

Atypical Antipsychotic Drug - Quetiapine Fumerate and its Analytical Techniques: A Review

R. Valarmathi*, S. Akilandeswari, CS. Dhivya dharshini,
S. Farishabanu and R. Senthamarai

Department of Pharmaceutical Analysis, Periyar College of Pharmaceutical Sciences, Trichy-21,
Tamil Nadu, India.

ABSTRACT

Psychosis is a mental illness of severe type in which the patient loses touch with reality. A person with this problem change in his way of thinking, believing or perceiving and behaving. Since nowadays youngsters are greatly affected by this disease, many Antipsychotic drugs are introduced and used for the treatment. The present review describes information regarding a atypical antipsychotic drug – Quetiapine fumerate approved for the treatment of schizophrenia, bipolar disorder, and as an add-on to treat depression. The present review includes all available information like pharmacokinetics, pharmacological action and side effects. It also provides information regarding various analytical methods developed for this drug along with its validation parameters.

Keywords: Quetiapine fumerate, Analytical methods like UV, HPLC, HPTLC, UPLC.

INTRODUCTION

Psychosis¹ is a mental illness of severe type in which the patient loses touch with reality. In normal terminology, Psychosis means abnormal condition of the mind. A person with this problem change in his way of thinking, believing or perceiving and behaving. The patient may also neglect his appearance and may stop talking or talk only "nonsense." **Antipsychotic drugs**² are medicines used to treat Psychosis and other mental and emotional conditions. An antipsychotic medicine, also referred as neuroleptic medicine, is a tranquilizing psychiatric medication mainly used to manage psychosis, specially in schizophrenia and bipolar disorder.

Quetiapine fumerate³ is an is an atypical antipsychotic approved primarily for the treatment of schizophrenia, bipolar disorder, as an add-on to treat depression and "off-label" to treat chronic insomnia and restless legs syndrome; it is a powerful sedative. It works by helping to restore the balance of certain natural chemicals (neurotransmitters) in the brain.

Quetiapine^{3,4} received its initial indication from the U.S. Food and Drug Administration for treatment of schizophrenia in 1997. In 2004, it received its second indication for the treatment of mania-associated bipolar disorder. In 2007

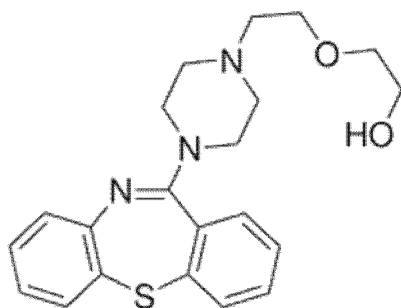
and 2008, studies were conducted on quetiapine's efficacy in treating generalized anxiety disorder and major depression. In April 2009, the Psychopharmacologic Drugs Advisory Committee of the US Food and Drug Administration (FDA) held a public meeting to discuss whether study results supported the FDA's approval for anxiety and depression, with risks of metabolic side-effects and of tardive dyskinesia and sudden cardiac death.

DRUG PROFILE^{3,4,5}

Chemicalname:2-(2-(4-dibenzo[b,f][1,4]thiazepine-11-yl-1-piperazinyl)ethoxy)ethanol

Synonyms

- Ethanol,2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-,(2E)-2-butenedioate (2:1) (salt) (9CI);
- Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-,(E)-2-butenedioate (2:1) (salt);
- Dibenzo[b,f][1,4]thiazepine, ethanol deriv.,

Chemical structure

Molecular formula : C₂₁H₂₅N₃O₂S
Molecular mass : 383.5099 g/mol
Route of administration : oral
Melting Point : 174-176 °C

Boiling Point : 556.5 °C at 760 mmHg

Flash Point : 290.4 °C

Appearance : white crystalline solid

Storage : Store at room temperature

Solubility : Soluble in methanol, ethanol, Chloroform, 0.1 M HCl, phosphate buffer, sparingly soluble in water

PHARMACOKINETIC PROPERTIES^{4,5}

Bioavailability : 9%
Half life : 6 hours (for parent compound)
 12 hours (for active metabolites)
Metabolism : Hepatic
Excretion : Renal

MECHANISM OF ACTION^{5,6}

Quetiapine is a dopamine, serotonin, and adrenergic antagonist, and a potent antihistamine with clinically negligible anticholinergic properties. Quetiapine binds strongly to serotonin receptors. Serial PET scans evaluating the D₂ receptor occupancy of quetiapine have demonstrated that quetiapine very rapidly disassociates from the D₂ receptor. Theoretically, this allows for normal physiological surges of dopamine to elicit normal effects in areas such as the nigrostriatal and tuberoinfundibular pathways, thus minimizing the risk of side-effects such as pseudo-parkinsonism as well as elevations in prolactin. Some of the antagonized receptors (serotonin, norepinephrine) are

actually autoreceptors whose blockade tends to increase the release of neurotransmitters.

