Psychosis: An appropriate treatment with allusion to Quetiapine Fumarate with its analytical techniques

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Abstract
Psychosis is a mental illness of severe type in which the patient loses link up with reality. Quetiapine is dibenzo-thiazepine derivative and considered as an atypical antipsychotic for the treatment of schizophrenia, acute mania, and bipolar depression. This review article signifies summarized results of available analytical methods in the literature for the determination of Quetiapine Fumarate in biological and pharmaceutical formulations. Various techniques such as spectrophotometry, HPLC, RP-HPLC, RP-HPLC-PDA, HPTLC, RP-UPLC, UPLC-ESI-MS/MS, Polarographic analysis and Potentiometric determination were reported.

Keywords: Psychosis, analytical methods, Quetiapine Fumarate, antipsychotic, polarography, potentiometric

1. Introduction
Psychosis [1-3] is a mental illness of severe type in which the patient loses link up with reality. In normal terminology, Psychosis means unusual condition of the mind. A person with this problem changes his way of thinking, believing or recognizing and behaving. The patient may also become shabby and may stop communicating or talk only "rubbish." Psychotic person suffers from difficulty in concentrating, depressed mood, anxiety, suspiciousness, isolation from family and friends, delusions, hallucinations, disorganized speech, depression, suicidal thoughts or action.

Causes of psychosis are unknown and the exact cause isn’t clear. There are certain illnesses that cause psychosis (Parkinson’s disease, Huntington’s disease, brain tumors or cysts). There are also triggers like drug use, lack of sleep, and other environmental factors in certain situations can lead to specific types of psychosis development.

Antipsychotic [4-8] are agents used to treat Psychosis and other mental illness. Antipsychotics, also referred as neuroleptic medicine, are a tranquilizing psychiatric medication mainly used to manage psychosis, especially in schizophrenia and bipolar disorder in short term. The long-term use of antipsychotics produces adverse effects such as involuntary movement disorders, excessive development of breasts in males, erectile dysfunctioning in males, weight gain and metabolic syndrome.

Quetiapine (QTP) [7, 9-16] is considered as an atypical antipsychotic and has been approved by the FDA (Food and Drug Administration) for use in the treatment of schizophrenia [8, 17-22], acute mania [8, 23, 24], and bipolar depression [8, 25]. 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 dibenzo-thiazepine derivative [15, 26-28] of which the mechanism of action is unknown. It produces antagonistic effect on serotonin 5-HT1A and 5-HT2A, dopamine D1 and D2, histamine H1, and adrenergic α1 and α2 receptors.

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. Studies were conducted on quetiapine’s efficacy in treating generalized anxiety disorder and major depression in 2007 and 2008. In 2009, the Psychopharmacologic Drugs Advisory Committee of the USFDA held a 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 [16, 29-31].

2. Drug profile [32-37].
2.1 Chemical name: 2-(2-(4-dibenzo [b,f] [1, 4] thiazepine- 11-yl- 1-piperaziny1ethoxy)ethanol
Chemical structure: Fig.1
Fig 1: Chemical structure of quetiapine fumarate

Molecular formula: C_{32}H_{32}N_{2}O_{8}S
Molecular mass: 583.5099 g/mol
Route of administration: oral
Melting Point: 174-176 °C
Boiling Point: 556.5 °C at 760 mmHg
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.
Bioavailability: 9%
Half life: 6 hours (for parent compound) 12 hours (for active metabolites)
Metabolism: Hepatic
Excretion: Renal

2.2 Mechanism of action [8, 37-40].
Quetiapine is a short acting and has an antagonistic effect on serotonin 5-HT1A and 5-HT2A, dopamine D1 and D2, histamine H1, and adrenergic α1 and α2 receptors in the brain. It has a much higher level of occupancy of 5-HT2A receptors compared to D2 receptors, a factor generally considered to be predictive of an atypical antipsychotic. Quetiapine has negligible affinity for cholinergic muscarinic receptors, thereby contributing to its low risk for anticholinergic side effects. There is also evidence from animal models of low potential for extrapyramidal side effects.

