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A Review on Analytical Methods for Estimation of Quetiapine Fumarate, an Antipsychotic Drug.

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ABSTRACT

Quetiapine fumarate is a new generation atypical antipsychotic drug indicated for the treatment of schizophrenia and related psychoses. Various analytical methods used for the estimation of quetiapine has been reviewed in this paper. These include Ultraviolet spectrometry, High performance thin layer chromatography, High performance liquid chromatography, Potentiometry, Polarography, Ion titrimetry and Voltametry to determine the amount of quetiapine fumarate in bulk drugs, pharmaceutical formulations and biological fluids. Stability indicating and impurity profiling methods for quetiapine are also described. These analytical methods can be used for qualitative and quantitative estimation of quetiapine and / or its related impurities or degradants in bulk, formulation and biological fluids.

Keywords: Quetiapine, analytical methods, estimation, formulation, biological fluids.

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INTRODUCTION

Quetiapine (QTP) fumarate is a dibenzothiazepine atypical new generation antipsychotic drug, structurally similar to clozapine and olanzapine, chemically known as 2-[2-(4-dibenzo [b,f][1,4]thiazepin-11-yl)piperazin-1-yl]ethoxy)ethanol] fumarate. QTP is indicated for the treatment of schizophrenia, acute mania and acute bipolar depression [1].

QTP is a dopamine D_2 and serotonergic $5HT_2$ antagonist [2]. By blocking dopamine and serotonin receptors in brain, QTP reduces both, the positive symptoms of schizophrenia (like hallucinations and delusions) at dose 150-750 mg/day and the negative symptoms of schizophrenia (like improper speech, emotional withdrawal, apathy) at dose equal or higher than 300mg/day [3, 4].

QTP is well and rapidly absorbed following oral administration. The mean maximum plasma concentration of QTP after 200mg administration was reported to be 811.3µg/L reached at 1.1 hr following Seroquel and 886.6µg/L at 1.08 hr following Quantia 200®[5]. QTP is widely distributed throughout the body with apparent volume of distribution 10±4L/kg. It is 83%bound to plasma protein at therapeutic concentrations[6].

It is extensively metabolised in the liver [7] by the cytochrome P450 (CYP450) isoenzyme 3A4 and the major metabolites formed are the sulfoxide and carboxylic acid metabolites which are excreted in urine (73%) and faeces (20%) [8]. At least 20 metabolites have been detected but only 7-hydroxy quetiapine and 7-hydroxy-N-dealkyl-quetiapine are active metabolites[9]. Elimination is mainly through hepatic metabolism [6]. Less than 1% of orally administered dose is excreted unchanged in urine and faeces. Only small quantities are excreted in the breast milk [10].

The tolerability of QTP is higher than the classical neuroleptics- it causes an incidence of extrapyramidal symptoms much lower than that of haloperidol [11] and does not induce reproductive / hormonal side effects [12]. It also does not cause significant changes in haematological parameters [13] such as agranulocytosis which is the most severe side effect of clozapine therapy[14].

The main side effects of QTP even with overdosing are hypotension, tachycardia and somnolence [15].QTP's high degree of safety leads to better compliance and higher efficacy of therapy in patients [16]. Recent studies suggest that QTP can be beneficial for the treatment of obsessive –compulsive disorders when co-administered with selective serotonin reuptake inhibitors antidepressants [17].

ANALYTICAL METHODS FOR QUETIAPINE:

Many different analytical methods have been reported for the estimation of QTP fumarate in bulk and dosage form as well as in biological fluids.

FOR ESTIMATION IN BULK DRUG AND PHARMACEUTICAL FORMULATION

Spectrometric methods:

Reddy SP et al.[18] developed and validated UV spectrophotometric method for determination of QTP fumarate in pharmaceutical formulation (tablets) by measuring the absorption at 254.76 nm with water as background solvent. The method was found to be linear in the concentration range of 10 to 50 µg/ ml with percent mean recovery of 99.2. The proposed method was found to be useful for routine analysis of pharmaceutical formulation.

V G Prasanth et al.[19] developed and validated a simple, sensitive, selective and reproducible UV spectrophotometric method for the quantitative determination of QTP fumarate in bulk drug and in pharmaceutical dosage forms (tablets). The method was based on measurement of absorbance of QTF solution in ethanol at 207nm. The method obeyed Beer's law showing linearity in the concentration range 1-5µg/ml of QTP with apparent molar absorptivity value of 1434.41281 L $mol^{-1}cm^{-1}$ with percent recoveries of 99.34-100.11%. the proposed UV spectrophotometric method was said to be applicable for the quality control and routine analysis and may also be proposed for determination from biological fluids or other solid dosage form containing same drugs .

Kanakpura B et al.[20] developed and validated two simple, sensitive, selective, economical and reproducible UV spectrophotometric methods for quantitative determination of QTP fumarate in bulk drug and in dosage form (tablets). The methods were based on the measurement of QTP solution either in 0.1N HCl at 209 nm (method A) or in methanol at 208nm (method B). Beer's law was obeyed over the linear range 1.25-12.50µg/ml for both the methods A and B with molar absorptivity $6.21x10^4$ and $5.93x10^4$L/mol/cm and r=0.9997 and 0.9998, respectively. The recoveries obtained were in the range of 101.5% -108.25%. They were simple without involving heating or extraction step, with no interference from co-formulated substance when applied to tablets determination and high sensitivity. Therefore, the methods were proposed to be used for routine quality control analysis.

Sahu D et al.[21] developed and validated a simple, sensitive, specific, precise spectrophotometric method for the detection of QTP fumarate in pure form and in pharmaceutical formulations (tablets). In this method, QTP fumarate showed absorption at 242nm and obeyed Beer's law in the concentration range 5 to 25µg/ml. The sample solution was found to be stable up to 24 hrs. The proposed method was found to be useful for routine quality control.

Bagade SB et al.[22] reported a simple, fast and reliable derivative spectrophotometric method for determination of QTP fumarate in pharmaceutical formulation (tablets). Second order derivative ultraviolet spectrophotometric method was developed. Spectrophotometrically, QTP fumarate was determined by measuring the absorption at 254.76nm with 0.1 N HCl as background solvent. Analytical Calibration curves were linear within a concentration range from 10to30µg/ml. The developed method was applied directly and easily to the analysis of the pharmaceutical tablet preparations.

Chromatographic methods

The high performance thin layer chromatography (HPTLC), high performance liquid chromatography (HPLC), ultra performance liquid chromatography (UPLC) and gas chromatography (GC) methods has been reported for the analysis of fumarate in pharmaceutical formulation as well as in bulk.