This can be simply explained as Quetiapine inhibits communication between nerves of the brain. It does this by blocking receptors on the nerves for several neurotransmitters, the chemicals that nerves use to communicate with each other. It is thought that its beneficial effect is due to blocking of the dopamine type 2 (D₂) and serotonin type 2 (5-HT₂) receptors.

FORMULATION AVAILABLE⁵

Tablets: 25, 50, 100, 200, 300, and 400 mg

DRUG INTERACTIONS^{5,6}

Increased risk of drowsiness and postural hypotension when used with alcohol. CYP3A4 inducers eg. phenytoin and carbamazepine may decrease plasma levels of quetiapine while CYP3A4 inhibitors eg. ketoconazole and erythromycin may increase its plasma levels.

SIDE EFFECTS^{4,5,6}

Headache, abdominal pain, back pain, fever, chest pain, postural and orthostatic hypotension, hypertension, constipation, dry mouth, dyspepsia, diarrhoea, leucopenia, elevations in serum transaminase level, weight gain, myalgia, somnolence, dizziness, anxiety, rhinitis, rash, dry skin, ear pain, UTI.

VARIOUS ANALYTICAL METHODS⁷⁻¹⁸

Various analytical methods^{8,9,11} have been developed for the determination of quetiapine fumarate like UV, HPLC^{12,13}, UPLC, UV derivative methods, polarographic studies, potentiometric, complexation studies etc. and they are validated with respect to ICH guidelines^{15,16,17,18}. Those methods are briefly explained in this article.

1. By Simple Spectrophotometric Method Using Ion Pair Complexation¹⁹

The method is based on the reaction of quetiapine fumarate with wool fast blue, the formed ion pair complex extracted into chloroform at pH 1.5. The chloroform extractable layer is measured at 585 nm against reagent blank.

2. By Liquid Chromatography Using UV Detector²⁰

The chromatography separations were carried out on Agilent Eclipse plus C-8 (4.6 X 75 mm, 3.5 µm) column. The mobile phase consisted of 10 mM ammonium acetate and 100% methanol. Initially the run started with 100% aqueous

phase and reached to 100% organic phase in 5 minutes, then 100% organic phase for 3 minutes and subsequently 100% aqueous phase for 2 minutes and followed by stabilization for 4 minutes with 100% aqueous phase. Milli-Q water: methanol (50:50 v/v) mixture was used as diluent. The flow rate was 1.0 mL/min with detection at 254 nm. Injection volume was 10 μ L and column temperature was 40 °C. Auto-sampler temperature was 10 °C. The LC method was validated with respect to various parameters, as required under ICH guideline. The response of QPF was strictly linear (r^2 : 0.9999) in the concentration range of 2.80 to 200 μ g/mL. Intra-day and inter-day precision were <0.59% and <0.83% (relative standard deviation) respectively and the mean recovery was 100.46%. The validated method was further used for all the pre-formulation and formulation analytical studies (*viz.*, purity and assay) targeted towards development of controlled drug delivery systems for QPF.

3. By RP - HPLC METHOD Using Isocratic Elution Of Mobile Phase²¹.

Isocratic elution at a flow rate of 1.0ml/min was employed on a symmetry C18 (250x4.6mm, 5 μ m in particle size) at ambient temperature. The mobile phase consisted of methanol: water: O.P.A 90:10:01 (V/V/V). The UV detection wavelength was 250 nm and 20 μ l sample was injected. The retention time for Quetiapine was 3.64 min. The percentage RSD for precision and accuracy of the method was found to be less than 2%. The method was validated as per the ICH guidelines. The method was successfully applied for routine analysis of Quetiapine in tablet dosage form.

4. By Reverse Phase High Performance Liquid Chromatographic Method (RP-HPLC) Using XTERRA C18 (4.6x150mm) Column²².

The method was performed isocratically on XTERRA C18 (4.6X150mm), analytical column using a mobile phase consisting of 2.5PH buffer and acetonitrile in the Ratio of 40:60v/v, with a flow rate of 0.8ml/min. The analyte was monitored with UV detector at 294nm. The developed method Quetiapine fumarate elutes at a retention time of 2.839min. The proposed method is having linearity in the concentration range from 10 to 50 μ g/mL of Quetiapine fumarate. The present method was validated with respect to system suitability, linearity, precision, limit of detection (LOD) and limit of

quantification (LOQ), accuracy (recovery), ruggedness, and robustness.