2.3 Formulation available [35, 41].
Tablets: Quetipin (sun pharma) 25, 50, 100, 200 mg Seroquin (cipla) 50, 100, 200 mg Quatan (intas) 50 mg Seroquel (AstraZeneca pharms) 25, 50, 100, 200, 300, and 400 mg SeroquelXR (sustained release) (AstraZeneca pharms) 50 mg, 150 mg, 200 mg, 300 mg, 400 mg

2.4 Drug interactions [33-37, 41].
Increased risk of drowsiness and postural hypotension when used with alcohol.
CYP3A4 (Cytochrome P450) inducers e.g. phenytoin and carbamazepine may increase clearance of quetiapine while CYP3A4 inhibitors e.g. ketoconazole and erythromycin may increase its plasma levels.
Increases the effect of antihypertensive.
Antagonizes levodopa and dopamine agonists.
QTP decreases oral clearance of Lorazepam.

2.5 Adverse reactions [37, 40-41].
CNS: dizziness, sedation, cognitive impairment, extrapyramidal symptoms, tardive dyskinesia, neuroleptic, malignant syndrome, seizures, suicide.
CV: tachycardia, palpitations, peripheral edema, orthostatic hypotension, hypertension, QT-interval prolongation.
EENT: cataracts, ear pain, rhinitis, pharyngitis.
GI: constipation, dyspepsia, dry mouth, anorexia.
Hematologic: leukopenia.
Metabolic: hypothyroidism.
Respiratory: cough, dyspnea.
Skin: rash, sweating.
Other: weight gain, flulike symptoms, and acute withdrawal symptoms with abrupt cessation.
QTP may make dizzy or drowsy or blur vision. Alcohol or marijuana can make more dizzy or drowsy. Person should not drive, use machinery, or anything that needs alertness and clear vision unless they can do it properly. To overcome this, they should avoid alcoholic beverages.

3. Analytical Methodology
3.1 Ultraviolet (UV) spectrophotometric method
In the literature survey, these methods were reported for the estimation of Quetiapine Fumarate using spectrophotometric method in bulk drug as well as in pharmaceutical dosage forms.

3.1.1 V G Prasanth et al. [42] developed a UV Spectrophotometric method for the quantitative determination of Quetiapine Fumarate in bulk drug and in pharmaceutical dosage forms. The QTP shows maximum at 207 nm in ethanol. Beer’s range for calibration curve was 1-5 μg/mL for the method with apparent molar absorptivity value of 1434.41281 L mol⁻¹ cm⁻¹. The methods were validated according to current ICH (International Conference on Harmonization) guidelines. The precision results, expressed by intra-day and inter-day relative standard deviation values, were within the limit i.e. % RSD 100.22% and 99.83 % respectively. The percentage recoveries are in the range 99.34- 100.11% with the standard deviation of 0.39. Method have excellent linearity and range (r²=0.998).

3.1.2 S.S. Chhajed. et al. [43] developed two UV-spectrophotometric methods and validated for the estimation of Quetiapine Fumarate in bulk drug and dosage formulation. Quetiapine shows absorption at 239 nm in 0.1N hydrochloric acid (HCL) (pH 1.2) and at 250 nm in ethanol. Beer’s law was in the concentration range of 1-12 9gmL⁻¹ (r² = 0.9999) in hydrochloric acid and 1-14 9gmL⁻¹ (r² = 0.9998) in the ethanol. The molar absorptivity and methods sensitivity were found to be 4.63×104 L mol⁻¹ cm⁻¹ and 9.5 ng cm⁻²/0.001A in hydrochloric acid; and 4.08 ×104L mol⁻¹ cm⁻¹ and 10.8 mg cm⁻²/0.001A in ethanol, respectively showing the high sensitivity of the proposed methods. These methods were tested and validated for as per ICH guidelines. The detection and quantitation limits were found to be 0.0402, 0.1217 9gmL⁻¹ with the standard deviation of 0.39. Method have excellent linearity and range (r²=0.998).