HPTLC methods

Sahu D et al.[23] reported a simple, accurate, low cost and specific HPTLC method for estimation of QTP fumarate in tablet using silica gel 60 F_{254} aluminium plates and Acetonitrile: Chloroform in the ratio of 1:9 as mobile phase. The plate was scanned and quantified at 242 nm. The R*f* value of QTP was found to be 0.45. The calibration curve response was observed between 5-25µg/spot. The linear regression data showed good linear relationship with r = 0.999.

Dhandapani B et al.[24] developed and validated HPTLC method which was simple, precise and accurate for estimation of QTP in bulk drug and in tablet dosage form. The chromatographic separation was carried out on precoated silica gel 60 F_{254} aluminium plates using mixture of Methanol: Toluene (4:3%v/v) as mobile phase and densitometric evaluation of spots at 235nm. The drug was satisfactorily resolved with R*f* value 0.41 ± 0.01.The method showed linearity in the concentration range of 100-500ng/spot. The proposed method provided a faster and cost effective quality control tool for routine analysis of QTP as bulk drug and in tablet formulation.

Sathiya R et al.[25] developed and validated a simple sensitive precise and rapid HPTLC method for analysis of QTP fumarate in pharmaceutical formulation (tablets). The method involved the use of thin layer chromatographic aluminium plates precoated with silica gel 60F_{254} as the stationary phase. The solvent system consisted of Toluene: Ethyl Acetate: Diethylamine (5:3:2v/v/v) as the mobile phase. Densitometric analysis of QTP fumarate was carried out in the absorbance mode 291nm. The system gave compact spots for QTP fumarate (R*f* =0.54). The method was linear within the concentration range of 25-225ng/spot.

Skibinski R et al.[26] developed and validated two new, simple and accurate methods for

determination of QTP in tablets- Normal phase (NP) and Reverse phase (RP) HPTLC, each with densitometric and video-densitometric detection. NP-HPTLC was developed with precoated silica F_{254} plates and Hexane-Dioxane-Propylamine 1:9:0.4 (v/v) as mobile phase. RP-HPTLC was carried out using HPTLC RP8 F_{254}plates with Tetrahydrofuran- Phosphate buffer pH 9.0, 5:5 (v/v) as mobile phase. Both analyses were performed in horizontal chambers and scanned with densitometric detection at 243 nm and a video-densitometric at 254 nm. Calibration plots were linear in the range 0.2-1.2µg/spot of QTP for NP-HPTLC and in the range 0.1-1.1µg/spot for RP-HPTLC. The methods were found to be used in routine pharmaceutical analysis.

Dhaneshwar SR et al.[27] developed and validated a sensitive, selective, precise, linear ,accurate, selective, specific and stability-indicating HPTLC method for quantitative analysis of QTP fumarate both as the bulk drug and in formulations (tablets). The stationary phase was silica gel and the mobile phase was Toluene–Methanol 8:2 (*v*/*v*) with densitometric detection in absorbance mode at 254nm. It gave compact bands for QTP fumarate (*Rf*= 0.37 ± 0.02). QTP fumarate was subjected to acid and alkaline hydrolysis, oxidation and photo-degradation. The degradation products obtained were well resolved from the pure drug with substantially different *Rf* values. Because the method effectively separated the drug from its degradation products, it can be used as a stability indicating method.

HPLC methods

Reddy SP et al.[28] developed HPLC method for the analysis of the novel antipsychotic drug QTP in tablet dosage form. The analysis was carried out on a Phenomix Stainless Steel C_{18} (250 x 4.6 mm, 5µm) reversed-phase column, using a mixture of Phosphate buffer (pH 3): Acetonitrile: Methanol (50:40:10) as the mobile phase with flow rate at 0.8ml/min at 247nm using photodiode array detector. The retention time of the QTP was 4.69 min. The method was linear in the concentration range of 1 to 5µg/ml of QTP fumarate. The method showed good recovery results and therefore was found to be applicable for determination of the drug in tablets.

Pant M et al.[29] developed and validated a simple, rapid, accurate and precise RP-HPLC method for estimation of QTP fumarate from tablet dosage form using Zorbax ODS C_{18}, (150 mm x 4.6 mm, 5.0 µm) as stationary phase required for separation with Buffer : ACN (65:35) as mobile phase at flow rate 0.6ml/min using photodiode detector at 257nm. The retention time for QTP was 8.98mins. The proposed method was simple, economical, accurate and rapid for estimation of QTP fumarate.

Rao SB et al.[30] reported a rapid sensitive and specific HPLC method for the determination of QTP fumarate in the pharmaceutical formulations (tablets) using Lamotrogine as the internal

standard. The method gave accurate and precise results in the concentration range of 2.01 to 49.500 x 10^{-3}g/Lt. The mobile phase composition is 50**:**50 Acetonitrile**:** 0.1% orthophosphoric acid, at the flow rate of 0.6 ml/min. The retention times of internal standard and the drug are 1.45 ± 0.05 and 3.6 ± 0.05 respectively. The column is a C18 column (50 mm x 4.6 mm, 3µ). PDA-UV detector was used with detection at 294nm. QTP fumarate is tested for the stress conditions like photo stability, acid stability, alkaline, oxidation and thermal conditions for the 24hrs. QTP fumarate is stable and did not show any signs of degradation under stress conditions.

Trivedi SK et al.[31] reported a stability indicating reversed phase- Ultra performance liquid chromatography (RP-UPLC) method for the quantitative determination of QTP in pharmaceutical dosage form (tablets). The chromatographic separation was carried on an Agilent Eclipse Plus C_{18}, RRHD (50 mm x 2.1 mm, 1.8 µm) column using gradient elution with mobile phase consisting of 0.1 % aqueous Triethylamine (pH 7.2) as solvent-A and 80:20 v/v mixture of Acetonitrile and Methanol as solvent-B. The eluted compounds were monitored at 252 nm using a UV detector. The method separated QTP from its five impurities/degradation products within a run time of 5 min. Stability indicating capability of the developed method was established by analyzing forced degradation samples in which the spectral purity of QTP was ascertained along with the separation of degradation products from analyte peak.

Rao BM et al.[32] developed a simple and accurate RP-HPLC method for the determination of related substance and degradants of QTP fumarate. Chromatographic separation between QTP fumarate, its related substances and degradants obtained from samples generated after stress degradation was achieved using a X-bridge C_{18},(150 mm x 4.6 mm, 3.5µm) 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 1ml/min. The sample concentration was 0.5 mg/ml and the detection wavelength was 220 nm. The resolution between the critical pair of peaks (Impurity & analyte) was found to be greater than 4.5. The test solution and mobile phase was observed to be stable up to 24 h after the preparation. The proposed method was found to be suitable and accurate for the quantitative determination of related substances and degradants during quality control of QTP fumarate API.

