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Development and Validation of UV Spectrophotometric Estimation of Quetiapine Fumarate in Bulk and Tablet Dosage Form Using Area Under Curve Method

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ABSTRACT

The present work was defined to develop area under curve method for antipsychotic drug by UV spectrophotometric analysis which was economical, precise and an accurate method for estimation of Quetiapine fumarate. This method was based on area under curve of UV spectrum between 287 to 297 nm and validated as per ICH guideline Q2 (R1). The linearity in the range was found to be 4-14 µg/ml. The result of correlation coefficient was 0.999. The results of percent relative standard deviation for the intra-day and inter-day precision indicated that method is precise. The values of the recovery studies (99.65 % to 101.04 %) showed good accuracy of the method. LOD and LOQ were calculated as 0.3806 and 1.153µg/ml, respectively. The developed method can be applied for routine estimation of Quetiapine fumarate in bulk and tablet dosage forms.

Keywords: Quetiapine fumarate, Area under Curve, UV Spectrophotometry, Validation, ICH

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INTRODUCTION

Quetiapine fumarate is used in the condition of atypical or second-generation antipsychotic agent [1, 2]. Quetiapine fumarate is antipsychotic drug that is used to treat symptoms of psychiatric disorders such as schizophrenia and bipolar disorder[3, 4]. The chemical name of this drug is [2-(2-[4-(dibenzo[b,f][1,4]-thiazepin-11-yl)piperazin-1-yl]ethoxy)ethanol] fumarate (Figure 1). This drug is not official in any pharmacopoeia. Quetiapine has no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors[5]. The nor-quetiapine metabolite 7-hydroxy nor-quetiapine also has affinity for histaminergic H1 and 5HT2B and 2C receptors at clinically relevant concentrations[6].

A detailed literature survey for quetiapine revealed that few analytical methods are available using HPLC were; S. Radha Krishna *et al.*[7], describe stability indicating method for related substances of quetiapine drug substance; F. Belal*et al.*[8], demonstrated separation of two impurity fromquetiapine; V. Pucci et al.[9], determination of quetiapine was describe with non-stability indicating method; Polarography method is also reported for the analysis of quetiapine in pharmaceuticals[10]; HPTLC method is also reported by S.R. Dhaneshwar*et al*[11]; Determination of quetiapine by Capillary zone electrophoretic method is reported by S. Hillaert*et al.*[12]; A Volta metric analysis of quetiapine in human serum and urine is also reported[13]; Determination of an antipsychotic agent (ICI 204, 636) and its 7-hydroxy metabolite in human plasma by GC/MS[14]; LC-MS[15] method has been reported for determination of quetiapine in drug substance, pharmaceutical formulations and biological matrices. Development and Validation of a Stability Indicating RP-UPLC Method for Determination of Quetiapine in Pharmaceutical Dosage Form[16];Identification and characterization of quetiapine impurities were also reported.

Figure:1 Chemical structure of Quetiapine fumarate

MATERIALS AND METHODS:

Instrumentation and apparatus:

Shimadzu UV 1800 (Japan) with matched quartz cells, connected to computer using UV Prob Software was employed for this research work. Single pan electronic balance (Shimadzu, AX 200, Japan) was used for weighing purpose. Sonication of the solutions was carried out using an Ultrasonic Cleaning Bath company made Spectra lab UCB 40, India. Calibrated volumetric glassware's (Borosil) were used in this study.

Materials:

Active pharmaceutical ingredient of Quetiapine fumarate was supplied as a gratis sample from MicroLabs Ltd., Mumbai(Maharashtra, India). Commercially available tablets (Quetipin SR containing 50 mg of Quetiapine fumarate) were purchased from local pharmacy. HPLC-grade of Methanol (as a solvent) was purchased from Merck India Ltd., Mumbai.

METHOD DEVELOPMENT:

Preparation of standard solution:

The standard stock solution of drug was prepared by transferring, accurately weighed 10 mg of Standard API into 100 mL of volumetric flask. The drug was dissolved by adding 50 ml of methanol and then sonicated; volume was made up to the mark by using methanol. The standard stock solution of 100µg/mL was further diluted with methanol to get the concentration of 10µg/mL

Selection of wavelength range:

The standard solution of 10µg/mL concentration was scanned between 400 nm to 200 nm in UV spectrophotometer against methanol as blank after baseline correction. Wavelength range was selected around wavelength maxima 292 nm. Different working standards were prepared between 4-14 µg/mL, various wavelength ranges were tried and final range between 287-297 nm was selected on the basis of linear relationship between area &corresponding concentration (Figure 2).