5. By Reverse Phase HPLC Method Using PDA Detector²³.

The analysis was carried out on a Phenomix Stainless Steel C18 (250 x 4.6 mm, 5 μ) reversed-phase column, using a mixture of phosphate buffer (pH 3), acetonitrile, methanol (50:40:10) as the mobile phase using a low pressure gradient mode with flow rate at 0.8ml/min. The injection volume was 20 μ l. The retention time of the drug was 4.69 min. The method produced linear responses in the concentration range of 1 to 5 μ g/ml of Quetiapine fumarate. The LOD and LOQ values for HPLC method were found to be 0.0167 and 0.0506 μ g/ml respectively.

6. By UV Spectroscopy Method Using Water As Solvent²⁴.

Spectrophotometrically, Quetiapine fumarate was determined by measuring the 2D-values at 254.76nm with water as background solvent. Analytical Calibration curves were linear within a concentration range from 10 to 50 μ g/ml. The developed method was applied to directly and easily to the analysis of the pharmaceutical tablet preparations. %R.S.D was found to be 0.33 (Quetipin® tablet; 200 mg) respectively. The percentage recoveries were 98 - 100% for given methods. The method was completely validated and proven to be rugged. The excipients did not interfere in the analysis.

7. By RP- HPLC Method Using Internal Standard Method²⁵.

The assay involved an isocratic elution of quetiapine fumarate in Grace C18 column using mobile phase composition of 0.1%ortho phosphoric acid with tri ethyl amine as modifier buffer and acetonitrile in the ratio of 50:50(v/v).The wavelength of detection is 294nm. The method showed good linearity in the range of 2.01-50.2 x10⁻³g/Lt. The runtime of the method is 5 mins. The developed method was 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.

8. By Ultra Performance Liquid Chromatography^{26,27,28}.

The determination of four potential genotoxic impurities namely 2-Chloro aniline, 1- Chloro-2-

nitro benzene, 2-Amino diphenyl sulphide and 2-Nitro diphenyl sulphide at trace levels in Quetiapine fumarate by applying the concept of threshold of toxicological concern (TTC), a limit of 1.63 ppm each were calculated based on the maximum daily dose of the drug substance. The proposed method is specific, linear, accurate and precise. The calibration curves show good linearity over the concentration range of 8.1–32.6ng/mL for genotoxic impurities in Quetiapine fumarate. The correlation coefficient obtained is >0.999 in each case. Method has very low limit of detection (LOD) and quantification (LOQ). LOD and LOQ of all genotoxic impurities are as low as 8.1 ng/mL and 2.0 ng/mL respectively. Method has accuracy with recovery in the range of 95.5–104.4% for all the genotoxic impurities. This method is a good quality control tool for quantitation of all the genotoxic impurities at very low levels in Quetiapine fumarate.

9. By Titrimetric And Spectrophotometric Method²⁹.

Titrimetric and spectrophotometric assay of quetiapine fumarate (QTF) using perchloric acid and acetic acid as reagents are described. The first method (method A) is a non-aqueous titrimetric method and is based on the titration of QTF in glacial acetic acid with 0.01 M acetous perchloric acid using crystal violet as indicator. In the second method (method B), QTF has been measured in 0.1M acetic acid spectrophotometrically at a wavelength of 222 nm. The titrimetric method was applicable over the range of 2.0–20.0 mg of QTF. The reaction stoichiometry of 1:3 is obtained which served as the basis for calculation. In spectrophotometry, Beer's law was obeyed over the concentration range of 1.25–15.0 $\mu\text{g mL}^{-1}$. The linear regression equation of the calibration graph was $A = 0.0115 + 0.0673c$ with a regression coefficient (r) of 0.9986 ($n = 7$). The apparent molar absorptivity was calculated to be $4.25 \times 10^4 \text{ L mol}^{-1}\text{cm}^{-1}$ and the Sandell sensitivity was $0.0145 \mu\text{g cm}^{-2}$. The limits of detection (LOD) and quantification (LOQ) calculated as per the ICH guidelines were 0.07 and $0.21 \mu\text{g mL}^{-1}$, respectively. Accuracy and precision of the assays were determined by computing the intra-day and inter-day variations at three different levels of QTF. The intra-day and inter-day relative standard deviation (%RSD) were in the range of 0.99–2.88 and 1.65–2.32%, for method A and B, respectively, with an acceptable percentage relative error (%RE) < 2%. The methods were successfully

applied to the determination of QTF in two different brands of tablets with good accuracy and precision and without detectable interference by excipients.

10. By UV Spectrophotometric Method Using Phosphate Buffer As Solvent³⁰.

Quetiapine fumarate exhibiting absorption at 242 nm and obeyed Beer's law in the concentration range 5- 25 $\mu\text{g/ml}$. The lower limit of detection was found to be 3.5×10^{-2} and the limit of quantification to be 11.6×10^{-2} . The regression equation was $Y = 0.037X + 0.007$. The precision of the method was found to be 100.14 mg at 242 nm against the label claim of 100 mg. The sample solution was stable upto 24 hours. The assay results were found to be in good agreement with labelclaim. This method is very useful for routine quality control analysis.