3.1.3 R. Valarmathi. et al. [44] developed UV Spectrophotometric method for the estimation of QTP in two different marketed tablet dosage form (BRAND A & BRAND B) 25 mg was developed. The absorbance was obtained at wavelength of 290 nm by using Methanol: water in the ratio 50:50/v/v as solvent. The method obeys Beers law over a concentration range 15.99 - 24.09 μg/mL. Results of proposed
method for precision and repeatability of both the brands i.e. 100.41% and 99.77% respectively. Accuracy values were found to be 100% and 99.83 % respectively which were within limit. The proposed method shows excellent linearity and range (r2 =0.9997).

3.1.4 Chennupati Venkata Suresh, et al. [45] developed three UV Spectrophotometric methods for the determination of QTP in bulk and pharmaceutical dosage forms. Method A was developed by formation of Ion-association complex of the drug with solochrome Black T (Imax: 520 nm). Method B was developed by oxidative coupling of the drug with 3-methyl-2-benzothiazolinone hydrazone (Imax: 620 nm).

Method C was developed by oxidation followed by complex formation with 1,10-phenanthroline (PTL) in the presence of ferric chloride to form a colored chromogen (Imax: 510 nm). These methods were evaluated and found to be precise and accurate.

3.1.5 Bagade S.B. et al. [46] developed UV spectrophotometric method Second order derivative ultraviolet Spectrophotometric methods were developed for determination of Quetiapine fumarate in pharmaceutical formulation. Quetiapine Fumarate was determined by measuring the 2D-values at 254.76nm with 0.1 N HCl as solvent. Calibration curves shows linearity within a concentration range from 10 to 30μg/ml. R.S.D was found to be 0.20% (Quetiapin® tablet; 200 mg) and 0.16% (Quetiapin® tablet; 300 mg) respectively. The percentage recoveries were approx. 100% for given methods. The method was validated as per ICH. The excipients did not interfere in the analysis. The results showed that method can be used for determination of QTP in pharmaceutical tablet with precision, accuracy and specificity.

3.1.6 Sahu Deepak, et al. [47] developed UV Spectrophotometric method for the detection of Quetiapine Fumarate in pure and in pharmaceutical formulations. Quetiapine Fumarate exhibited absorption at 242nm and obeyed beers law in the range of 5 to 25μg/ml. The Limit of determination (LOD) was found to be 3.5 × 10⁻² and the Limit of quantification (LOQ) was found 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 was stable up to 24 hrs. The assay was found within a limit.

3.1.7 K. Basavaiah, et al. [48] developed two UV spectrophotometric methods for the quantitative determination of QTP in bulk drug and in pharmaceutical dosage forms. The drug shows maximum absorbance at 209 nm in 0.1 N HCl (method A) and at 208 nm in methanol (method B). Beer’s law is obeyed over the linear range 1.25-12.50 μg ml⁻¹ QTP for both the methods with apparent molar absorptivity values of 6.21 × 10⁴ and 5.93 × 10⁴ L mol⁻¹ cm⁻¹ for method A and method B, respectively. Sandell sensitivity, LOQ and LOD are also reported. The methods were validated as per ICH guidelines. The precision results, expressed by intra-day and inter-day relative standard deviation values, are satisfactory (RSD ≤ 2.50%). The accuracy is also satisfactory (RE ≤ 2.50%). Specificity 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 ≤ 1.12%.

3.1.8 Borkar Bhaskar Hiraman, et al. [49] developed two different spectrophotometric analytical methods for the quality control of QTP 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. 290.0 nm and that of for other 295.0 nm to 281.0 nm respectively. The absorbance data was obtained by the measurements at selected wavelengths by using Milli-Q water as solvent. The method obeys Beer’s law over a concentration range 12-60 mg/ml of Quetiapine for both spectrophotometric methods at selected wavelengths. Developed 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., were found satisfactory. Both spectroscopic methods have excellent linearity and range (r² =0.999). Ruggedness of both methods checks in terms of intraday and interday studies shows % RSD 0.55 %, 0.15% and 0.33%, 0.46% respectively. The procedures do not require any separation step. These methods were applied to solid dosage form containing same drug and was found to be utter, swift and efficient for their estimation from pharmaceuticals. The Summary of reported spectrophotometric methods is shown in Table 1.

