-HT1A and 5-HT2A, dopamine D1 and D2, histamine H1, and adrenergic α1 and α2 receptors. [16-17] Quetiapine received its initial indication from the Food and Drug Administration (FDA) for treatment of schizophrenia in 1997. It received its second indication for the treatment of mania-associated bipolar disorder in 2004. Its molecular formula is $C_{21}H_{25}N_3O_2S$, having molecular mass 383.5099 g/mol. QTP appears as white crystalline solid. It is soluble in methanol, ethanol, Chloroform, 0.1 M HCl, phosphate buffer, sparingly soluble in water. [18- 22]

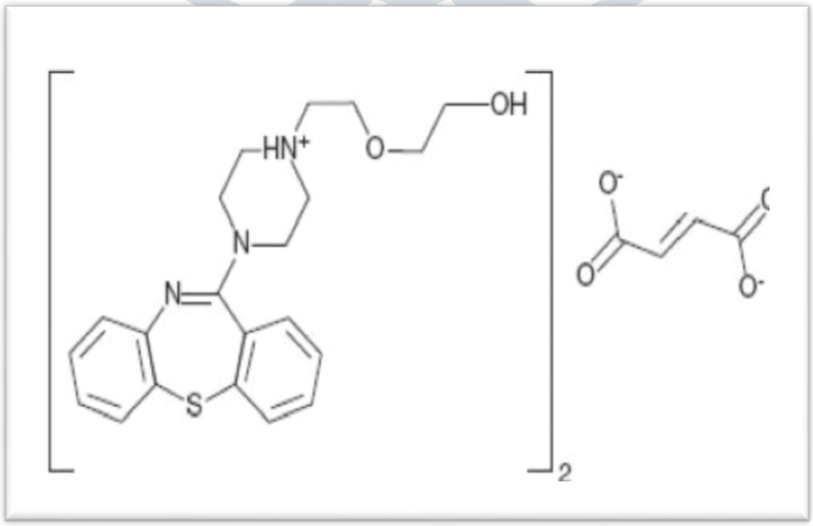

Figure 1: Chemical structure of Quetiapine Fumarate

Literature review reveals that several methods have been reported for the quantitative determination of quetiapine in bulk, and pharmaceutical and biological samples. These methods include Zero order derivative, Area under curve [23], Second order derivative

[24], UV-Visible spectrophotometric [25-26], HPLC methods [27-30], RP-HPLC-PDA [31], HPTLC [32], RP-UPLC [33], UPLC-ESI-MS/MS [34], Polarographic analysis [35] and Potentiometric determination [36].

2. EXPERIMENTAL

2.1. *Chemicals and Reagents*

All the chemical reagents used were of analytical grade. Tablets of Quetiapine Fumarate (Quetipin 50mg) were purchased from the local market.

2.2. *Instruments*

Single beam Agilent Carry 60 UV spectroscopy, 1 cm quartz cells with a fixed slit width, the wavelength range (200-400) nm.

2.3. *Preparation of Standard Drug Solution*

Standard stock solution was prepared by dissolving 50 mg of Quetiapine Fumarate in 50 ml of volumetric flask with sufficient amount of solvent Ethanol: Water (50:50) to get concentration of 1000µg/ml.

2.4. *Determination of Absorption Maxima*

Dilute 1 ml of standard drug solution with Ethanol: Water (50:50) in 10 ml volumetric flask up to the mark. The solution containing 10 µg/ml of QTP was scanned at the range of 200-400 nm to determine the wavelength of maximum absorption for QTP was found to be 295 nm. (Fig.2) The calibration curve was prepared for QTP in the concentration range of 5-50 µg/ml at selected wavelength. The plots of Beer's law limit are shown in (Fig. 3).