Narendra Kumar R et al.[33] a liquid chromatographic method (HPLC) was developed and subsequently validated for the determination of QTP fumarate and its related substances in bulk and pharmaceutical formulation (tablets). Separation was achieved in gradient mode using Kromasil 100, C_{18}, (30 x 3.0 mm, 3.5µm) column with mobile phase A containing 0.5% Triethylamine buffer (pH adjusted to 4.8±0.05 with Orthophosphoric acid and mobile phase B

containing 100%Acetonitrile at different time intervals as eluent at a flow rate 1.0mL/min. UV detection was performed at 240nm.The retention time for drug was found to be 4.244mins.The described method was accurate and linear over a range of about 0.052µg/mL to 3.289µg/mL. The method was found to be useful in the quality control of bulk manufacturing and also in pharmaceutical formulations.

Nalluri BN et al.[34] developed and validated a stability indicating RP- HPLC method for the estimation of QTP fumarate in bulk and pharmaceutical dosage forms (tablets). The proposed RP-HPLC method utilizes an Inertsil ODS (250 x 4.6 mm, 5µm) column, with optimum 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 QTP was 13.4min. The bulk active pharmaceutical ingredient was subjected to thermal, photolytic, hydrolytic (acidic and basic) and oxidative stress conditions and analyzed. Considerable degradation was found to occur only in oxidative stress conditions. The method was found to be linear in the concentration range of 10-50µg/mL. The proposed RP-HPLC-PDA method is specific, accurate, precise and high sensitive enough for the estimation of QTF in bulk and pharmaceutical dosage forms.

Stolarczyk EU et al.[35] used hyphenated LC-MS/MS technique for characterization of impurity profile of QTP during drug development. This technique was used to develop methods for the separation and identification of the impurities resulting from both, synthesis and degradation processes. First, the parent drug was analyzed with LC-MS. The retention time and molecular weight information were obtained. Using LC-MS/MS, the product-ion analysis of the parent drug was obtained, and specific product ions and neutral losses were assigned to the substructures of the molecule. The MS/MS identification strategy was based on the assumption that much of the parent drug structure will be retained in the impurities or decomposition products. The product-ion mass spectrum of the parent drug and fragmentation pattern of the parent drug was used as the templates for the identification of the unknown structure.

Suneetha D et al[36] developed RP-HPLC method for the estimation of QTP in bulk and pharmaceutical formulations. QTP was chromatographed on a RP-C_{18} Waters column (75mm x 4.6mm, 3.5µm) in a mobile phase consisting of phosphate buffer (pH 3.0 adjusted with orthophosphoric acid) and Acetonitrile in the ratio 40:60 v/v. The mobile phase was pumped at a flow rate of 0.8ml/min with detection at 291nm. The proposed method can be applied for routine quality control analysis of QTP in bulk and pharmaceutical formulations.

SravanKumar et al[37] developed a simple, sensitive, rapid, robust and reproducible method for the determination of QTP fumarate in bulk and pharmaceutical formulation (tablets) using RP-

HPLC. The RP-HPLC analysis was performed isocratically on C_{18} (4.6 mm x 150 mm) analytical column using mobile phase consisting of mixture of 2.5pH buffer- Acetonitrile (40:60) v/v at the flow rate of 0.8ml/min. The wavelength of detection was adjusted to 294nm. The retention time of QTP was 2.839. The proposed method can be readily utilized for bulk drug and pharmaceutical formulations.

Bhagyakumar et al[38] reported a simple, selective, linear, precise and accurate RP-HPLC method for rapid assay of QTP in tablet dosage form. Isocratic elution at flow rate of 1ml/min was employed on an Intersil ODS C_{18} column (250 mm x 4.6 mm 5µm). Methanol: Acetonitrile: Orthophosphoric acid (35:35:30) v/v/v was selected as mobile phase. The detection wavelength was 238nm with retention time of QTP at 7.33. The proposed method can be successfully applied for the estimation of QTP in pharmaceutical dosage forms.

Pallikonda SK et al[39] established a simple, sensitive, rapid, robust and reproducible method for determination of QTP fumarate in bulk and pharmaceutical dosage form (tablets) using RP-HPLC. The RP-HPLC analysis was performed isocratically on C_{18} column (4.6 mm x 150mm) using mobile phase consisting of orthophosphorous buffer and Acetonitrile in the ratio of 60:40 v/v with flow rate of 0.6ml/min and wavelength of detection at 290nm. The retention time was 10 mins for QTP. The method can be applied for estimation of QTP in bulk and formulations.

Rao B et al [40] developed a simple, sensitive, linear, precise and accurate RP-HPLC method and validated for rapid assay of QTP in tablet dosage form. Isocratic elution at a flow rate of 1ml/min was employed on a symmetric C_{18} (250 x 4.6mm, 5µm) at ambient temperature. The mobile phase consisted of Methanol: Water: Orthophosphoric acid 90:10:0.1. The UV detection was done at 250nm. The retention time of QTP was 3.64 min. The method was successfully applied for routine analysis of QTP in tablet dosage form.

Gas Chromatography

Mathad VT et al.[41] developed and validated a rapid and sensitive gas chromatographic method using flame ionization detection (GC–FID) for five process related non-chromophoric impurities generated during the chemical synthesis of QTP hemifumarate. All five non-chromophoric impurities ranging from 0.05 to 0.1% were detected using DB-5 (30 m x 0.53 mm, 5 µm) column with a good peak separation. The five unknown impurities were detected and identified by using the developed GC–MS and characterized by MS, 1H NMR and FT-IR spectroscopy.

Others

Nahed El-Enany et al.[42] conducted polarographic analysis of QTP in pharmaceuticals. In this, the voltammetric behaviour of QTP (QTP) was studied using direct current (DC_t), differential pulse

(DPP) and alternating current (ACt) polarography. The DC_t and DPP modes could be successfully applied over concentration range of 8-44µg/ml and 4-44µg/ml respectively with lower detection limits of 0.06µg/ml using DC_t and 0.04µg/ml using DPP modes which are more applicable for dosage forms.

Nagaraju R et al.[43] reported a simple, precise, accurate and cost effective titrimetric method for the determination of QTP fumarate in bulk drug and in its dosage forms. The method was based on the potentiometric titration of QTF in glacial acetic acid with aqueous perchloric acid using a modified glass-saturated calomel electrode system and 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.

Kanakapura B et al.[44] reported two simple, rapid, precise and accurate titrimetric methods employing sodium tetraphenylboron (STPB) and sodium lauryl sulphate (SLS) as titrants for the quantitative determination of QTP fumarate in bulk drug and tablets based on the solvent extraction-titration of QTF with STPB (method A) and with SLS (method B) using tetrabromophenolphthalein ethyl ester (method A) and dimethyl yellow (method B) as indicators. The methods were applicable over the ranges of 4.0-18.0 and 5.0-25.0 mg of QTF for method A and method B, respectively. The proposed methods yielded the reaction stoichiometries of 1:1 and 1:2 for method A and method B, respectively. The methods were applied successfully to the determination of QTF in tablets.