### Table 1: Spectrophotometric method for the analysis of quetiapine fumarate

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Method</th>
<th>Amax</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTP</td>
<td>UV Spectrophotometry</td>
<td>207 nm</td>
<td>Ethanol</td>
</tr>
<tr>
<td>QTP</td>
<td>Method A</td>
<td>239 nm</td>
<td>0.1N HCl (pH 1.2)</td>
</tr>
<tr>
<td>QTP</td>
<td>Method B</td>
<td>250 nm</td>
<td>Ethanol</td>
</tr>
<tr>
<td>QTP</td>
<td>UV Spectrophotometry</td>
<td>290 nm</td>
<td>Methanol: water (50:50v/v)</td>
</tr>
<tr>
<td>QTP</td>
<td>Ion-association complex</td>
<td>520 nm</td>
<td>Solochrome Black T</td>
</tr>
<tr>
<td>QTP</td>
<td>Oxidative coupling</td>
<td>620 nm</td>
<td>3-methyl-2-benzothiazolinone hydrazone</td>
</tr>
<tr>
<td>QTP</td>
<td>oxidation by complex formation</td>
<td>510 nm</td>
<td>1,10-phenanthroline (PTL)</td>
</tr>
<tr>
<td>QTP</td>
<td>Second order derivative</td>
<td>254.76nm</td>
<td>0.1N HCl</td>
</tr>
<tr>
<td>QTP</td>
<td>UV Spectrophotometry</td>
<td>242nm</td>
<td>Phosphate Buffer pH (6.8)</td>
</tr>
<tr>
<td>QTP</td>
<td>Method A</td>
<td>209nm</td>
<td>0.1N HCl</td>
</tr>
<tr>
<td>QTP</td>
<td>Method B</td>
<td>208nm</td>
<td>Methanol</td>
</tr>
<tr>
<td>QTP</td>
<td>Zero order derivative spectroscopy</td>
<td>290.0 nm</td>
<td>Milli-Q water</td>
</tr>
</tbody>
</table>

QTP*: Quetiapine Fumarate, UV*: Ultraviolet, HCL*: Hydrochloric acid
3.2 High performance liquid chromatography (HPLC)

3.2.1 In Biological specimens

3.2.1.1 Rasha M. Youssef, et al. Studies [50] Incidence of suicidal attempts presents an explanation for the high prevalence of quetiapine (QTP) in forensic cases. Thus, the interpretation of its concentrations in biological specimens is needed, but in forensic toxicology, potential postmortem such as instability of the target drugs should be taken in consideration. High performance liquid chromatography (HPLC) method has been developed for determination of QTI. This method was based on reverse phase (RP)-HPLC separation of QTP on a C-18 column (150 mm × 4.6 mm, 5 μm) with elution system of acetonitrile–methanol–0.025 M phosphate buffer (pH 2.5), containing 1 mL TEA in each 250 mL, in a ratio of 40:30:30%, v/v, at the flow rate of 1.2 mL/min using mirtazapine as internal standard (IS). The proposed method was applied to the determination of QTP in plasma in latency of coadministered drugs. The application of the proposed method was extended for long-term stability study of two different concentration levels of QTP in the whole blood.

3.2.1.2 R. Mandrioli, et al. [51] developed High-performance liquid chromatographic (HPLC) method for the analysis, Quetiapine in plasma. The analysis was carried out on a C8 (150 X/4.6 mm i.d., 5nm) reversed-phase column, using a mixture of acetonitrile, methanol and pH 1.9 phosphate buffer as the mobile phase; triprolidine was used as the internal standard. Cautious pretreatment of the biological samples was implemented by means of solid-phase extraction (SPE). A good linearity was found in the 4-400 ng/ml quetiapine plasma concentration range. The application to some plasma samples of patients treated with Seroquel tablets gave satisfactory results. The accuracy and precision was found to be 92%, RSD/3.3%.

Methods for determination of QTP in biological samples are shown in Table 2.

