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ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF QUETIAPINE FUMARATE: REVIEW

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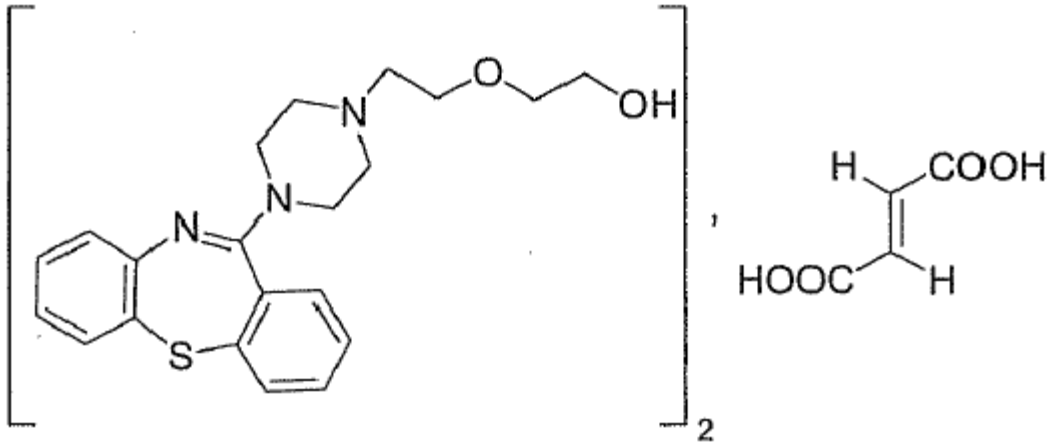
ABSTRACT

Analytical method development and Validation are the continuous and inter-dependent task associated with the research & development, quality control and quality assurance departments. Analytical procedures play a critical role in equivalence and risk assessment, management. It helps in establishment of product-specific acceptance criteria and stability of results. Validations determine that the analytical procedure is suitable for its intended purpose. Literature survey reveals that the analytical methods based on UV spectrometry, RP-HPLC, UPLC and HPTLC for the determination of Quetiapine fumarate personally and in combination with different drugs. The parameters were validated according to ICH guideline in terms of accuracy, precision, robustness, and other components of analytical validation. The developed methods are simple, sensitive and reproducible and can be used for the analysis of Quetiapine fumarate in bulk and Tablet dosage form.

KEYWORDS: Quetiapine fumarate, Literature Survey, UV, HPLC, HPTLC, UPLC, Validation, ICH Guidelines.

INTRODUCTION

Quetiapine fumarate is a second generation atypical antipsychotic medication used to treat certain mental /mood disorders (Such as schizophrenia, bipolar disorder, sudden epoisodes of mania or depression associated with bipolar disorder).[1]



Quetiapine fumarate is chemically known as 2-(2-(4-Dibenzo[b,f][1,4]thiazepine-11-yl-1-piperazinyl)ethoxy)ethanol with a molecular formula of $C_{21}H_{25}N_3O_2S$ and a molecular weight of 383.51 g/mol. Quetiapine fumarate drug substance is White to off-white Crystalline powder and it is Soluble in methanol, ethanol & 0.1NHCL.

Review of literature

1. **Bagade S. B.**[2] ***et al.,*** have developed a Simple, fast and reliable derivative Spectrophotometric method for determination of Quetiapine fumarate in pharmaceutical formulation. Second order derivative ultraviolet Spectrophotometric methods were developed. Spectrophotometrically, Quetiapine fumarate was determined by measuring the 2D-values at 254.76nm with 0.1N HCl as background solvent. Analytical Calibration curves were linear within a concentration range from 10 to 30µg/ml. The method was completely validated. The results showed that this method can be used for rapid determination of Quetiapine fumarate in pharmaceutical tablet with precision, accuracy and specificity.

2. **K. Basavaiah**[3] ***et al.,*** have developed two simple, sensitive, selective, economical and reproducible UV spectrophotometric methods are described for the quantitative determination of Quetiapine fumarate in bulk drug and in pharmaceutical dosage forms. The methods are based on measurement of absorbance of Quetiapine fumarate solution either in 0.1N HCl at 209nm (method A) or in methanol at 208nm (method B) Simple, sensitive UV-spectrophotometric methods for the determination of quetiapine fumarate in bulk drug and in pharmaceutical dosage forms were developed and validated for accuracy, precision, linearity and ruggedness.