Nagaraju R, Kanakapura B, Kanakapura VB [45] reported two direct, simple, sensitive and rapid extraction-free spectrophotometric methods for the determination of QTP fumarate in pure form and in its dosage forms. The methods are based on the formation of ion-pair complex between the drug and two sulphonthalein acidic dyes, namely, bromophenol blue (method A) and thymol blue (method B), followed by the measurement of absorbance at 410 and 380 nm, respectively. Conformity to Beer's law enabled the assay of the drug in the range 1-20 and 1.5-30 µg mL-1 in method A and method B, respectively. The stoichiometry of the reaction in both cases was found to be 1:2 (drug: dye). The methods were successfully applied to the determination of drug in tablets without interference by the common co-formulated substances.

FOR ESTIMATION IN BIOLOGICAL FLUIDS

There are many methods available for estimation of QTP fumarate in biological matrices like blood, serum, plasma, urine, cerebrospinal fluid. Case reports on estimation of QTP have also been reported.

Plasma

Raggi MA et al.[46] reported a precise and feasible high-performance liquid chromatographic (HPLC) method for the analysis of the novel antipsychotic drug QTP in plasma on a C_8 (150 mm x 4.6 mm, 5 µm) reversed-phase column, using a mixture of Triethylamine: Acetonitrile: Methanol (18:3:4 v/v/v) and pH 1.9 phosphate buffer as the mobile phase at flow rate of 1ml/min and detected at 254nm. Triprolidine was used as the internal standard. Solid phase extraction (SPE) technique was used for sample preparation. The proposed method was found to be suitable for the clinical monitoring of patients treated with QTP.

Davis PC et al.[47] performed an analysis and pharmacokinetics of QTP and two metabolites 7-hydroxylated and 7-hydroxylated, *N*-dealkylated metabolites in human plasma using RP-HPLC with UV detection of QTP at 225nm and electrochemical detection of its metabolites by oxidation at +0.55V. The assay employs a three-step liquid–liquid extraction of QTP and its metabolites by ethyl acetate from human plasma using stable bond phenyl (150mm x 2.1 mm, 5µm) column with Phosphate buffer pH 7.4 : Methanol : Acetonitrile (40:50:10 v/v/v) as mobile phase at flow rate of 0.25ml/min. The present assay method was used to support a study comparing the pharmacokinetic profile of QTP with the time course of dopamine D2 and serotinin 5-HT2 receptor occupancy in the brain using positron emission tomography (PET).

Kundlik ML et al.[48] developed and validated a rapid liquid chromatographic method with electrospray ionization tandem mass spectrometric detection for quantification of QTP in human plasma. Plasma samples were extracted using solid phase extraction method and eluted with Acetonitrile. The analyte (QTP) and zolpidem tartrate (internal standard, IS) were separated on a C_{18} column; the mobile phase used was 85:15 (v/v) Acetonitrile–5 mM Ammonium formate, pH adjusted to 4.5 with formic acid at a flow rate of 0.5 mL min-1. The retention times of QTP and the IS were 1.25 and 1.05 min, respectively, and the run time was 1.8 min per sample. The assay was successfully used for analysis of QTP in healthy human subjects in a bioequivalence study.

Davis PC et al.[49] developed and validated liquid–chromatography tandem mass spectrometry (LC–MS/MS) method for pharmacokinetic measurement of QTP four related metabolites in human plasma using single liquid–liquid extraction of QTP and its related four metabolites by *tert*-butyl methyl ether. The separation of QTP and its metabolites was done by using dual-column Luna C18 columns (50 mm × 2.0 mm, 5µm) and tandem MS detection. This methodology enabled the determination of the pharmacokinetics of QTP and its metabolites in human plasma.

Barrett B et al.[50] validated high-pressure liquid chromatography–tandem mass spectrometry (LC–MS/MS) method for the quantitative determination of QTP in human plasma using

clozapine as an internal standard. Samples preparation technique involved solid phase extraction (SPE). Separation was carried on C_{18} column (100 mm x 3 mm; 3µm) using Methanol: Acetonitrile: Ammonium acetate buffer pH 3.5 (31:19:50 v/v/v) as mobile phase at flow rate of 0.4ml/min. The SRM mode was used for MS/MS detection. The developed method was employed in the pharmacokinetic study of QTP.

Pan RN et al[51] reported a selective and sensitive liquid chromatography-tandem mass spectrometry (LC-MS-MS) method for determination of QTP using Clozapine as internal standard. Spiked plasma samples were extracted with liquid-liquid extraction using diethyl ether solvent. Phenomenex Luna C_{18} column (2.0 mm x 150 mm, 5µm) using 85% Acetonitrile (aq.) with 1mM Ammonium acetate and 0.1mM Formic acid at flow rate of 0.3ml/min and injection volume 5µL. Detection was performed on a triple- quadrupole tandem mass spectrometer using positive electrospray ionization and quantification was performed by selected reaction monitoring mode.

Nirogi R et al[52] developed and validated a sensitive liquid chromatography-tandem mass spectrometric method for the quantification of QTP in rat plasma. The method used liquid-liquid extraction technique by mixture of diethyl ether: dichloromethane (70:30) for sample preparation following which, the analyte was separated on reverse phase column C_8 (50 mm x 4.6 mm) using gradient mobile phase 10mM Ammonium acetate buffer and Acetonitrile and further analyzed by tandem mass spectrometry. This method in rodent plasma could be adapted for QTP assay in human plasma and can be applied in pre-clinical pharmacokinetic studies.

Pullen et al[53] reported HPLC-UV and GC-MS method for determination of an antipsychotic drug and its7-Hydroxy metabolite in human plasma. Methods were developed for the simultaneous determination of both analytes in human plasma using HPLC-UV and GC-MS. The analytes were extracted from plasma using phenyl solid-phase extraction columns. Quantification by isocratic HPLC was performed in the reversed-phase mode with detection at 250 nm. Extracts were derivatized to trimethylsilyl ethers for quantification by GC-MS using selected-ion monitoring.

Zhou Z et al[54] developed a sensitive method for simultaneous determination of CLZ, OLZ, RIP and QTP in human plasma by HPLC–electrospray ionization mass spectrometry (MS/ESI). Multiple liquid-liquid extraction by ether was performed as sample preparation technique using C_{18} column (2 mm x 125 mm; 3µm) using Water (Formic acid: 2.7mM Ammonium acetate: 10mM) – Acetonitrile (53:47) as mobile phase with flow rate of 0.16ml/min. the compounds were ionized and detected by electrospray ionization mass spectrometer.