Area under curve (Area calculation):

This method involves calculation of integrated value of absorbance with respect to wavelength in indicated range. Area calculation processing method calculates the area bounded by the curve and horizontal axis[17, 18]. Here horizontal axis represents baseline.

$$\text{Area calculation } (\alpha+\beta) = \int_{\lambda 2}^{\lambda 1} A d\lambda$$

Whereas, α is area of portion bounded by curve data and a straight line connecting the start and end point, β is area of portion bounded by a straight line connecting the start and end point on curve data and horizontal axis,λ_1 and λ_2 are wavelengths representing start and end point of curve

region. In this study area was integrated between wavelength ranges from 287 to 297 nm.

Preparation of calibration curve:

Working solutions were prepared from standard stock solution by further dilution with methanol to obtain the concentration of 4, 6, 8, 10, 12 and 14 µg/ml, respectively. These solutions were scanned from 400 to 200 nm and area under curve (AUC) was integrated[12] in the range of 287-297 nm. The calibration curve was plotted between area under curve against concentration (Figure 3).

Assay of tablet formulation:

The 20 tablets were accurately weighed and average weight was calculated. These tablets were crushed and powdered in a glass mortar. The powder equivalent to 10 mg of Quetiapine fumarate was accurately weighed and transferred to a 100 mL of volumetric flask and diluted up to mark with methanol. The solution was filtered through Whatmann filter paper No. 41 and the first 5 mL of filtrate was discarded. This solution was further diluted to obtain 10µg/mL solution with same solvent and subjected for UV analysis. This procedure was repeated in triplicate (Table 1).

METHOD VALIDATION:

The objective of this an analytical procedure is to validate and demonstrate whether the procedure is suitable for its intended purpose. The proposed method was validated for various parameters such as Linearity, Precision, Accuracy, Limit of detection (LOD) and Limit of Quantitation (LOQ) according to ICH Q2 (R1) guideline[19].

Linearity and Range:

The linearity was validated by using working standard solutions between 4-14 µg/mL. The observed spectrums of these solutions were recorded and area under curve was integrated in wavelength range 287-297 nm. Calibration curve of Area under curve vs. Concentration was plotted after suitable calculation and simple linear regression was performed (Figure 3). The correlation coefficient and regression equation were obtained. The range of solutions has been decided according to statistical parameters of generated equation.

Method Precision:

Intermediate precision (Reproducibility):

The intra-day and inter-day precision of the proposed method was determined by analyzing the corresponding responses 3 times on the same day and on 3 different days over a period for 3 different concentrations of standard solutions of Quetiapine fumarate (6, 10 and 14 µg/mL). The results were reported in terms of relative standard deviation (%RSD). The results were calculated and given in Table 2.

Repeatability:

The precision of the method was checked by repeatedly injecting (n = 6) standard solutions of Quetiapine fumarate (10 µg/mL). Area under curve of each of these solutions was measured in the range of 287-297 nm. Percentage relative standard deviation (%RSD) was calculated (Table 3).

Accuracy:

The accuracy for the analytical procedure was determined at 80 %, 100 % and 120 % levels of standard solution. Area under curve was measured in the range of 287-297 nm and results were expressed in terms of % recoveries. Three determinations at each level were performed and % RSD was calculated. The results were tabulated in Table 4.

Limit of Detection (LOD) and Limit of quantitation (LOQ):

Six sets of known concentrations (4-14 µg/ml) were prepared. Calibration curves were plotted for each set. LOD and LOQ were calculated using the formulae as

$$LOD = 3.3\frac{SD}{S}$$

$$LOQ = 10\frac{SD}{S}$$

Where, SD is standard deviation of y-intercept of the calibration curves;

S is slope of six calibration curves.

RESULTS AND DISCUSSION:

An attempt was made to develop a simple, precise and specific AUC spectrophotometric method for the determination of Quetiapine fumarate in tablet dosage form. The generated regression equation was $\int_{297}^{287} Ad\lambda$= 0.0015C + 0.0025 ($R^2$ = 0.999). Where, $\int_{297}^{287} Ad\lambda$ is area under curve between 287 to 297 nm, C is concentration and R is correlation coefficient. The R^2 value as 0.999 indicates that developed method was linear. The proposed method was found to be precise as % R.S.D values for intraday as well inter-day precision were satisfactory. The drug at each of the 80 %, 100 % and 120 % levels showed good recoveries was 99.65 % to 101.04 % (with mean 100.27). Hence, it can be said that this method was accurate. The LOD and LOQ result shows that lowest amount of drug that can be detected using this analytical method as 0.3806 and lowest amount of drug in sample that can be quantitatively determined with precision and accuracy is 1.153µg/ml. The results of the analysis obtained from pharmaceutical formulation by the develop method was consistent with the label claim was highly reproducible and reliable. There was no interference from the excipients of tablet formulation. The method can be used for the routine analysis of the Quetiapine fumarate in tablet dosage form. The validation parameters are summarized in Table 5