![Table 2: Analytical HPLC methods for determination of QTP in biological samples.](image)

**QTP**: Quetiapine Fumarate, UV*: Ultraviolet

3.2.2 In Pharmaceutical dosage forms

3.2.2.1 Kiran B. Venkata, et al. [52] developed a rapid, specific, and accurate isocratic HPLC method was developed and for the estimation of quetiapine fumarate in pharmaceutical dosage forms. The method involved an isocratic elution of quetiapine fumarate in Grace C18 column using mobile-phase composition of 0.1% ortho phosphoric acid with triethyl amine as modifier buffer and acetonitrile 50:50 (v/v). The wavelength detected at 294 nm. The method showed good linearity in the range of 2.0–50.2 × 10−3 g/Lt. 5 min was the run time. The developed method was applied to directly and easily analyze of the pharmaceutical tablet preparations. The percentage recoveries were approx. 100% for given methods. The method was validated and proved to be rugged. The excipients did not interfere in the analysis. The results showed that this method can be used for determination of quetiapine fumarate in pharmaceutical tablet with precision, accuracy, and specificity.

3.2.2.2 Sudarshan Reddy P. et al. [53] developed a precise and feasible high-performance liquid chromatographic (HPLC) method for the analysis of the novel antipsychotic drug quetiapine in tablet dosage. The analysis was performed 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 (ACN), methanol (50:40:10) as the mobile phase with a low pressure gradient mode with flow rate at 0.8ml/min. The injection volume was 20μl. The retention time of the drug was 4.69 min. The method produced linear responses in the concentration range of 1 to 5μg/ml of QTP. The LOD and LOQ values for HPLC method were found to be 0.0167 and 0.0506 μg/ml respectively.

3.2.2.3 Lakshmi Sivasubramanian, et al. [54] developed HPLC method for estimation of Quetiapine fumarate in bulk and tablet dosage form. The separation was achieved on a C18 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. 5.08 min was found to be the retention time of QTP. Linearity of the method was found to be in the concentration range of 10-80 μg/ml with correlation coefficient of 0.999. The method was validated. LOD and limit of LOQ were found to be 18.815 and 57.016 μg/ml respectively.

3.2.2.4 Sharath Kumar Pallikonda. et al. [55] developed a RP-HPLC method for the determination of Quetiapine fumarate in bulk and pharmaceutical formulation (Tablets). The RP-HPLC analysis was performed isocratically on XTERRA C18 (4.6X150mm), analytical column using a mobile phase consisting of ortho phosphorous buffer and acetonitrile in the Ratio of 60:40v/v, with a flow rate of 0.6ml/min. The analyte was monitored at 290nm with UV detector. The developed method Quetiapine Fumarate elutes at a run time of 10 min. It obeys Beer’s law over a concentration range from 40 to 80μg/mL. The method was validated according to ICH guidelines.

3.2.2.5 Priyanka Teeppoju. et al. [56] Developed a RP-HPLC method by trial and error and validated for the estimation of Quetiapine Fumarate in tablet dosage form. Chromatography was carried out by using pre-packed Luna C18, 5μ (250 x 4.6) mm phenomex column as a stationary phase with the mobile phase containing a mixture of 0.1% Formic acid (pH 4 Adjusting with Triethylamine) and Acetonitrile in the ratio of 50:50v/v. The flow rate is 1ml/min. The effluent was monitored at 290nm and the retention time of drug is 3.5 mins. The calibration curve was plotted with a range of 1-6μg/ml for Quetiapine fumarate and the correlation was found to be 0.999. The assay was validated in terms of linearity, precision, accuracy, and specificity, limit of quantification and limit of detection. The accuracy range was found between
3.2.2.6 K.K. Patel. et al. [57] RPHPLC method for the assay of Quetiapine in tablet formulation. The separation was carried out on a hypersil BDS C18 (25cm x 0.46cm) 5 μ particle size with mobile phase ACN, Water (85:15%v/v) at a flow rate of 1.0 ml/min. The detection is carried out at 226.4nm. The retention time of the drug was 4.48 min. The Linearity was validated in terms of linearity, correlation range was 5 (100.28 %) recoveries of the drug. The quantification accuracy, precision, LOD & LOQ of the sample solution. Quetiapine stock solutions were subjected to acid, base, oxidation, Photo and thermal degradation.