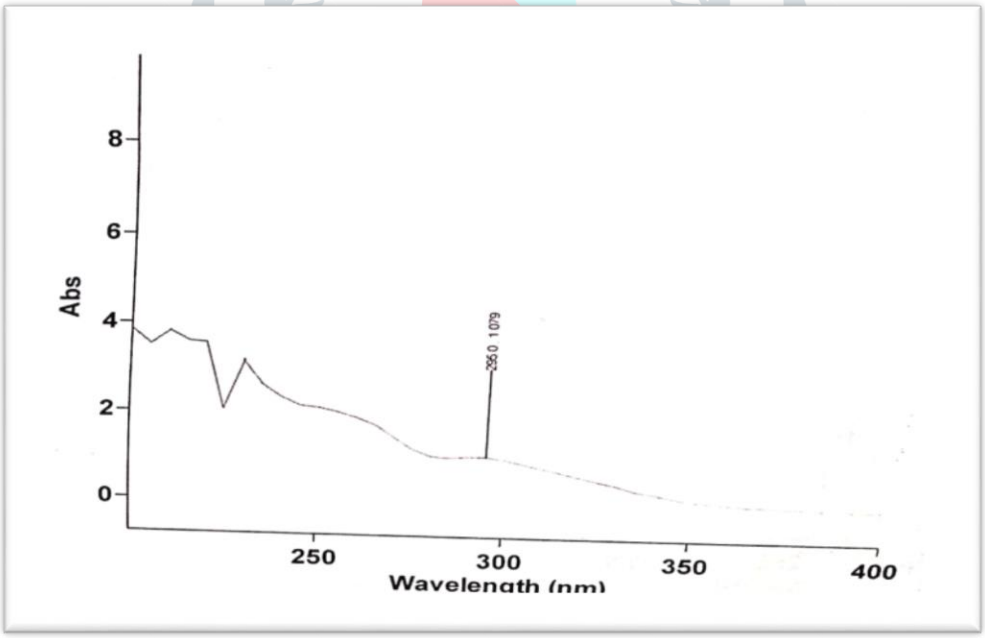

Figure 2: UV spectrum of QTP at 295nm.

2.5. *Method validation parameters*

Validation of the developed method performed according to ICH guidelines [37]

2.5.1. *Linearity and Range*

The linearity of the analytical procedure was performed by taking series of solutions 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0 ml of (100µg/ml) standard solution of stock sample and transfer into 10 ml volumetric flasks. Solvent was added and volumes were made up to the mark to obtain the solutions in the concentration range of 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 µg/ml of

drug solution. Absorbance of the resultant solution was measured at 295 nm. A calibration curve was plotted over a concentration range (5-50 µg/ml) of Quetiapine Fumarate at 295 nm. A graph was plotted between the concentrations and their respective absorbance (Fig. 3). The line equation was found to be y = 0.0184x + 0.0174 and correlation coefficient was found to be 0.9992.

Table 1: Linearity profile of QTP.

S.NO	Conc.(µg/ml)	Absorbance at 295 nm
1	5	0.1027
2	10	0.2038
3	15	0.2820
4	20	0.3910
5	25	0.4839
6	30	0.5766
7	35	0.6691
8	40	0.7584
9	45	0.8411
10	50	0.9265