Mercolini et al[55] developed and validated RP-HPLC method for simultaneous determination of classical neuroleptics (chlorpromazine, haloperidol, clotiapine and loxapine), atypical antipsychotic (resperidone, QTP and clozapine) and their active metabolites in human plasma using C_{18} reversed phase column and mobile phase composed of 70% aq Phosphate buffer containing Triethylamine at pH 3 and 30% Acetonitrile. Sample preparation technique used was solid phase extraction. Amitriptyline was used as internal standard. Detection was performed by UV at 238nm. The method was applied with success to schizophrenic patients undergoing polypharmacy with two or more different antipsychotics.

Saracino et al[56] reported a HPLC-UV method for simultaneous determination of the atypical antipsychotic QTP and the geometric isomers of second generation antidepressant fluvoxamine using citalopram as internal standard on reversed phase C_8 column (150 mm x 4.6 mm, 5µm). The mobile phase was Acetonitrile (30%) and 10.5 mM pH 3.5 phosphate buffer containing 0.12% triethylamine (70%) at flow rate of 1.2ml/min with detection wavelength at 245nm. Solid phase extraction technique was employed for sample preparation. The method could be successfully applied to plasma samples withdrawn from human patients undergoing polypharmacy with two drugs.

A stability indicating method was also reported for determination of QTP in both plasma as well as pharmaceutical tablets by Belal et al[57]. A RP-HPLC with UV detection method was developed for determination of QTP in presence of two of its degradation products using Zorbax SB-Phenyl column (250 mm x 4.6 mm, 5µm). Mobile phase containing a mixture of 50:50 Acetonitrile and 0.02 M phosphate buffer at pH5.5 at flow rate of 1ml/min with UV detection at 254nm. Multiple liquid-liquid extraction technique was employed using ether. The method was successfully applied for analysis of QTP in bulk, tablets and human plasma along with other co-administered drugs like clomipramine, carbamazepine and fluconazole.

There are few other methods also reported for estimation of QTP in plasma as well as in other matrices like human liver microsomes and cerebrospinal fluid.

A liquid chromatographic method- electrospray- tandem mass spectrometric method (LC-ESI-MS-MS) for quantitation of QTP in human plasma and liver microsomes was established by Shen-Nan Lin et al[58] The method used simple liquid-liquid extraction for measurement of QTP in human plasma. Clozapine was used as internal standard. The plasma samples quenched with methanol (100µl) was made basic and extracted with n-butyl chloride. The reconstituted extracts were analysed by LC-ESI-MS-MS. The method has also been used to study in-vitro metabolism of QTP by incubating it with Human Liver Microsomes or with cDNA-expressed human

cytochrome P450s. It was concluded that QTP was extensively metabolized by CYP3A4 and CYP2D6 and to a lesser extent by CYP3A7, CYP3A5 and CYP2C19.

Huan-De Li et al[59] developed a rapid and sensitive Ultra performance liquid chromatographic – tandem mass spectrometric method (UPLC- MS/MS) for analysis of QTP and its two active metabolites in plasma and cerebrospinal fluid of rats. The assay used liquid-liquid extraction with *t*-butyl methyl ether after alkalinization with ammonia. Carbamazepine was used as internal standard. The separation was achieved on C_{18} column using 63:37 (v/v) aq formic acid 0.3mM and Ammonium acetate 50mM and Acetonitrile at flow rate of 0.25ml/min. The method was applied to study pharmacokinetics and CSF properties of QTP and its active metabolite by using rat plasma and cerebrospinal fluid of rats.

Serum

Hasselstrom J et al[60] developed a fully automated on-line quantification of QTP in human serum by solid phase extraction and liquid chromatography. The solid phase extraction is done by using C2 cartridge eluted with methanol. The eluate obtained is then injected onto silica column with mobile phase consisting of Methanol: 20mM Ammonium acetate buffer, pH 5.0 (99:1). QTP was quantified by UV absorbance at 257 nm with trifluoperazine as internal standard. The method could be successfully applied in therapeutic drug monitoring.

Rao ML et al[61] devised an isocratic RP-HPLC with Ultra violet detection for analysis of eighteen antidepressants, four atypical antipsychotics and active metabolites in serum. Solid phase extraction technique was used for sample preparation of these drugs. Separation was achieved on Nucleosil 100-Protect 1 column (250 mm x 4.6 mm, 5µm) (endcapped) with Acetonitrile: 25mM Potassium dihydrogen phosphate buffer pH7.0 (40:60) at flow rate of 1ml/min. The eluted substances were detected by UV detector at 230nm. The method was found to be applicable to rapidly and effectively analyze serum or plasma samples for therapeutic drug monitoring of about 30 antidepressants and atypical antipsychotics.

Kirchherr H et al[62] reported RP-HPLC-MS/MS method for simultaneous determination of forty-eight antidepressants and antipsychotics in human serum using protein precipitation as sample preparation technique. Chromatographic separation was performed on monolithic C_{18} (50mm x 4.6mm) with methanol gradient and 5mM acetate buffer at pH 3.9. A set of three internal standards clonidine, dehydromethylrisperidone and methabenzthiazurone were used for quantification of drugs with widely varying hydrophobicity. Detection was done by electrospray ionization tandem mass spectrometer.

Sachse J et al[63] described an automated RP-HPLC-UV method for determination of QTP,

clozapine, perazine and metabolites in serum. Solid-phase extraction technique was used for sample clean up (online) using deionized water containing 8% Acetonitrile at flow rate of 1.3ml/min for 5 minutes. Acetonitrile-water-tetramethylethylene diamine (37.5: 62.1: 0.4 v/v/v) adjusted to pH6.5 by acetic acid (95%) used used for separation of sample. Drugs were separated on ODS Hypersil C_{18} column (250 mm x 4.6 mm, 5µm) and quantified by UV detection at 254nm. Fluperlapine was used as internal standard. The method was thus suitable for routine therapeutic drug monitoring and may be extended to other drugs.

Urine

Atanasov VN et al[64] reported a method for detection and identification of atypical antipsychotic QTP metabolite in urine by GC-MS using liquid-liquid extraction technique. The extraction technique employed ethyl acetate as extracting solvent. The separation was carried out on capillary fused silica column DB-5 MS (30 mm x 0.25 mm, 0.25µm film), helium as carrier gas and split injection of the sample. The method can be used as an indicative marker of QTP-intake in routine GC-MS urine screening analysis although it is not a major metabolite of the parent compound.

Kanakapura VB et al[65] reported a spectrophotometric method for determination of QTP fumarate in pharmaceuticals and human urine by two charge transfer complexation reactions. The methods are based on charge transfer complexation reactions of free base form of the drug (QTP), as n-electron donor, with either p-chloranilic acid (method A) or 2,3 -dichloro-5,6-dicyanoquinone (method B) as π-acceptors. The coloured charge transfer complexes produced exhibit absorption maxima at 520 and 540 nm, in method A and method B, respectively. The proposed methods were successfully applied for the determination of QTF in pharmaceutical formulations and spiked human urine.