3. **Borkar Bhaskar Hiraman**[4] ***et al.*,** have developed two different spectrophotometric analytical methods for the quality control of Quetiapine Fumarate in commercial marketed formulation. One is the zero order derivative spectroscopic method (Method-I) and other is area under curve method (Method-II), for the first method, wavelength selected i.e. 290nm and that of for other 295nm to 281nm respectively. The absorbance data was obtained by the measurements at selected wavelengths by using Milli-Q water as solvent. Beers Lambert's law obeyed at concentration range 12-60mg/ml concentration range of Quetiapine for both spectrophotometric methods at selected wavelengths. Validation parameters consents, the applied spectrophotometric methods of analysis are simple, sensitive, accurate, precise and satisfactorily capable for determination of Quetiapine fumarate in tablet formulation with reproducible specific results.

4. **S. S. Chhajed**[5] ***et al.*,** have developed a simple, cost effective, accurate and reproducible UV-spectrophotometric method for the estimation of quetiapine fumarate in bulk drug and tablet formulation. Quetiapine was estimated at 239nm in 0.1N hydrochloric acid (pH 1.2) and at 250nm in ethanol. Beer's law was obeyed in the concentration range of 1–12 µgm/ml. The proposed analytical methods are simple, rapid, accurate, precise and inexpensive.

5. **Anand Babu K**[6] ***et al.*,** have developed a simple rapid, accurate, precise and reproducible validated UV spectrophotometric method for the determination of Quetiapine fumarate. The absorption maximum of the drug was found to be 237nm by using Ethanol, 1N sodium hydroxide (1:1) as a solvent. It obeys the beer's lamberts law in the range of 75-175µg/ml. Quetiapine fumarate is soluble in Methanol, Ethanol, 0.1N HCl, and Water, but the lambda max of Quetiapine fumarate in above solvents is 207-215. Normally the solvent peak appears in the region of 200 to 220, so it may interfere the analysis, in order to avoid that extended conjugation Bathochromic shift method was followed by increasing the polarity of the solvent. The developed spectrophotometric method is found to be simple, precise, specific, and accurate and can be used for routine analysis of Quetiapine fumarate.

6. **R. A. Fursule**[7] ***et al.*,** have developed a Simple, rapid, sensitive and accurate UV-Spectrophotometric methods for estimation of Quetiapine fumarate and Cilostazol in pharmaceutical formulation. In water, Quetiapine fumarate showed absorbance maxima at 290nm. In acetonitrile (30% v/v) Cilostazol showed maximum absorbance at 258nm.

Amounts of drug estimated from the tablet formulations were in good agreement with label claim. The proposed methods are simple, rapid, accurate, economical and used for the routine analysis of Quetiapine fumarate and Cilostazole from marketed formulations**.**

7. **Pappula Nagaraju**[8] ***et al.,*** have developed a simple, rapid, accurate and precise RP-HPLC method for the determination of Quetiapine fumarate in pure and tablet dosage forms. Separation of the drug was achieved on a isocratic Shimadzu prominence HPLC instrument on a Waters Xterra C_{18} column (250x4.6 mm, 5µ). The method showed a linear response for concentration in the range of 50–150 µg/ml using buffer (9.2 ± 0.05) and acetonitrile in the ratio of 51:49 v/v with detection at 254nm with a flow rate of 1.0ml/min and retention time was 6.588min. The method was statistically validated for linearity, accuracy, precision and selectivity.

8. **Mehdi Rezaei**[9] ***et al.,*** have developed a precise, specific, rapid and feasible reversed-phase high-performance liquid chromatographic,UV spectrophotometric and reversed phase ultra-performance liquid chromatography methods for the determination of an antipsychotic drug quetiapine fumarate in pharmaceuticals,spiked human urine and plasma sample have been developed and collected in this review. The methods also find applications in clinical, biological and pharmacokinetic studies of quetiapine fumarate. Proposed methods found to be the simple, accurate, economic and rapid for routine estimation of the quetiapine.

9. **Sawsan MA**[10] ***et al.,*** have developed a two chromatographic methods for determination of quetiapine fumarate in presence of three related compounds; namely quetiapine N-oxide, des-ethanol quetiapine and quetiapine lactam, in pure form and pharmaceutical preparation. The first method depended on densitometric thin layer chromatography where the separation was achieved using silica gel 60F(254) plates as stationary phase and toluene:1,4-dioxane:dimethylamine (5:8:2,v/v/v) as a mobile phase. The second method utilized the reverse phase high performance liquid chromatographic technique, using C_{18} column and methanol: acetonitrile: phosphate buffer (pH 5.3) in a ratio (19:40:41, v/v/v) as a mobile phase. The flow rate was 1ml/min and UV-detection was at wavelength 220nm. The validation parameters of the developed methods were calculated and the results obtained were statistically compared with those of the HPLC manufacturer method. The proposed HPLC method offers high sensitivity, short run time and the use of

isocratic elution mode for the mobile phase with good resolution between the four proposed components compared with the reported HPLC methods.