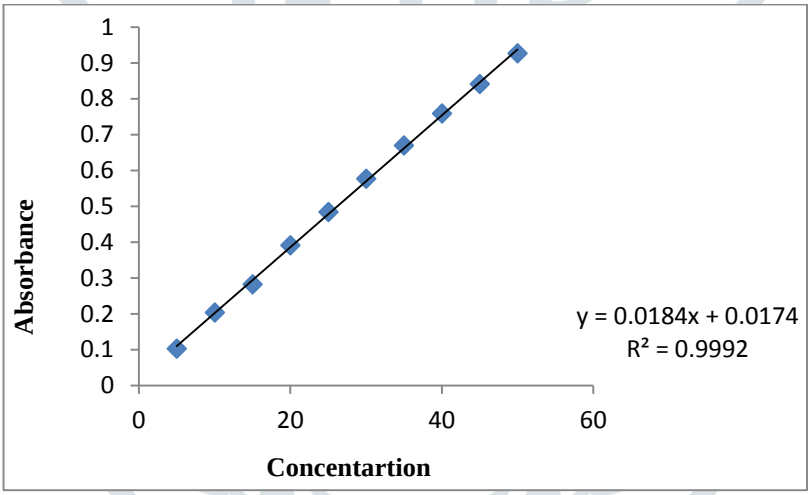

Figure 3: Calibration Curve of QTP

2.5.2. *Precision*

2.5.2.1. *Repeatability*

Pipette out 1 ml working solution and transfer into 10 ml volumetric flasks. Dilute it to get 10 µg/ml solutions. Nine replicates of 10 µg/ml solutions of the drug were prepared. Absorbance of the resultant solutions was measured at 295 nm using Ethanol: Water (50:50) as blank. The result obtained is in the table 2.

Table 2: Results of repeatability

Nominal Conc.(µg/ml)	Absorbance	Observed Conc.(µg/ml)
10	0.1965	9.53
	0.1952	9.50
	0.1954	9.49
	0.1978	9.58
	0.1989	9.61
	0.2003	9.64
	0.1994	9.60
	0.2002	9.64
	0.2002	9.63
Mean	9.58	
S.D.	0.0047	
%RSD	0.24	

2.5.2.2. *Intra-day Precision*

Pipette out 1.0, 2.0 and 3.0 ml working solution and transfer into separate 10 ml volumetric flasks. Dilute it to get solution of concentrations 10, 20 and 30µg/ml, respectively. Absorbance of the resultant solutions was measured at 295 nm. It is determined by analyzing the corresponding responses three times within a day at 0, 3 and 6 hours interval. The result obtained is in the table 3.

Table 3: Results of Estimation in Intra-day studies

Nominal Conc.(µg/ml)	**Absorbance**		
	0 hr	**3 hrs**	**6 hrs**
10	0.1965	0.2008	0.2003
20	0.3742	0.4103	0.4098
30	0.5784	0.5953	0.5929
Mean	0.3956		
S.D.	0.00779		
%RSD	0.0496		

2.5.2.3. *Inter-day Precision*

Pipette out 1.0, 2.0 and 3.0 ml working solution from standard stock solution and transfer into separate 10 ml volumetric flasks. Dilute the solutions to get solution of concentrations 10, 20 and 30µg/ml, respectively. Absorbance of the resultant solutions was measured at 295 nm. It is determined by analyzing the solutions once on three consecutive days 0, 24 and 48 hours interval. The result obtained is in the table 4.

Table 4: Results of Estimation in Inter-day studies

Nominal Conc.(µg/ml)	**Absorbance**		
	1 day	**2 day**	**3 day**
10	0.2006	0.1915	0.1950
20	0.4098	0.3991	0.4111
30	0.5921	0.5846	0.5884
Mean	0.3966		
S.D.	0.0035		
%RSD	0.12998		

2.5.3. *Accuracy*

Accuracy is the percent of analyses recovered from the assay from a known added amount. Data from nine determinants from three concentration levels covering the specified range were obtained. To verify the capability of regression equations to predict the absorbance behavior of Quetiapine fumarate in dosage forms, the method was tested for accuracy and recovery. To study the recovery of the preanalyzed sample solutions, a known amount of standard solutions of the pure drugs were added at different level i.e. 80, 100 and 120 %. Recovery study was determined by following formula; % Recovery = [A-B/ C] X 100

Where, A = Total amount of drug estimated

B = Amount of drug found on pre-analyzed basis

C = Amount of drug added

Table 5: Results of estimation of QTP under recovery Study.

Recovery at	Nominal Conc.(µg/ml)	Absorbance	Observed Conc. (µg/ml)	% Recovery
80%	18 = 10+8	0.3503	17.9	99.4
80%	18 = 10+8	0.3506	18.01	100
80%	18 = 10+8	0.3501	17.87	99.2
100%	20 = 10+10	0.3736	19.8	99
100%	20 = 10+10	0.3810	19.9	99.5
100%	20 = 10+10	0.3892	20.2	101
120%	22 = 10+12	0.4320	22.2	100.9
120%	22 = 10+12	0.4309	22.04	100.1
120%	22 = 10+12	0.4298	21.9	99.5
			Mean	99.84±0.70

2.5.4. *Specificity*

Specificity study was carried out by observing any interference in absorbance of drug in the presence of common excipients like starch, talc, lactose, magnesium stearate etc. Absorbance of 10 µg/ml drug solution with and without excipients was measured at 295 nm. The result obtained is summarized in the table 6.