Nagaraju R et al[66] established an extractive spectrophotometric method for QTP fumarate estimation in pharmaceuticals and human urine using Calmagite as ion-pair reagent. A sensitive and selective method based on dichloromethane-extractable ion-pair of QTF with calmagite (CGT), which exhibited an absorption maximum at 490 nm. The proposed method has its application in the determination of QTF in spiked human urine without any prior-extraction procedure thus, the method allows determination of QTF in human urine samples in the physiological concentration range obtained after the usual therapeutic dose of QTF has been administered.

Kanakapura VB et al[67] developed and validated an extractive spectrophotometric method for determination of QTP fumarate in pharmaceuticals and spiked human urine. The method was

based on the formation of a chloroform extractable yellow ion-pair complex between basic nitrogen of QTP and the dye quinoline yellow in acetate-hydrochloride buffer (pH 2.56) medium. The formed ion-pair complex exhibited an absorption maximum at 420 nm. The proposed method was successfully applied for the determination of QTP fumarate in bulk drug, tablets and spiked human urine without any interference.

The above methods could also be applied for the estimation of QTP fumarate in pharmaceuticals.

Serum and Urine

Barnett NW et al.[68] reported an HPLC method with tris (2,2'-bipyridyl) ruthenium(II) chemiluminescence detection methodology for determination of QTP and its metabolites in human serum and urine. The method uses monolithic chromatographic column allowing high flow rate of 3ml/min enabling rapid quantification and also negated the need for extensive sample preparation due to its bimodal pore design making it resistant to blocking. Flow injection analysis (FIA) with tris (2,2-bipyridyl)ruthenium(II) chemi-luminescence detection and HPLC time of flight mass spectrometry (TOF-MS) were used for the determination of QTP concentrations and the observation of its major metabolite in human urine and serum.

Uslu B et al.[69] performed voltammetric analysis of QTP drug in human serum and urine. The electro-oxidative behaviour and determination of QTP on a glassy carbon disc electrode was investigated using cyclic, linear sweep, differential pulse and Oster young square wave voltammetry. QTP in pH 3.5 acetate buffer solution presents a well-defined anodic response due to the irreversible, diffusion-controlled, one-electron and one-proton oxidation of the aliphatic nitrogen of the piperazine ring. The methods developed for the determination of QTP are based on the anodic oxidation of the piperazine ring on a carbon electrode. The procedure was successfully applied to the determination of the drug in tablets, human serum and human urine with good recoveries.

Blood

Gerostamoulos D et al[70] reported stability assessment of thirty antipsychotic drugs in stored blood specimens. The stability of 30 common antipsychotics in spiked whole blood was investigated over ten weeks in a preliminary experiment by spiking pool of blank blood with drugs at two different therapeutic levels and stored at four different temperatures: 20^0 C, 4^0 C, -20^0C, and -60^0 C and extracted once weekly in duplicate. A loss of >15% of the initial drug concentration was considered to indicate possible instability which were included for further studies. However, quetiapine fumarate was found to be stable. Therefore, excluded from further experiments on stability evaluation. Chlorpromazine, chlorprothixene, fluspirilene, droperidol,

olanzapine, thioridazine, trifluprομazine, and ziprasidone were studied further. The same conditions were used in both experiments, however only a high therapeutic drug concentration was chosen and the storage time was extended to 20 weeks. All drugs of interest for further studies showed significant losses after 20 weeks of storage under at least one storage condition. The time period and temperature of storage of biological samples can have a significant influence on the stability of several APs. It is therefore important to be aware of potential changes in drug concentrations during storage when interpreting analytical results.

Case Reports

Langman LJ et al[71] presented three case reports on fatal overdoses associated with QTP. The blood specimens were initially subjected to a thorough qualitative analysis. QTP was assayed in biological specimens by basic extraction with n-chlorobutane and derivatised with 50µL of N-[tert-butyldimethyl-silyl] N-methyltrifluoroacetamide (MTBSTFA) using 4-hydroxytriazolam as an internal standard and separated by gas chromatography-nitrogen phosphorous detection using a 12-m Ultra-1 capillary column (0.2-mm i.d., 0.33-µm film thickness). These cases were chosen for study because they were all deaths as a result of suicidal ingestion of drugs in which QTP was considered a significant factor. The concentrations of QTP in these cases are 6-16 times greater than the upper reported therapeutic range (0.1-1.0 mg/L). In all cases, drugs in addition to QTP were detected, but in cases #1 and #2, the cause of death was considered to be a QTP overdose and the other drugs were not considered to be contributory. Case #3 was considered a mixed drug overdose.

Flammia DD et al[72] reported tissue distribution of QTP in 20 postmortem cases in Virginia. QTP was extracted from blood using a basic drug SPE and identified by electron impact GC-MS. QTP quantification was done by forming the trimethylsilyl derivative with bis(trimethylsilyl) trifluoracetamide / trimethylchlorosilane and using selected ion monitoring GC-MS. Methapyrilene was used as internal standard. A capillary column (30m x 0.25mm i.d., 0.25µm film thickness) was used for separating the analytes. Helium was used as the carrier gas with a flow rate of 1.0 mL/min. The average of all blood concentrations in 18 cases in which QTP contributed to the cause of death was 7.95 mg/L (0.4-76 mg/L). These case studies suggested that when post-mortem blood QTP concentrations are more than 1 mg/L QTP may have contributed to the cause of death.

Mozayani A et al[73] determined the concentrations and distribution of the atypical antipsychotic drug, QTP, in postmortem tissues from eight Medical Examiner cases using prochlorperazine as internal standard. QTP was isolated from blood specimens and tissue homogenates by extraction

at an alkaline pH into 1-chlorobutane, decanted and back-extracted into 0.1 N sulphuric acid. The acid layer was made basic and re-extracted into 1-chlorobutane.Quantitation was by gradient, high-pressure liquid chromatography on a C-8 ODS (2.1 x 150mm, 5 µm) column with Acetonitrile /0.1M ammonium hydroxide (pH 10) mobile phase and a photodiode array detector set at 258 nm. The determination of QTP in specimens from these eight postmortem cases demonstrates a range of tissue concentrations expected in postmortem cases, after therapeutic and overdose exposure.