3.2.2.7 Rajendra Chandra. et al. [58] developed reversed-phase high performance liquid chromatography (RP-HPLC) for the determination of Quetiapine Fumarate from marketed bulk tablets. The active ingredient of Quetiapine Fumarate separation achieved with C18 column using the methanol: water mobile phase in the ratio of 30:70 (v/v). The active ingredient of the drug content shows maximum absorption at 359 nm with UV detector. The retention time for Quetiapine Fumarate was 5.27 min. A good linearity relation (R²=0.999) was obtained between drug concentration and average peak areas. The LOD and LOQ were found to be 0.02 and 0.06 μg/mL, respectively. The accuracy of the method validation was determined with the inter-day (100.28 %) and intra-day (100.48 %) recoveries of the drug. The quantification correlation range was 5-50 ppm. The new method was validated according to ICH guidelines.

3.2.2.8 Pant, Mayank. et al. [59] developed RP-HPLC method for estimation of Quetiapine Fumarate from marketed bulk tablets. The Linearity was validated according to ICH guidelines, R²=0.9956. The method was validated for accuracy, precision, LOD & LOQ of the sample solution. Quetiapine stock solutions were subjected to acid, base, oxidation, Photo and thermal degradation.

3.2.2.9 Baldi Ashish et al. [60] developed and validated reverse phase high-performance liquid chromatographic (RP-HPLC) method for estimation of quetiapine fumarate. Methanol: Water: Acetonitrile (50: 40:10) was used as a mobile phase at a flow rate of 1 ml/min and pH value of 7.0, adjusted with ortho phosphosphoric acid. The detection was carried out at a wavelength of 251 nm. The developed method was found to be in accordance with ICH guidelines with respect to accuracy, precision, reproducibility, linearity and specificity.

3.2.2.10 Deepa Sharma et al. [61] Developed HPLC method for simultaneous determination of risperidone, olanzapine and quetiapine. Drugs samples were subjected acidic, alkaline and oxidative hydrolysis (stress conditions). Luna C18 (250x4.6, 56m) was used for Chromatographic separation of drugs with 50:50 (v:v) mixture of 20mM ammonium acetate and acetonitrile as mobile phase. 1.0 mL /min was set as flow rate and the analysis was monitored at 235 nm by UV detector. 

3.3 Reverse phase high performance liquid chromatography photo diode array (RP-HPLC-PDA) Sushmitha Korrapolu.et. al. 52 developed and validated a stability indicating reverse-phase HPLC method for the estimation of QTP in bulk and pharmaceutical dosage forms. Inertsl ODS (250 x 4.6 mm, 5m) column was used for RP-HPLC method, at ambient temperature, mobile phase consisted of 0.02%/v v/formic acid and methanol (90:10), effluent flow monitored at 1mL/min and UV detection at 220nm. The retention time of QF was 13.4min. The drug was for estimation of Quetiapine Fumarate from tablet dosage form. Assay method was developed using Zorbax ODS C-18, 150 mm x 4.6 Φ4m, 5.0 mm as stationary phase. Buffer: ACN (65:35) was used as mobile phase. % Assay was found to be 98.01-98.06. The method was validated in terms of linearity, precision, accuracy, specificity and robustness. Method was validated as per ICH guidelines.
sample was treated to thermal, photolytic, hydrolytic (acidic and basic) and oxidative stress conditions and stressed samples were analyzed by the developed method. The method was validated as per ICH guidelines, a good linearity was observed in the concentration range of 10- 50µg/mL with a correlation coefficient (R) of >0.999 and method showed good repeatability and reproducibility with percent relative standard deviation less than 2%. The percent assay and recovery values were found to be in the range of 98.56-99.06% and 99.60-100.85% respectively.