10. **Kanakapura B Vinay**[11] ***et al.,*** has been developed a precise and feasible reversed-phase high-performance liquid chromatographic method for the determination of an antipsychotic drug quetiapine fumarate in pharmaceuticals and spiked human urine sample. The analysis was carried out using a ODS (250 mm × 4.6 mm i.d.,5µm particle size) chromatopack column. Mobile phase containing a mixture of acetonitrile and 0.1% phosphate buffer (pH 3.1) (40:60) was pumped at a flow rate of 1ml/min with UV detection at 240nm at ambient column temperature (25 ºC). The method is accurate, precise, sensitive and selective for routine analysis in quality control laboratories.

11. **Alapati Dihitha Chowdary**[12] ***et al.,*** have developed a quality improvement and robustness testing method for related substance of Quetiapine fumarate by reversed-phase high- performance liquid chromatography. In this study, the DoE Combined- Randomized method was used. The drug was analyzed on Zorbax Eclipse Plus C_{18} Column (250×4.6mm, 5µ) using UV Detector. The Mobile phase consisting of Di-ammonium Hydrogen Phosphate (0.02M), methanol, and acetonitrile with a flow rate of 1.3ml/min. In DoE, evaluated variables are Solvent composition and salt concentration. The detection wavelength was 230nm.

12. **Pragati Talusani**[13] ***et al.,*** have developed a simple, sensitive, precise and accurate high performance liquid chromatography method for analysis of Quetiapine fumarate in bulk and tablet dosage form. To develop and validate high performance liquid chromatographic method for estimation of Quetiapine fumarate from bulk and tablet dosage form. The separation was achieved on a C_{18} column using a mixture of phosphate buffer, acetonitrile and methanol in the ratio 50:40:10v/v/v with a flow rate of 1ml/min and detection wavelength at 245nm. The method was validated for linearity, accuracy, precision and specificity as per ICH guidelines.The developed and validated method was successfully used for the quantitative analysis of commercially available dosage form.

13. **Patricia C. Davis**[14] ***et al.,*** A sensitive and specific HPLC assay for the measurement of the antipsychotic compound quetiapine in human plasma has been developed and validated. The assay employs a three-step liquid–liquid extraction of quetiapine and its 7-hydroxylated and 7-hydroxylated, N-dealkylated metabolites from human plasma, and

utilizes ultraviolet (UV) detection of quetiapine and electrochemical detection of the metabolites. The method provides a linear response from a quantitation limit of 2.50 to 500 ng/ml for each analyte using 0.4 ml plasma. The assay is applicable from 500 to 5000 ng/ml by sample dilution with de-ionized water. The inter-assay precision of quetiapine in plasma calibration standards across 4 validation days averaged 11.9% relative standard deviation (RSD) over the range 2.50 to 500 ng/ml, with intra-assay precision averaging 16.0% RSD and mean accuracy of 98.6% of theory. Similarly, the inter-assay precision of the 7-hydroxylated metabolite in plasma calibration standards across 4 validation days averaged 13.7% RSD over the range 2.50 to 500 ng/ml, with intra-assay precision averaging 17.6% RSD and mean accuracy of 109% of theory. The 7-hydroxylated, N-dealkylated metabolite demonstrated inter-assay precision of 16.2% RSD, intra-assay precision of 19.9% RSD, and mean accuracy of 104% of theory over the range 2.50 to 500 ng/ml.

14. **B. Venkateswara Reddy**[15] ***et al.,*** A new, simple, rapid, selective, precise and accurate isocratic reverse phase high performance liquid Chromatography assay method has been developed for estimation of Fumaric acid in Quetiapine hemi fumarate drug substance. The separation was achieved by using column Hypersil C18 (250×4.6mm, 5µm), in mobile phase consisted of acetonitrile and pH 3.0 phosphate buffer, adjusted to pH 3.0 with the help of dilute orthophosphoric acid in the gradient elution. The flow rate was 1.0 mL/min-1 and the separated Fumaric acid was detected using UV detector at the wavelength of 210 nm. Column temperature 25°C and sample temperature ambient and injection volume 20µl. The retention time of Fumaric acid, was noted to be 3.65 min respectively, indicative of rather shorter analysis time.