Table 6: Results of specificity studies

Nominal Conc.(µg/ml)	Without Excipients		With Excipients		%Interference
	Absorbance	Observed Conc.(µg/ml)	Absorbance	Observed Conc.(µg/ml)	
10	0.1949	10.5	0.2006	10.9	0.96
	0.1987	10.7	0.2008	11.01	0.97
	0.1995	10.2	0.2003	10.4	1.98
	0.1979	10.8	0.2060	11.03	0.97
	0.1929	10.1	0.1872	9.97	1.02
	0.1947	10.2	0.2004	10.67	0.95
				Mean	0.975

2.5.5. *The limits of detection (LOD) and quantitation (LOQ)*

LOD and LOQ calculated using the formulae: LOD = 3.3 S/b and LOQ = 10 S/b, where S is the standard deviation of blank absorbance values, and b is the slope of the calibration plot. The high values of molar absorptivity (ε), low values of Sandell sensitivity and LOD indicated the high sensitivity of the proposed methods. The LOD and LOQ was found to be 0.552 and 1. 6728 µg/ml respectively.

2.5.6. *Estimation of Quetiapine Fumarate in Pharmaceutical Dosage Form (Qutipin, 50mg)*

Weigh 10 tablets and calculate the average weight. Powder those tablets. Weigh accurately a quantity of powdered tablets containing about 50 mg of Quetiapine Fumarate and transfer it into 50 ml volumetric flask. Add 35 ml Ethanol: Water (50:50) and sonicated for 15 minutes. Make up the volume to 50 ml, mix and filter. Dilute 2.5 ml of the filtrate to 25 ml with solvent. Further dilute 1 ml of the resulting solution to 10 ml with solvent to get 10 µg/ml solution and absorbance of the resulting solution was measured at 295 nm. The above procedure was repeated for three times. The result obtained is in the table 7**.**

Table 7: Estimation of QTP in tablet formulation

Sr. No.	Absorbance	Conc. (µg/ml)	Dil. Factor	Content (mg)	Label Claim (mg)	% Assay
1	0.1946	10.5	5000	50.38	50	99.87
2	0.1912	10.4	5000	49.45	50	98.87
3	0.1932	10.4	5000	50.01	50	99.27
Mean ± SD						99.89±0.50

RESULTS AND DISCUSSION

The drug follows Beer-Lambert's law over the concentration range of 5-50 µg/ml with a correlation coefficient of 0.9992. For calibration curve method Quetiapine Fumarate showed wavelength maxima at 295 nm .The present study of proposed method showed precision in terms of the repeatability and, reproducibility is found to be not more than 2%. The recovery results are in the range of 98 to 102%. Specificity was found to be NMT 2%. LOD and LOQ was found to be 0.552 and 1.6728 respectively. The percentage purity of pharmaceutical dosage form of QTP was found to be 99.89%. Hence, the results of the analysis are validated as per ICH guidelines. Quantitative determination of Quetiapine Fumarate in API and tablet dosage form by employed the method, the assay values found 100.50% and 99.08%, respectively.

Table 8: Validation parameters of Quetiapine Fumarate

S. No.	Parameters	Results
1.	Λ max (nm)	295nm
2.	Beer's law limit (µg/ml)	5 - 50 µg/ml
3.	Regression equation (Y*)	Y= 0.0184x + 0.0174
4.	Correlation coefficient (r)	0.999
5.	Precision	
(a)	Repeatability	0.24
(b)	Intra-day	0.0496
(c)	Inter-day	0.12998
6.	Accuracy	99.84±0.70
7.	Specificity	0.975
8.	LOD	0.552
9.	LOQ	1. 6728

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