11. By High Performance Thin Layer Chromatography At 291 nm³¹.

The method was employed in thin layer chromatographic aluminum plates precoated with silica gel 60F-254 as the stationary phase. The solvent system consist of Toluene: Ethyl acetate: Diethyl amine (5:3:2, v/v/v) as the mobile phase. Densitometric analysis of quetiapine fumarate was carried out in the absorbance mode at 291 nm. The system was found to give compact spots for quetiapine fumarate (R_f value of 0.54). The linear regression analysis data for the calibration plots showed good linear relationship with $r^2 = 0.9915$ in the concentration range 25-225 ng per spot. The method was validated for precision, accuracy, recovery and sensitivity. The method has been successfully applied in the analysis of oral solid dosage formulation.

12. By Spectrophotometric Determination Using Two Charge Transfer Complexation Reactions³².

The developed two methods are based on charge transfer complexation reactions of free base form of the drug (quetiapine, QTP), as n -electron donor (D), with either p -chloranilic acid (p -CAA) (method A) or 2,3-dichloro-5,6-dicyanoquinone (DDQ) (method B) as π -acceptors (A). The coloured charge transfer complexes produced exhibit absorption maxima at 520 and 540 nm, in methods A and B, respectively. The experimental conditions such as reagent concentration, reaction solvent and time have been carefully optimized to achieve the maximum sensitivity. Beer's law is obeyed

over the concentration ranges of 8.0–160 and 4.0–80.0 $\mu\text{g mL}^{-1}$, for methods A and B, respectively. The calculated molar absorptivity values are 1.77×10^3 and $4.59 \times 10^3 \text{ L mol}^{-1} \text{cm}^{-1}$, for methods A and B, respectively. The Sandell sensitivity values, limits of detection (LOD) and quantification (LOQ) have also been reported. The stoichiometry of the reaction in both cases was accomplished adopting the limiting logarithmic method and was found to be 1:2 (D:A). The accuracy and precision of the methods were evaluated on intra-day and inter-day basis.

13. By Spectroscopic Method Using Ion Pair Complexation With Tropaeolin ooo³³.

The method includes the formation of a 1:2 chloroform extractable ion pair complex between the drug and the dye Tropaeolin ooo (TP) in acidic medium (pH 1.83 ± 0.03). The resulting orange – red colour ion pair complex exhibits an absorption maximum at 480 nm. The optimum conditions for the ion pair formation have also been established. The method permits the determination of QTF over a concentration range 2 to 20 $\mu\text{g/ml}$. The apparent molar absorptivity and sandell's sensitivity values are found to be $2.30 \times 10^4 \text{ litremol}^{-1} \text{cm}^{-1}$ and $0.0264 \mu\text{g cm}^{-2}$ respectively. The limit of quantitation and detection values are also reported. The accuracy and precision results of the method evaluated on intra-day and interday basis are found to be satisfactory.

14. By Spectroscopic Method Using Ethanol As Solvent³⁴.

The methods are based on measurement of absorbance of QTF solution in ethanol at 207 nm. Beer's law is obeyed over the linear range 1-5 $\mu\text{g/mL}$ of QTF for the method with apparent molar absorptivity value of $1434.41281 \text{ L mol}^{-1} \text{cm}^{-1}$. Limits of quantification (LOQ) and detection (LOD) are also reported. The methods were validated in accordance with the current ICH guidelines. The precision results, expressed by intra-day and inter-day relative standard deviation values, are satisfactory i.e. % RSD 100.22% and 99.83 % respectively. The accuracy is also satisfactory (%RSD 0.39) and percentage recoveries are in the range 99.34-100.11% with the standard deviation of 0.39. Method have excellent linearity and range ($r^2 = 0.998$).

15. By Spectrophotometric Method Of Zero Order Derivative And AUC Curve Method³⁵.

Two different spectrophotometric analytical methods for the quality control of Quetiapine Fumarate in commercial marketed formulation have been developed. 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. 290.0nm and that of for other 295.0nm to 281.0nm 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 12-60 mg ml^{-1} concentration range of Quetiapine for both spectrophotometric methods at selected wavelengths. Proposed methods gave satisfactory results in terms of repeatability and precision i.e. % RSD 0.60% and 0.73% resp. Also accuracy values were very good for both methods i.e. % RSD 0.60 and 0.75% resp. which is drawn out by recovery studies, were found satisfactory. Both spectroscopic methods have excellent linearity and range ($r^2 = 0.999$). Ruggedness of both methods checks in terms of intraday and interday studies having % RSD 0.55 %, 0.15% and 0.33%, 0.46% respectively.