Steven Wise et al[74] reported the detection of QTP in 13 postmortem cases. Following a basic liquid-liquid extraction by n-butyl chloride, QTP was identified and quantitated by capillary gas chromatography with nitrogen phosphorus detection. Promazine was used as internal standard. Separation was achieved using RTx-50 column or equivalent (30 m × 0.32 mm, 0.25 µm film thickness) with capillary direct interface to the MSD. Helium gas was used with a constant flow of 1.0 mL/min. Confirmation was accomplished by full scan electron impact gas chromatography/mass spectrometry. In three cases, the cause of death was determined to be QTP toxicity. In these cases heart blood concentrations ranged from 0.72 to 18.37 mg/L (N=3). These data may provide a basis for establishing levels associated with QTP toxicity as well as therapeutic concentrations in postmortem specimens.

Anderson DT et al[75] first reported the presence of quetiapine (Seroquel®) concentrations in post-mortem cases. The analysis of QTP from postmortem specimens consisted of an *n*-butyl chloride basic extraction using gas chromatography-nitrogen phosphorous detector. The tissue distribution of QTP was as follows: heart blood present, but less than 0.10–49 mg/L (seven cases); femoral blood less than 0.10–1.4 mg/L (five cases); liver less than 0.10–112 mg/kg (five cases); spleen 4.0 mg/kg (one case); urine 0–3.0 mg/L (two cases); bile 0.60–7.5 mg/L (three cases); and gastric contents less than 0.01–18 mg total (five cases).

CONCLUSION

Several analytical methods have been reported for the estimation of QTP fumarate in pharmaceutical formulations and biological matrices. It can be concluded that UV spectrophotometry and HPTLC are the most simple and easy methods for QTF estimation in pharmaceutical formulations while HPLC-UV and LC/MS/MS can be widely used for QTF estimation in biological fluids like plasma, urine and serum. It was also found that LC/MS/MS and GC-FID methods are used for impurity profiling of QTF. Stability indicating methods for QTF by HPTLC and HPLC-UV has also been reported. Thus, this current review gives complete

detail of the analytical methods available on quetiapine fumarate which can be helpful for further research work studies on it.

REFERENCES:

1. Fulton B, Goa KL. ICI-204,636 An Initial Appraisal of its Pharmacological Properties and Clinical Potential in the Treatment of Schizophrenia. CNS Drugs 1995;4(1):68-78.
2. Schotte A, Janssen PFM, Gommeren W, Luyten WH, Van Gompel P, Lesage AS et al. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology 1996;124(1-2):57-73.
3. Caley CF, Rosenbaum S. Focus on quetiapine-the fourth atypical antipsychotic. Formulary 1998;33(2):105-17.
4. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: A comparison with haloperidol and placebo. Biol Psychiatry 1997;42(4):233-46.
5. Mahatthanatrakul W, Rattana K, Sriwiriyanjan S, Wongnawa M, Ridtitid W. Bioequivalence study of a generic quetiapine in healthy male volunteers. Int J Clin Pharmacol Ther 2008;46(9):489-96.
6. Astrazeneca-us.com [Internet]. USA: Seroquel (quetiapine fumarate) tablets Astrazeneca pharmaceuticals LP. Database; [revised on 04/2013]. Available from: http://www1.astrazeneca-us.com/pi/seroquel.pdf.
7. Prior TI, Chue PS, Tibbo P, Baker GB. Drug metabolism and atypical antipsychotics. Eur Neuropsychopharmacol 1999;9(4):301-9.
8. DeVane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. Clin Pharmacokinet 2001;40(7):509-22.
9. Goren JL, Levin GM. Quetiapine, an atypical antipsychotic in. Pharmacotherapy 1998;18(6):1183-94.
10. Lee A, Giesbrecht E, Dunn E, Ito S. Excretion of quetiapine in breast milk. Am J Psychiatry 2004;161(9):1715-6.
11. Weiden PJ. Quetiapine ('seroquel'): a new 'atypical' antipsychotic. J Prac Psychiatry and Behav Health 1997;3(6):368-374.
12. Kasper S, Muller-Spahn F. Review of quetiapine and its clinical applications in schizophrenia. Expert Opin Pharmacother 2000;1(4):783-801.
13. Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CG. Quetiapine in patients with

schizophrenia. A high and low-dose double-blind comparison with placebo. Seroquel study group. Arch Gen Psychiatry 1997;54(6):549-97.

14. Hasegawa M, Cola PA, Meltzer HY. Plasma clozapine and desmethylclozapine levels in clozapine-induced agranulocytosis. Neuropsychopharmacology 1994;11(1):45-7.
15. Pollak PT, Zbuk K. Quetiapine fumarate overdose: clinical and pharmacokinetic lessons from extreme conditions. Clin Pharmacol Ther 2000;68(1):92-7.
16. Casey DE. The relationship of pharmacology to side effects. J Clin Psychiat 1997;58:55-62.
17. Mohr N, Vythilingum B, Emsley RA, Stein DJ. Quetiapine augmentation of serotonin reuptake inhibitors in obsessive-compulsion disorder. Int Clin Psychopharmacol 2002;17(1):37-40.
18. Reddy SP, Reddy AS, Varma AK, Rao ND, Satyanarayana P, NagaRaju TM. Method development and validation of quetiapine fumarate bulk and in tablet dosage form by using UV spectrophotometry. Int J Pharm and Ind Res 2011;1(3):195-99.
19. Prasanth VG, Eapen SC, Kutty SV, Jyothi TS. Development and validation of Quetiapine fumarate in pure and pharmaceutical formulation by UV-Spectrophotometric method. Der Pharmacia Sinica 2011;2(6):52-8.
20. Kanakapura B, Nagaraju R, Pavagada RJ, Kanakapura BV. Sensitive ultraviolet spectrophotometric determination of quetiapine fumarate in pharmaceuticals. Thai J Pharm Sci 2010;34:146-54.
21. Sahu D, Rana AC. Development of analytical method for quetiapine fumarate by UV spectrophotometry. Int J Res Ayur & Pharm 2011;2(2):588-591.
22. Bagade SB, Narkhede SP, Nikam DS, Sachde CK. Development and validation of UV-spectrophotometric method for determination of quetiapine fumarate in two different dose tablets. Int J ChemTech Res 2009;1(4):898-904.
23. Sahu D, Rana AC. Estimation of quetiapine fumarate in tablet dosage form by HPTLC method. World J Pharm Res 2012;1(2):326-331.
24. Dhandapani B, Somasundaram A, Raseed S, Raja M, Dhanabal K. Development and validation of HPTLC method for estimation of quetiapine in bulk drug and in tablet dosage form. Int J PharmTech Res 2009;1(2):139-141.
25. Sathiya R, Krishnaraj K, Muralidharan S, Muruganantham N. A simple and validated HPTLC method of evaluation for quetiapine fumarate in oral solid dosage form. Eurasian J Anal Chem 2010;5(3):246-253.

