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Application of QbD Approach to Development and Validation of a Novel UV-Spectrophotometric Method for Quantitative Estimation of Quetiapine Fumarate in Bulk and Pharmaceutical Formulation (Tablets)

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Original Research Article

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Abstract: Stability Indicating UV-spectrophotometric analytical method validation for the estimation of Quetiapine fumarate have already been reported, but no studies reported so far include the application of Analytical Quality by Design (AQbD) concept to the development of a comprehensive analytical UV-method for the analysis of model drug (Quetiapine fumatrate). In the present work, a simple, economic and sensitive UV spectrophotometric method has been developed using AQbD approach for the quantitative estimation of Quetiapine fumarate in bulk and pharmaceutical dosage forms i.e. tablets. The estimation of drug was done at 242 nm in simulated nasal fluid (SNF) using UV-Visible double beam spectrophotometer. In the developed method, linearity over the concentration range of 4-24µg/ml of QP was observed and was found in agreement of Beer's law. The linear regression was found to be 0.999. The results of analysis have been validated statistically and recovery studies confirmed the accuracy of the proposed method. The precision (intra-day & inter-day) of method was found within limits (RSD < 2%). The sensitivity of the method was assessed by determining limit of detection and limit of quantification. The method was found to be repeatable as well as robust. The percentage of QP in the marketed formulation (Qutipin-100) was observed to be 99.46%. It could be concluded from the results obtained in the present investigation that the method for estimation of Quetiapine fumarate in pure form and in pharmaceutical dosage form is simple, rapid, accurate, precise and economical and can be used, successfully, in the quality control of pharmaceutical formulations and other routine laboratory analysis.

Keywords: Quetiapine fumarate, Analytical Quality by Design (AQbD), Simulated Nasal Fluid (SNF), UV-Spectrophotometer, Validation.

INTRODUCTION

Quality by Design (QbD) is a concept which was first outlined by well-known quality expert Joseph M. Juran in various publications, most notably Juran on Quality by design [1-2]. QbD principle has been used to advance product and process quality in every industry. They have most recently been adopted by U.S. Food and Drug administration as a vehicle for transformation of how drugs are discovered, developed as well as commercially established. QbD has become an important concept for all pharmaceutical industries which is further defined in International Conference on Harmonization (ICH) guidance on pharmaceutical development as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" [3-5].

QbD approach has been successfully implemented in generic formulation development. Similar to QbD, the outcome of AQbD (Analytical Quality by Design) is well understood and fits completely for intended purpose with robustness throughout the life. AQbD has different tools such as ATP (Analytical Target Profile), CQA (Critical Quality Attributes) [6], risk assessment, method optimization and developed with DoE (design of experiment), MODR (Method Operable Design Region), control strategy and risk assessment, AQbD method validation and continuous method monitoring. Figure 1 represents AQbD along with its all tools.

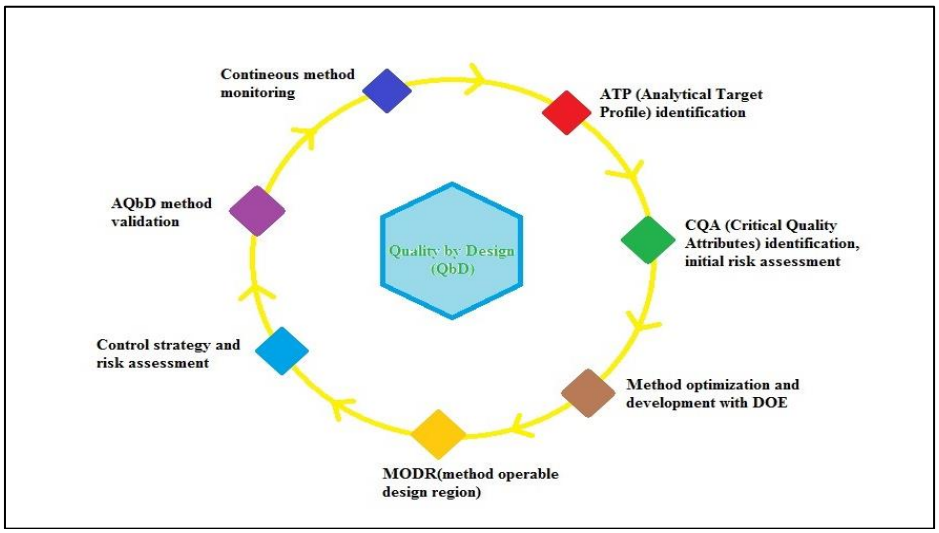

Fig-1: AQbD tools and their life cycle

It is recommended to implement QbD approach in analytical method developed which is termed as AQbD. Nowadays, AQbD concept is mainly applied to the development step as an alternative approach to the quality-by-testing methodology widely discussed in scientific literature [7-11].