16. By Spectrophotometric Method Performing Second Order Derivative Method³⁶.

Spectrophotometrically, Quetiapine fumarate was determined by measuring the 2D-values at 254.76nm with 0.1 N HCl as background solvent. Analytical Calibration curves were linear within a concentration range from 10 to 30 $\mu\text{g/ml}$. The developed method was applied to directly and easily to the analysis of the pharmaceutical tablet preparations. R.S.D was found to be 0.20% (Quetipin® tablet; 200 mg) and 0.16% (Quetipin® tablet; 300 mg) respectively. 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.

17. By Polarographic Analysis³⁷.

The voltammetric behaviour of quetiapine (QTP) was studied using direct current (DCt), differential pulse (DPP) and alternating current (ACt) polarography. The drug manifests cathodic waves over the pH range of 6 – 11.8. The waves were characterized as being irreversible, diffusion-controlled with limited adsorption properties. At pH 8, the diffusion current-concentration relationship was rectilinear over

the range of 8 – 44 µg/mL and 4 – 44 µg/mL using DCt and DPP modes, respectively, with minimum detection limits (LOD) of 0.06 µg/mL and 0.04 µg/mL using the DCt and DPP modes, respectively. The diffusion-current constant (I_d) is 1.36 ± 0.04 ($n = 10$). The proposed method was successfully applied to the determination of the studied compound both in pure form and in formulations. The results obtained were favourably compared with those obtained using a reference method. A pathway for the electrode reaction was postulated.

18. By Stability Indicating RP – HPLC Method For Determining The Related Substances³⁸.

Chromatographic separation between Quetiapine Fumarate its related substances and degradants was obtained from samples generated after stress degradation. The separation was achieved using a X-bridge C18, 150x4.6 mm, 3.5 µm column, mobile phase contains 5 mM ammonium Acetate as mobile phase A and Acetonitrile as Mobile phase B using a binary gradient mode with flow rate of the mobile phase kept at 1.0 ml/min. The sample concentration was 0.5 mg/ml. The column temperature was maintained at 40°C and the detection wavelength was 220 nm. The injection volume was 10 µL. The resolution between the critical pair of peaks (Impurity-B & analyte) was found to be greater than 4.5. The limit of detection (LOD) and limit of quantification (LOQ) of Impurity-A, Impurity-B and analyte were 27 ng mL⁻¹ and 80 ng/ml, for Impurity-3 was 14 ng/ml and 40ng/ml respectively, for 10 µl injection volume. The test solution and mobile phase was observed to be stable up to 24 h after the preparation. The validated method yielded good results of precision, linearity, accuracy, and robustness.

19. By High Performance Thin Layer Chromatography at 235 nm³⁹.

The chromatographic separation was carried out on precoated silica gel 60 F254 aluminium plates using mixture of methanol and toluene (4:3%v/v) as mobile phase and densitometric evaluation of spots were carried out at 235nm using Camag TLC scanner – 3 with WINCAT 1.3.4 version software. The experimental parameters like band size of spot applied, chamber saturation time, solvent front migration, slit width etc were critically studied and optimum conditions were evolved. The drug was satisfactorily resolved with R_f value 0.41 ± 0.01 . The accuracy and reliability of the proposed

method was ascertained by evaluating various validation parameters like linearity (100-500ng/spot), precision (intra day 0.53 – 0.78, inter day 0.53-1.62), accuracy (98.87 ± 0.2) and specificity according to ICH guide lines.

20. By Stability Indicating RP_ UPLC Method Using UV Detector⁴⁰.

The chromatographic separation is performed on an Agilent Eclipse Plus C18, RRHD 1.8 µm (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 252 nm wavelength using a UV detector. The developed method separates quetiapine from its five impurities/degradation products within a run time of 5 min. Stability indicating capability of the developed method is established by analyzing forced degradation samples in which the spectral purity of quetiapine is ascertained along with the separation of degradation products from analyte peak. The developed RP-UPLC method is validated as per International Conference on Harmonization (ICH) guidelines with respect to system suitability, specificity, precision, accuracy, linearity, robustness and filter compatibility.

21. By High Pressure Liquid Chromatography Mass Spectrometry In Human Plasma⁴¹.

A validated high-pressure liquid chromatography–tandem mass spectrometry (LC–MS/MS) method was developed for the quantitative determination of quetiapine (QUE) in human Na₂EDTA plasma with mass spectrometry (MS) detection. Clozapine (CLO) was employed as an internal standard. Samples were extracted using solid phase extraction (SPE). Oasis HLB cartridges and the concentration of quetiapine was determined by isocratic HPLC–MS/MS. The SRM mode was used for MS/MS detection. The method was validated over a concentration range of 1.0–382.2 ng/mL. Inter- and intra-day precision and accuracy of the proposed method were characterized by relative standard deviation (R.S.D.) and the percentage of deviation, respectively; both were lower than 8%. The developed method was employed in the pharmacokinetic study of quetiapine.