3.4 High Performance thin layer chromatography (HPTLC)
B. Dhandapani et al. developed HPTLC method for estimation of QTP as bulk and in tablet dosage form. Precoated silica gel 60 F254 aluminium plates was used for the chromatographic separation 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 conditions (band size of spot applied, chamber saturation time, solvent front migration, slit width etc.) were critically studied and optimum conditions were evolved. The drug resolved with Rf value 0.41 ± 0.01. The proposed method was validated by 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.

3.5 Reverse phase ultra-performance liquid chromatography (RP-UPLC)
Nagaraju Rajendraprasad. et al. developed an isocratic and reversed phase ultra-performance liquid chromatographic (RP-UPLC) for estimation of QTP in bulk and in its dosage form. 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) 30:70 (v/v) used as a mobile phase with AQUITY UPLC HSS T3 (2.1 x 50 mm, 1.8 µm) column. The UV detected the eluted compound at 252 nm. 1.0 ml/min was set as the flow rate of the mobile phase. The injection volume was set at 5.0 µL. A linear calibration curve was obtained for the concentration range 1.0-15.0 µg/mL QTP with regression coefficient (r) value of 0.9999. The limit of detection and quantification were found 0.04 and 0.1 µg ml−1, respectively, and which is at signal to noise ratio of 3 and 10.

3.6 Ultra-performance liquid chromatography–tandem mass spectrometry (UPLC–ESI-MS/MS)
Kun- YanLi. et al. developed the ultra-performance liquid chromatography–electrospray tandem mass spectrometry (UPLC–ESI-MS/MS) method for determination of quetiapine, perospirone, aripiprazole and quetiapine sulfoxide in in vitro samples in less than 3 min. The UPLC separation was carried out using an Acquity UPLC™ BEH C18 column (100 mm × 2.1 mm i.d. (internal diameter), 1.7 µm particle size) that provided high efficiency and resolution in combination with high linear velocities. The UPLC system was coupled to a Waters Micromass Quattro Premier XE tandem quadrupole mass spectrometer. This system permits high-speed data acquisition without peak intensity degradation, and produces sharp and narrow chromatographic peaks (about 2.5 s) of compounds. The determination was executed in multiple reactions monitoring (MRM) mode. The quantification parameters of the developed method were established, obtaining instrumental LODs lower than 0.005 µg/l and a repeatability at a low concentration level lower than 10% CV (n = 10). The method was successfully applied to the analysis of atypical antipsychotics and some metabolites in in vitro samples.

3.7 Polarographic Analysis of Quetiapine in Pharmaceuticals
Nahed El-Enany. et al. studied the voltammetric behaviour of quetiapine (QTP) using direct current (DC), differential pulse (DPP) and alternating current (AC) polarography. The drug exhibits 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 linear over the range of 8 – 44 μg/mL and 4 – 44 μg/mL using DC and DPP modes, respectively. LOD was found to be 0.06 μg/mL and 0.04 μg/mL using the DC, and DPP modes, respectively. 1.36 ± 0.04 (n = 10) was the diffusion-current constant (Ia).

3.8 Potentiometric Determination
K.B. Vinay. et al. developed a simple, precise, accurate and cost-effective titrimetric method for the determination of QTP in bulk drug and in its dosage forms has been developed and validated. The method is based on the potentiometric titration of QTP in glacial acetic acid with acetic per chloric acid using a modified glass-saturated calomel electrode system. The method is applicable over the range of 2– 20mg of QTP. The proposed method was successfully applied to the determination of QTP 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 ≤ 1.2%). The accuracy was found to be (RE ≤ 1.33%). Excipients used in pharmaceutical formulations did not interfere in the anticipated procedures, as shown by the recovery study with percentage recoveries in the range 98.25-101.0 %, with a standard deviation of ≤ 0.62-1.52%.

4. Conclusion
A broad range of analytical techniques is available for the analysis of quetiapine fumarate in biological samples and pharmaceutical formulations. The study of the reported data revealed that the UV spectrophotometry and chromatographic techniques (HPLC, RPHPLC) is valid because these methods provides accurate, precise and low cost compared to more advanced detection techniques.

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