Quetiapine fumarate, (2-[2-(4-dibenzo[b,f] [1,4]thiazepin-11-yl-1- piperazinyl) ethoxy] ethanol fumarate (2:1 salt), an atypical antipsychotic agent, has a unique receptor binding profile belonging to a new chemical class known as dibenzothiazepine derivatives [12-13]. Quetiapine acts as an antagonist at a broad range of neurotransmitter receptors. Quetiapine is used for the treatment of schizophrenia or manic episodes associated with bipolar disorders.

For the determination of quetiapine, several HPLC methods have been reported most of which require ultraviolet detection [14-18] since the drug is not electro active [19]. 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 [20]. Some gas chromatography-mass spectrometry [GC-MS] methods have been employed; however quetiapine needs to be derivatized before analysis [21].

So, the goal of our work was to apply AQbD technique to develop a simple UV- spectrophotometric method for the determination of quetiapine in solid dosage form so that the results obtained from this work may be used for analysis of drug in commercial pharmaceutical dosage forms in most economic way.

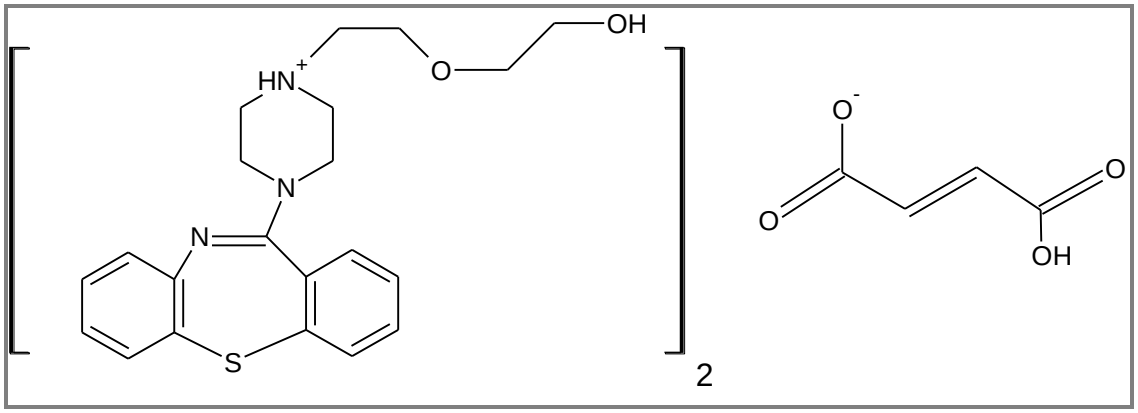

Fig-2: Chemical structure of Quetiapine Fumarate

EXPERIMENTAL SECTION

Instruments

Absorption Spectral measurements were carried out with a UV-Visible spectrophotometer was employed with spectral bandwidth of 1 nm and wavelength accuracy of 0.3 nm with a pair of 5 cm matched quartz cells.

Chemicals

Quetiapine fumarate and other chemicals used were analytical reagent grade (AR grade). Pure sample of Quetiapine fumarate (QF) was generous gift from Raks Pharma Pvt. Ltd. Sodium chloride, potassium chloride and calcium chloride dehydrate were used in simulated nasal fluid preparation. Qutipin-100

manufactured by Sun Pharmaceutical Ltd. was purchased.

Preparation of simulated nasal fluid (SNF)

Composition of SNF includes 7.45 mg/ml sodium chloride, 1.29mg/ml Potassium chloride and 0.3 mg/ml of calcium chloride dihydrate were dissolved in double distilled water and shaken continuously for 24 hours in thermostat water bath [22].