15. **Ramesh L. Sawant**[16] ***et al.,*** The objective of the existing study was to develop a simple, precise, accurate, rapid, and economical UV Spectrophotometric and isocratic reversed-phase high performance liquid chromatography (RP-HPLC) method for the simultaneous estimation of fluoxetine HCl and quetiapine fumarate in synthetic mixture. In UV spectrophotometric method 0.1N HCl is used as solvent. Method I is based on simultaneous equation method, known as Vierodt's method. Method II is based on principle of Q analysis, known as absorbance ratio method. Isocratic RP-HPLC separation was achieved on an Hibar R 250 × 4.6 mm HPLC column Purosphens R STAR RP-18, using a mobile phase of phosphate buffer (KH2PO4 and K2HPO4):acetonitrile

(55:45v/v) at a flow rate of 1.0ml/min. The method was used successfully for the simultaneous determination of fluoxetine HCl and quetiapine fumarate in synthetic mixture. In method I Fluoxetine HCl and quetiapine fumarate show absorbance maxima at 228nm and 254nm. In method II both drugs was measured at 233nm (Isobestic point) and 254 nm (λmax of Quetiapine fumarate). The developed methods are precise, accurate, rapid, simple, reproducible and economical for simultaneous estimation of fluoxetine HCl and quetiapine fumarate in synthetic mixture.

16. **Deepak Sahu**[17] ***et al.,*** A simple, accurate, low cost and specific HPTLC method for estimation of quetiapine fumarate in tablet has been developed. It was performed on Silica gel G60 F254 aluminium foil using acetonitrile:chloroform in the ratio of 1:9 as mobile phase. The mobile phase having chamber was saturated for 20 minutes at room temperature. The Rf value of quetiapine fumarate was found to be 0.45. The plate was scanned and quantified at 242 nm. The calibration curve response was observed between 5-25 µg. The linear regression data showed good linear relationship of r = 0.999. The percent recovery was found to be 100.0 ± 0.01.

17. **S. R. Dhaneshwar**[18] ***et al.,*** have developed a sensitive, selective, precise, and stability-indicating HPTLC method for quantitative analysis of quetiapine fumarate both as the bulk drug and in formulations. stationary phase was silica gel and the mobile phase toluene–methanol 8:2 (v/v). This system gave compact bands for quetiapine fumarate (RF 0.37 ± 0.02). Densitometric analysis of quetiapine fumarate was performed in absorbance mode at 254nm. There was no chromatographic interference from tablet excipients. Quetiapine fumarate was subjected to acid and alkaline hydrolysis, oxidation, and photodegradation. The method was validated for linearity, precision, accuracy, selectivity, and specificity in accordance with ICH guidelines. Because the method can effectively separate the drug from its degradation products, it can be used as a stability indicating method.

18. **Nagaraju Rajendraprasad**[19] ***et al.,*** has been developed a reverse phase high performance liquid chromatography for the determination of quetiapine fumarate in bulk drug and in its tablets. The method was developed using AQUITY UPLC HSS T3 (2.1 × 50 mm, 1.8µm) column with mobile phase consisting of 30:70 (v/v) mixture of potassium dihydrogen phosphate and dipotassium hydrogen phosphate (pH was adjusted to 6.5 with orthophosphoric acid) (mobile phase A) and methanol (mobile phase B). The UV

detection of the eluted compound was made at 252nm. The method was successfully applied to the determination of Quetiapine fumarate in pharmaceuticals. The developed rapid, isocratic reversed phase ultra performance liquid chromatography method for quantitative analysis of Quetiapine fumarate in pharmaceutical dosage forms is precise, accurate, linear, robust, and specific.

19. **Rakshit Kanubhai Trivedi[20] *et al.*,** have developed the work, reports a stability indicating reversed phase ultra performance liquid chromatography method for the quantitative determination of quetiapine in pharmaceutical dosage form. The chromatographic separation is performed on an Agilent Eclipse Plus C_{18}, RRHD 1.8µm (50 mm x 2.1 mm) column using gradient elution. The optimized mobile phase consists of 0.1 % aqueous triethylamine (pH 7.2) as a solvent-A and 80:20 v/v mixture of acetonitrile and methanol as solvent-B. The eluted compounds are monitored at 252nm wavelength using a UV detector. The developed reversed phase ultra performance liquid chromatography method is validated as per International Conference on Harmonization guidelines with respect to system suitability, specificity, precision, accuracy, linearity, robustness an and filter compatibility.

CONCLUSION

Literature survey suggested that various UV, HPLC, HPTLC and few UPLC methods were developed and reported. The published methods were validated for various parameters as per ICH guidelines. Statistical analysis proved that the published methods were reproducible and selective. Thus it can be concluded that the reported and published methods can be successfully applied for the estimation of the Quetiapine fumarate in pure and pharmaceutical dosage form.

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