22. By Liquid Chromatographic-Electrospray-Tandem Mass Spectrometric (LC-ESI-MS-MS) In Plasma And Liver⁴².

A liquid chromatographic-electrospray-tandem mass spectrometric (LC-ESI-MS-MS) method combined with a simple liquid-liquid extraction has been developed for the measurement of quetiapine in human plasma and in human liver microsomes (HLM). Clozapine is used as internal standard. Plasma samples or microsomes quenched with methanol (100 μ l) were made basic and extracted with 3 mL *n*-butyl chloride. The reconstituted extracts were analyzed by LC-ESI-MS-MS. Selective reaction monitoring of MH⁺ at *m/z* 384 and 327 resulted in strong fragment ions at *m/z* 253 and 192 for quetiapine and clozapine, respectively. Recovery of quetiapine and clozapine ranged from 62 to 73%. Intra-run accuracy and precision determined at 1.0 (lower limit of quantitation), 2.5, 200, and 400 ng/mL did not exceed 7% deviation from target and the %CV did not exceed 5.5%. The % target \cdot %CV for inter-run accuracy and precision were at least 95% \cdot 7.4% at concentrations of 2.5, 200, and 400 ng/mL. Plasma samples (2.5 and 400 ng/mL) stored at room temperature for 24 h or after 3 cycles of freeze/thaw were all stable (maximum % deviation $<$ 11.0%). Processed extracts (2.5 and 400 ng/mL) stored for 7 days at -20°C or 6 days on the autosampler were all stable (maximum % deviation $<$ 11.5%). The method has been used to study quetiapine utilization during incubation with HLM or with cDNA-expressed human cytochrom P450s (CYP). Quetiapine is extensively metabolized by CYP 3A4 and CYP 2D6 and to a lesser extent by CYP 3A7, CYP 3A5, and CYP 2C19.

23. By Potentiometric Titration⁴³.

A simple titrimetric method for the determination of QTF in bulk drug and in its dosage forms has been developed and validated. The method is based on the potentiometric titration of QTF in glacial acetic acid with acetic perchloric acid using a modified glass-saturated calomel electrode system. The method is applicable over the range of 2.0 – 20.0 mg of QTF. The proposed method was successfully applied to the determination of QTF in its pharmaceutical dosage forms. The results obtained were favorably compared with those obtained using a reference method. The precision results, expressed by intra-day and inter-day relative standard deviation values, were satisfactory (RSD \leq 1.2%). The accuracy was satisfactory as

well (RE \leq 1.33%). Excipients used as additives in pharmaceutical formulations did not interfere in the proposed procedures, as shown by the recovery study via standard addition technique with percentage recoveries in the range 98.25-101.0 %, with a standard deviation of 0.62-1.52%.

24. By Uv Spectrophotometric Method At Different nm Using 0.1N HCl As Solvent⁴⁴.

Two simple, sensitive, selective, economical and reproducible UV spectrophotometric methods are described for the quantitative determination of QTF in bulk drug and in pharmaceutical dosage forms. The methods are based on measurement of absorbance of QTF solution either in 0.1 N HCl at 209 nm (method A) or in methanol at 208 nm (method B). Beer's law is obeyed over the linear range 1.25-12.50 $\mu\text{g mL}^{-1}$ QTF for both the methods with apparent molar absorptivity values of 6.21×10^4 and 5.93×10^4 L mol⁻¹cm⁻¹ for method A and method B, respectively. Sandell sensitivity, limits of quantification (LOQ) and detection (LOD) are also reported. The methods were validated in accordance with the current ICH guidelines. The precision results, expressed by intra-day and inter-day relative standard deviation values, are satisfactory (RSD \leq 2.50%). The accuracy is also satisfactory (RE \leq 2.50%). Excipients used as additives in pharmaceutical formulations did not interfere in the proposed procedures as shown by the recovery study via standard addition technique with percentage recoveries in the range 101.50- 108.25% with the standard deviation of \leq 1.12%.

CONCLUSION

Quetiapine fumarate is an atypical antipsychotic drug commonly used for the treatment of schizophrenia, bipolar disorder. It can be used regularly due to its pharmacokinetic properties and mechanism of action. Since it blocks dopamine, serotonin, adrenergic and histamine receptors, it can be used over a wide range of diseases. From the above literature survey we could know the various analytical techniques developed for quetiapine fumarate. Also new analytical methods can be developed and some of them are under developing process.

REFERENCES

1. <http://en.wikipedia.org/wiki/psychosis>
2. <http://en.wikipedia.org/wiki/Antipsychotic>
3. <http://en.wikipedia.org/wiki/Quetiapine>.

4. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001030>.
5. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a698019.html>
6. <http://www.medicinenet.com/quetiapine/article.html>
7. Ashutosh Kar., Pharmaceutical Drug Analysis, 2nd ed., New Age International Publisher, New Delhi, 2005. pp. 111-115.
8. Chatwal G.R. and Anand S.K. Instrumental method of Chemical Analysis, 5th edition Published by Himalaya publishing house pvt ltd. pp.2.468-2.481
9. Christian. G.D., Analytical Chemistry, 6th ed., John Wiley & Sons (Asia) PTE. LTD, Singapore, 2008, p. 95.
10. Remington. The science and practice of pharmacy, volume I, 21st edition, Lipincott Williams & Wilkins publishers, Newyork, 2007: 621-626.
11. Skoog., Holler., and Nieman. Principles of instrumental analysis, 5th edition, Harcourt college publishers, fortworth, 2004: 725-739.
12. Synder. KL., Krikland .J.J, and Glajch .JL. Practical HPLC Method Development, 2nd Edition, Wiley-Interscience Publication,USA, 1983: 1-10.
13. Sethi PD. HPLC-Quantitative analysis of pharmaceutical formulations, CBS publishers& distributors, New Delhi, 2006: 118-120.
14. Guidance for Industry: Analytical Procedures and Methods Validation: Chemistry, Manufacturing and Controls Documentation; Draft Guidance. Rockville, MD. US FDA. 2000.
15. International Conference on Harmonization (ICH),. Q2 (R1), "Validation of Analytical Procedures: Text and methodology" 2000.
16. International Conference on Harmonization, "Q2A: Text on Validation of Analytical Procedures," Federal Register, 1995; 60(40): 11260-11262.
17. International Conference on Harmonization, "Q2B: Validation of Analytical Procedures: Methodology; Availability," Federal Register 1997; 62(96): 27463-27467.
18. Validation requirements of the U.S Food and Drug administraton, The U.S Pharmacopoeia and International Conference on Hanmonization. J Chromatogr A. 2003; 987: 57-66.
19. Srihari. G. and Chakravarthi. I. E. Simple Spectrophotometric method for determination of Quetiapine fumarate in tablets, Int. J. Chem. Sci. 2011; 9(2): 949-952.
20. Shahe Mahammad. S., Madhusudhana Chetty., Ramana Murthy. K.V.Validated LC-UV method for the estimation of Quetiapine in pharmaceutical dosage forms. Journal of Global Trends in Pharmaceutical Sciences. April-June 2012; 3 (2): 671-676.
21. Basaveswara Rao. M.V., Nagendrakumar. A. V. D. Validated RP - HPLC method for the estimation of Quetiapine in formulation. International Journal of Science Innovations and Discoveries, 2011; 1 (1), 45-52.
22. Sravan kumar. G., Vidyadhari. Ch., Vijay Kumar. B., Shameem sulthana, Sravan kumar. V., Aneela, Somnath De. S. Development and Validation of RP-HPLC method for determination of Quetiapine fumarate from pharmaceutical preparation. International Journal of Biological & Pharmaceutical Research. 2011; 2(1): 27-33.
23. Sudarshan Reddy. P., Panjagala Satyanarayana., Karthik Varma. K.,Naga Raju., Siva Kumar. G., Shanmugasundaram. P. Novel Reverse Phase HPLC method development and validation of Quetiapine fumerate in bulk and tablet dosage form, Int. J. Pharm & Ind. Res. 2011; 01 (02).
24. Sudarshan Reddy. P., Ashok Reddy. S., Karthik varma. K., Narasimha Rao. D., Panjagala Satyanarayana., NagaRaju. T. M. Method development and validation of Quetiapine fumerate bulk and in tablet dosage form by using Uv-Spectrophotometry, Int. J. Pharm & Ind. Res,2011; 01 (03).
25. Venkata Kiran. B., Battula Sreenivasa Rao., and Som Shankar Dubey. Validation of Quetiapine Fumarate in Pharmaceutical Dosage by Reverse Phase HPLC with Internal Standard Method.
26. European Medicines Agency (EMA), Committee for Medicinal Prouducts for Human Use (CHMP). Guidelines on the limits of genotixc impurities, London,