Preparation of standard stock solution

Standard stock solution of drug was prepared by dissolving 100mg QF in 100ml SNF to get concentration 1000µg/ml. Different aliquots of above solution were transferred into series of 10 ml volumetric flasks and volume was made upto the mark with SNF to obtain concentration 4-24µg/ml. Scanning ranges were finalized for study and solutions were scanned on UV spectrophotometer.

Determination of λ_{max}

From the stock solution, a working standard was prepared. The absorption spectrum of QF was recorded and maximum absorption was found to be 242nm. The calibration curves were prepared for quetiapine in the concentration range of 4-24µg/ml. UV spectrum of quetiapine fumarate is given below:

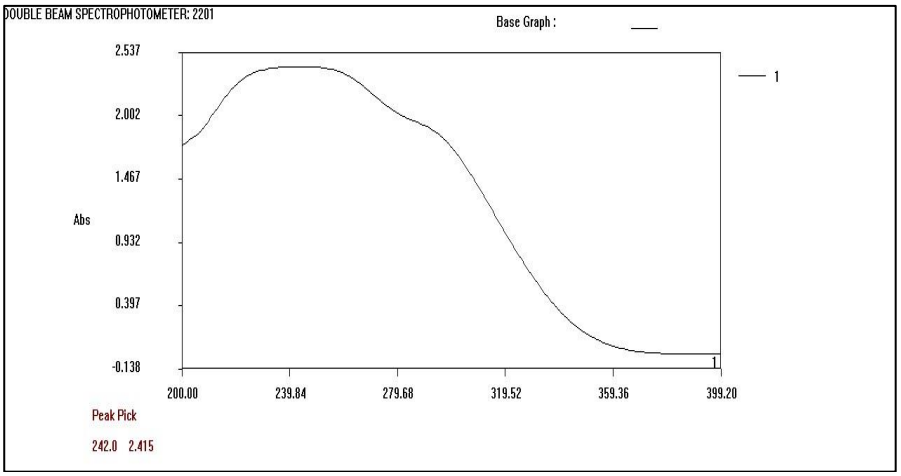

Fig-3: UV spectrum of Quetiapine Fumarate in SNF

Preparation of sample solution

Sample label claim 100mg. The average weight was determined with 20 tablets which were grounded in mortar until fine powder was obtained. Accurately weighed amount of powder equivalent to 100 mg was quantitatively transferred to 100ml volumetric flask with the aid of SNF. Volume was made up to the mark with SNF.

Method validation

Method was validated with the reference to linearity, accuracy, precision, limit of detection and limit of quantification.

Linearity

Linearity was performed by taking from working solution (40µg/ml) aliquots of 1,2,3,4,5 and 6 ml were taken in 10ml volumetric flask and diluted up to mark with SNF such that the final concentration of QF in the range of 4-24µg/ml. Graphs were obtained by plotting concentration vs absorbance. Calibration data and curve is shown in table 1 and figure 4.

Table-1: Optical characteristics and linearity data

Sr. No.	Parameter	QF
1	λ_{max}	242
2	Beer's law limits	4-24µg/ml
3	Correlation Coefficient	0.999
4	Regression equation	y=0.0404x-0.1081
5	Intercept (c)	-0.1081
6	Slope	0.0404

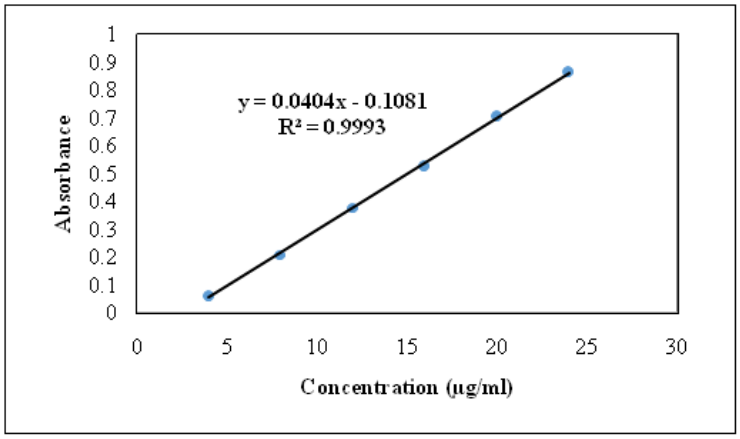

Fig-4: Calibration curve of Quetiapine Fumarate

Accuracy

Accuracy of the proposed method was assessed by recovery studies at three different levels 75%, 100%, 125%. The recovery studies were carried out by adding known amount of standard solution of three different levels. The resulting solutions were then reanalyzed; the results are shown in table 2.