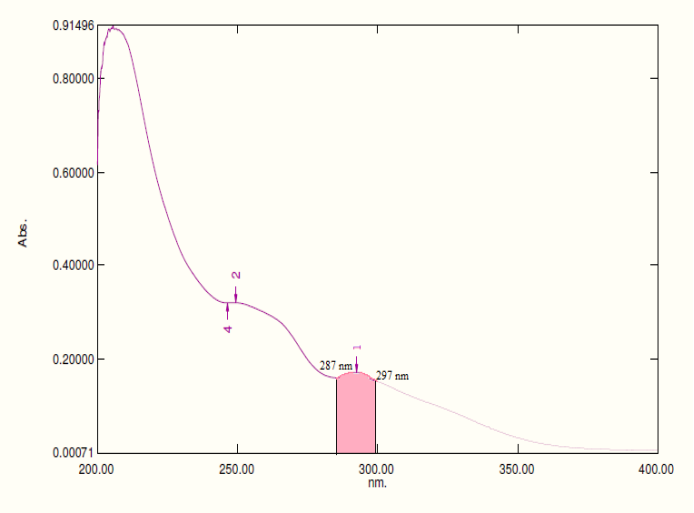

Figure 2: Ultraviolet visible spectrum of Quetiapine fumarate (10µg/mL) in methanol

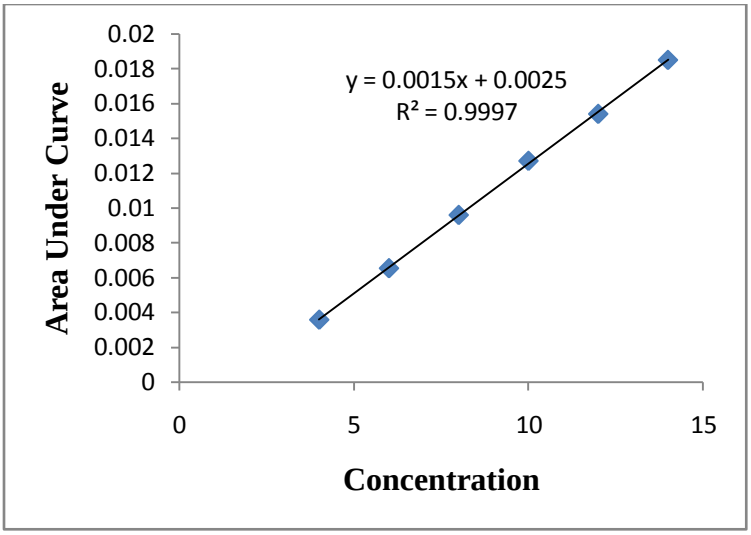

Figure 3: Linearity and Range graph of Quetiapine fumarate (4-14 µg/mL)

Table 1: Assay of marketed tablet dosage form (QUETIPIN)

Sr. No	Sample Concentration (µg/mL)	Amount recovered (%)	Mean Amount found (%)	%RSD*
1	10	99.73	100.06	0.63
2	10	99.66		
3	10	100.79		

%RSD= % Relative Standard Deviation, *n= 3

Table 2: Intermediate precision results for Quetiapine fumarate

Drug	Concentration (µg/mL)	%RSD*	
		Intraday	Interday
Quetiapine fumarate	6	0.559	0.493
	10	0.631	0.694
	14	0.679	0.688

*n= 3

Table 3: Repeatability results for Quetiapine fumarate

Sr. No	Sample Concentration (µg/mL)	%RSD*
1	10	0.79

*n= 6

Table 4: Accuracy results of Quetiapine fumarate

Accuracy Levels (%)	Concentration added (µg/mL)	%Recovery	%Mean recovery	%RSD*
80	8	101.04	100.27	0.771
100	10	99.76		
120	120	99.65		

*n=3

Table 5: Summary of validation parameters

Parameters	Results
λ max	292 nm
Linearity and Range	4-14 µg/mL
Correlation co-efficient	0.999
Method Precision (%RSD)	
i. Intraday	i. 0.623
ii. Interday	ii. 0.625
iii. Repeatability	iii. 0.79
% Recovery (Accuracy)	% RSD- 0.771, % Mean Recovery- 100.27 %
LOD (%RSD)	0.3806 µg/mL
LOQ (%RSD)	1.153 µg/mL

CONCLUSION:

From the analytical study it can be concluded that the proposed method was simple, precise and accurate for the determination of Quetiapine fumarate in tablet dosage form. This method was validated as per ICH guidelines Q2 (R1). Results of this analytical study suggest that this method can be used for routine laboratory estimation of Quetiapine fumarate in bulk and pharmaceutical dosage form.

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