- February 2008. Doc. Ref.: EMEA/CMDh/98694/2008.
27. International Conference on Harmonization (ICH), Q3A (R2), "Impurities in New Drug substances" 2006.
 28. Mudigonda Srinivas., Suresh kumar.R., Krishna murthy. M., Shakil Sai., and K.Mukkanti. A novel, sensitive and rapid method developed for simultaneous quantification of four potential genotoxic impurities in Quetiapine fumarate by UPLC *Journal of Pharmacy Research*, 2012; 5(4): 2042-2044.
 29. Kanakapura Basavaiah Vinay., Hosakere Oddarevanna Revanasiddappa., Pavagada Jagannathamurthy Ramesh., and Nagaraju Rajendraprasad. Titrimetric and Sensitive Spectrophotometric Methods for the Assay of Quetiapine fumarate in Pharmaceutical Formulations, *Chemical Industry & Chemical Engineering Quarterly*, (2011); 17 (1):99-106.
 30. Sahu Deepak., Rana .A.C. Development of Analytical Method for Quetiapine fumarate by UV Spectrophotometry, *international journal of research in Ayurveda & Pharmacy*, 2011; 2(2): 588-591.
 31. Ramu Sathiya., Kaliaperumal Krishnaraj., Selvadurai Muralidharan., and Nithyanantham Muruganatham. A Simple and Validated HPTLC Method of Evaluation for Quetiapine fumarate in Oral Solid Dosage Form, *Eurasian J Anal Chem*, 2011; 5(3): 246-253.
 32. Vinay. K.B., Revenasiddappa. H.D. Spectrophotometric Determination of Quetiapine Fumarate In Pharmaceuticals And Human Urine By Two Charge-Transfer Complexation Reactions, *Chemical Industry & Chemical Engineering Quarterly*, 2012; 18 (2): 263-272.
 33. Vinay. K.B., Revenasiddappa. H.D. Spectrophotometric Determination Of Quetiapine Fumarate through Ion-pair Complexation Reaction with Tropaeolin ooo, *Indian Journal Chemical Technology*, 2012; 19 (2): 205-212.
 34. Prasanth. V. G., Susamma Cicy Eapen., Sheeja Velayudhan Kutty., and Jyothi T S. Development and validation of Quetiapine fumarate in pure and pharmaceutical formulation by UV-Spectrophotometric method, *Der Pharmacia Sinica*, 2011; 2(6):52-58.
 35. Borkar Bhaskar Hiranman, Vidhate Sandip, Lohiya R. T., Umekar M. J. Spectrophotometric Determination Of An Atypical Antipsychotic Compound In Pharmaceutical Formulation, *Int.J. Chemtech Res.*2009;1(4).
 36. Bagade S.B., Narkhede S.P., Nikam D. S., Sachde C. K. Development and validation of UV-Spectrophotometric method for determination of Quetiapine fumarate in two different dose tablets, *Int.J. ChemTech Res.*2009;1(4).
 37. Nahed El-Enany, Amina El-Brashy, Fathalla Belal, Nihal El-Bahay. Polarographic Analysis of Quetiapine in Pharmaceuticals. *Portugaliae Electrochimica Acta* 2009; 27(2): 113-125
 38. Radha Krishna. S., Rao. B.M. And Someswara Rao. N. A Validated Stability Indicating HPLC Method For The Determination Of Related Substances In Quetiapine Fumarate, *Rasayan J. Chem*, 2008; 1(3): 466-474.
 39. Dhandapani. B., Somasundaram. A., Raseed. S. H., Raja. M., and Dhanabal.K. Development and validation of HPTLC method for estimation of Quetiapine in bulk drug and in tablet dosage form. *Int. J. Pharm. Tech. Res.*2009; 1: 139-141.
 40. Rakshit Kanubhai TRIVEDI., Mukesh C. PATEL. Development and Validation of a Stability Indicating RP-UPLC Method for Determination of Quetiapine in Pharmaceutical Dosage Form, *Sci Pharm.*2009; 79: 97-111.
 41. Barrett. B., Hol'capek. M., Huclov'a., Bo'rek-Dohalsk'y. V., Fejt. P., N'emec. B., Jel'inek. I. Validated HPLC-MS/MS method for determination of quetiapine in human plasma, *Journal of Pharmaceutical and Biomedical Analysis*, (2007); 44 :498-505.
 42. Shen-Nan tin., Yan Chang., David E. Moody., and Rodger t. Foltz. A Liquid Chromatographic-Electrospray-Tandem Mass Spectrometric Method for Quantitation of Quetiapine in Human Plasma and Liver Microsomes: Application to a Study of In Vitro Metabolism, *Journal of Analytical Toxicology*, September 2004; Vol. 28.

43. Vinay. K.B., Revanasiddappa. H.D., and Rajendra prasad. N. Potentiometric Determination of Quetiapine Fumarate in Pharmaceutical Formulations, Port. Electrochim. Acta, 2010; 28 :299-308.

44. Basavaiah. K., Rajendraprasad. N., Ramesh. P.J., and Vinay. K.B (2010). Sensitive ultraviolet spectrophotometric determination of quetiapine fumarate in pharmaceuticals, Thai J. Pharm. Sci. 34 146-154.