Table-2: Recovery studies Precision

%Conc.	Amount added	Amount found	%Recovery	%RSD
75	17.5	16.9	96.57	0.42
100	20	19.50	97.00	0.42
125	22.5	22.0	97.77	0.35

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility. Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample it may be investigated using artificially prepared samples or a sample solution. The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements. Data is shown in table 3 and table 4.

Table-3: Intraday Precision

Conc. (µg/ml)	Absorbance (10:00 am)	Absorbance (12:00 pm)	Absorbance (02:00 pm)	Precision (%age conc. ± SD)	% RSD
4	0.034	0.046	0.038	91.5 ± 0.008	0.155563
8	0.203	0.21	0.2	97.2 ± 0.004	0.565685
12	0.367	0.343	0.362	93 ± 0.016	0.919239
16	0.538	0.505	0.512	97.3 ± 0.023	1.484924
20	0.643	0.639	0.64	92.7 ± 0.002	1.668772
24	0.784	0.791	0.788	92.3 ± 0.004	0.643467

Table-4: Interday Precision

Conc. (µg/ml)	Absorbance (Day 1)	Absorbance (Day 2)	Absorbance (Day 3)	Precision (%age conc. ± SD)	% RSD
4	0.066	0.045	0.058	100 ± 0.263	0
8	0.183	0.183	0.187	90 ± 0.057	0.565
12	0.306	0.343	0.33	89.5 ± 0.461	0.883
16	0.459	0.449	0.455	86.9 ± 0.125	1.477
20	0.604	0.606	0.602	88.1 ± 0.05	1.68
24	0.825	0.825	0.828	96.2±0.046	0.629

Repeatability

Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision (Table-5).

Table-5: Repeatability data

Conc. (µg/ml)	Absorbance
20	0.598
20	0.601
20	0.599
20	0.601
20	0.601
20	0.601
Mean	0.600167
Standard Deviation	0.001213
RSD%	1.668772

Robustness and Ruggedness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage. The ruggedness of analytical method is the degree of reproducibility of test results obtained by the analysis of the same samples under a variety of conditions such as different laboratories, different instruments, different lots of reagents, different assay, temperatures, different days, different analysts etc. The data obtained is tabulated below.

Table-6: Result of the robustness study

	Conc. found (µg/ml)	
Conc. (µg/ml)	240 nm	244 nm
12	11.73	11.88
12	11.72	11.86
12	11.74	11.88
Mean	11.73	11.87
SD	0.01	0.011
RSD	0.190	0.091

Table-7: Result of the ruggedness study

	Change in day and analyst	
Test sample	Day 1/Analyst	Day 2/ Analyst
1	94.5	98
2	95	97.5
3	94.5	98
4	94.25	98
5	94.5	97.75
6	95	97.5
Mean	94.62	97.79
Standard	0.306	0.245

Limits of Detection (LOD) and Limit of Quantification (LOQ)

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value. The quantization 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 quantization limit is a parameter of quantitative assays for low levels of compounds in sample and is used particularly for the determination of impurities and/or degradation products. It is expressed as the concentration of analyte (e.g. parts per million) in the sample. It is calculated by using the formula:

LOD = 3.3 σ /S, LOQ = 10 σ/S (σ = Standard deviation and S = Slop of the calibration curve). The LOD and LOQ of Quetiapine were found to be 0.081and 0.247 respectively.

Stability studies (Forced degradation)

Stability studies were performed according to ICH guidelines under condition of hydrolysis (acidic and alkaline), oxidation and thermal stress.

Standard Stock solution

Accurately weighed quantity of QF (100 mg) was transferred to a 100 ml volumetric flask, dissolved and diluted up to the mark with SNF and was ultra-sonicated for 5 min (concentration: 1000µg/ml).

Alkali induced degradation

To 1ml of stock solution of QF, 1 ml 2N sodium hydroxide (NaOH) was added and allowed to keep aside for 6 hour, after that 1ml of acid was added to neutralize the base to the resulting solution. Add SNF sufficient to make up 10ml. Later, 4 ml of sample was diluted to 25 ml with SNF and analyzed.

Acid induced degradation

To 1ml of stock solution QF, 1 ml of 2N hydrochloric acid (HCl) was added and allowed to keep aside for 6 h, and then the acid was neutralized by base and diluted up to 10 ml with SNF. Then after 4 ml of sample was diluted to 25 ml with SNF and analyzed.

Hydrogen peroxide-induced degradation

One ml of 30% hydrogen peroxide (H_2O_2) was added to 1 ml of stock solution of QF and was allowed to keep aside for 6 h. Added SNF sufficient to make up 10 ml. Later, 4 ml of sample was diluted to 25 ml with SNF and analyzed.

Thermal degradation

A sample powder of QF (10 mg) was exposed to a temperature of 100ºC for 48 h in hot air oven. This drug sample (10 mg) was transferred to a 100 ml volumetric flask, dissolved and diluted up to the mark with methanol and was ultra-sonicated for 5 min. Later, 4 ml of sample was diluted to 25 ml with SNF and analyzed [23]. Observations are given in table 8.

Table-8: Result of stability study

Degradation Test	Sample Conc. (µg/ml)	Sample Recovered (µg/ml)	% Recovery
Acid	16	12.70	79.37
Alkaline	16	12.57	78.56
Oxidation	16	15.99	99.9
Thermal	16	14.45	90.9

Analysis of pharmaceutical formulation

Twenty commercial tablets of Quetiapine Fumarate were weighed, powdered and tablet powder equivalent to 100 mg of QF was dissolved in SNF in a 10-ml volumetric flask. The solution was sonicated for 5 minutes, centrifuged at 100 rpm for 15 min and filtered through Whitman filter paper. From clear solution, further dilutions were made to get 1 mg/ml of drug. From the filtrate aliquots were taken and suitably diluted with SNF as per the requirement. The data obtained was substituted in the regression equations obtained and the percentage purity was determined [24].

Table-9: Results of analysis of marketed formulation

Formulation	%Label claim (mg)	Amount Obtained (mg)	Label Claim ± SD
Quetin-100 Tablets	100	99.88	99.7±0.542

RESULTS AND DISCUSSIONS

The methods developed and discussed in the present work provide a convenient, precise and accurate way for estimation of Quetiapine Fumarate in its bulk and pharmaceutical dosage form (tablets). An absorbance maximum of QF at 242 nm was selected for the analysis. Regression analysis shows linearity over the concentration range of 4-24 µg/ml correlation coefficients of 0.999. The % RSD for repeatability (n=6), intraday and interday (n=3) precision were found to be less than 2% indicating the precision of method. Accuracy of proposed methods was studied by recovery studies and the results were expressed as % recovery within the range of 96 to 98%. Values of standard deviation and coefficient of variation were satisfactorily low indicating the accuracy the method. Robustness and ruggedness of developed method were studied by taking different wavelength, carrying out analysis by different analyst and analyzing the samples on different days respectively. Deliberate changes which were introduced in the study, did not affect the analysis. So the method developed for WF was found to be robust. The % purity of the drug in the commercial tablet was found to be 99.88.

CONCLUSION

The developed UV spectrophotometric method is accurate, simple, rapid, precise, reliable, sensitive, reproducible and economical for the determination of QF and its pharmaceutical tablet dosage forms. The reagents utilized in the proposed methods are economic, readily available and the procedure does not involve any critical reaction conditions or tedious sample preparation. The methods are more selective than many of the reported spectrophotometric methods and employs higher wavelength to measure absorbance

readings where the errors due to inactive ingredients are minimized to a large extent. The methods are free from interferences from the common excipients. The statistical parameters and the recovery data reveal good accuracy and precision of the methods. These methods can be used as general methods for the determination of QF in bulk powder and dosage forms. The methods have many advantages over the separation techniques such as HPLC and include reduced cost, and speed with high accuracy. Hence, the methods can be used in routine analysis of drug in quality control laboratories.

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