26. Skibinski R, Komsta L, Kosztyla I. Comparative validation of quetiapine determination in tablets by NP-HPTLC and RP-HPTLC with densitometric and videodensitometric detection. J Planar Chromatogr 2008;21(4):289-294.
27. Dhaneshwar SR, Patre NG, Mahadik MV. Stability-indicating HPTLC method for quantitation of quetiapine fumarate in the pharmaceutical dosage form. Acta Chromatographica 2009;21(1):83-93.
28. Reddy SP, Satyanarayana P, Varma KK, NagaRaju, SivaKumar G, Shanmugasundaram P. Novel reverse phase hplc method development and validation of quetiapine fumerate in bulk and tablet dosage form. Int J Pharm Res 2011;1(2):95-99.
29. Pant M, Khatri NC. Development and validation of assay method for estimation of quetiapine fumarate by RP-HPLC. Int J Pharm LifeSci 2012;3(7):1802-4.
30. Venkata KB, Battula SR, Dubey S. Validation of quetiapine fumarate in pharmaceutical dosage by reverse-phase HPLC with internal standard method. J Chem 2013;1-8.
31. Trivedi RK, Patel MC. Development and validation of a stability indicating RP-UPLC method for determination of quetiapine in pharmaceutical dosage form. Sci Pharm 2011;79:97-111.
32. Krishna SR, Rao BM, Rao NS. A validated stability indicating HPLC method for the determination of related substances in quetiapine fumarate. Rasayan J Chem 2008;1(3):466-74.
33. Kumar N, Rao NG, Naidu PY. Stability indicating fast LC method for determination of quetiapine fumarate related substances in bulk and pharmaceutical formulation. Der Pharmacia Lettre 2011;3(3):457-69.
34. Korrapolu S, Bollineni S, Nalluri BN. Stability indicating RP-HPLC-PDA method for the estimation of quetiapine fumarate in bulk and pharmaceutical dosage forms. J Chem Pharm Res 2012;4(8):3877-84.
35. Stolarczyk EU, Kutner A. Use of hyphenated LC-MS/MS technique for characterization of impurity profile of quetiapine during drug development. Acta Pol Pharm 2010;67(6):599-608.
36. Suneetha D, Rao LA. A validated RP-HPLC method for the estimation of quetiapine in bulk and pharmaceutical formulations. E-J Chem 2010;7(S1):S261-66.
37. Kumar SG, Vidyadhari C, Kumar VB, Sulthana S, Kumar SV, Aneela S et al. Development and validation of RP-HPLC method for determination of quetiapine fumarate from pharmaceutical preparation. Int J Bio Pharm Res 2011;2(1):27-33.

38. Bhagyakumar T, Manoranjani M. RP-HPLC method development and validation for the analyisis of quetiapine in pharmaceutical dosage forms. Int J Res Rev Pharm App Sci 2011;1(4):255-62.
39. Pallikonda SK, Subburu S, Reddy SS, Reddy C. Method development and validation of quetiapine fumarate by RP-HPLC method. Pharmatutor [Internet]. Reference Id: PHARMATUTOR-ART-1141. Available from: http://www.pharmatutor.org/articles/method development and validation of quetiapine fumarate by rp hplc method.
40. Rao MVB, Nagendrakumar AVD. Validated RP-HPLC method for the estimation of quetiapine in formulation. Int J Sci Inn Discov 2011;1(1):45-52.
41. Jadhav SA, Landge SB, Shelke S, Niphade NC, Panchangam RK, Mathad VT et al. Original GC–FID determination of non-chromophoric impurities in quetiapine: An antipsychotic drug. Chromatographia 2010;71(11-12):1055-61.
42. El-Enany N, El-Brashy A, Belal F, El-Bahay N. Polarographic Analysis of Quetiapine in Pharmaceuticals. Port Electrochim Acta 2009;27(2):113-25.
43. Kanakapura VB, Hosakere RD, Nagaraju R. Potentiometric determination of quetiapine fumarate in pharmaceutical formulations. Port Electrochim Acta 2010; 28(5): 299-308.
44. Nagaraju R, Kanakapura B, Kanakapura VB. Ion-pair titrimetric assays of quetiapine fumarate in pharmaceuticals using sodium tetraphenylboron and sodium lauryl sulphate. Thai J Pharm Sci 2011;35:89-97.
45. Nagaraju R, Kanakapura B, Kanakapura VB. Sensitive and selective extraction-free spectrophotometric determination of quetiapine fumarate in pharmaceuticals using two sulphonthalein dyes. J Pre-Clin & Clin Res 2010;4(1):24-31.
46. Mandrioli R, Fanali S, Ferranti A, Raggi MA. HPLC analysis of the novel antipsychotic drug quetiapine in human plasma. J Pharm Biomed Anal 2002;30: 969- 77.
47. Davis PC, Wong J, Gefvert O. Analysis and pharmacokinetics of quetiapine and two metabolites in human plasma using reversed-phase HPLC with ultraviolet and electrochemical detection. J Pharm Biomed Anal 1999;20:271–282.
48. Kundlik ML, Kambli S, Shah V, Patel Y, Gupta S, Sharma R et al. Quantification of quetiapine in human plasma by LC–MS–MS. Chromatographia 2009;70 (11-12): 1587-92.
49. Davis PC, Bravo O, Gehrke M, Azumaya C. Development and validation of an LC–MS/MS method for the determination of quetiapine and four related metabolites in

human plasma. J Pharm Biomed Anal 2010;51:1113–9.

50. Barrett B, Holˇcapek M, Huclov´a J, Boˇrek-Dohalsk´y V, Fejt P, Nˇemec B et al. Validated HPLC–MS/MS method for determination of quetiapine in human plasma. J Pharm Biomed Analy 2007;44:498-505.
51. Pan R, Kuo B, Pao L. Validated LC–MS-MS method for the determination of quetiapine in human Plasma: Application to a pharmacokinetic study. J Chromatogr Sci 2012;50:277-82.
52. Nirogi R, Bhyrapuneni G, Kandikere V, Mudigonda K, Ajjala D, Mukkanti K. Sensitive liquid chromatography tandem mass spectrometry method for the quantification of quetiapine in plasma. Biomed Chromatogr 2008;22:1043-55.
53. Pullen RH, Palermo KM, Curtis MA. Determination of an antipsychotic agent (ICI 204,636) and its 7-hydroxy metabolite in human plasma by high-performance liquid chromatography and gas chromatography-mass spectrometry. J Chromatogr1992 ;573(1):49-57.
54. Zhou Z, Li X, Li K, Xie Z, Cheng Z, Peng W et al. Simultaneous determination of clozapine, olanzapine, risperidone and quetiapine in plasma by high-performance liquid chromatography–electrospray ionization mass spectrometry. J Chromatogr B 2004;802:257–62.
55. Mercolini L, Grillo M, Bartoletti C, Boncompagni C, Raggi MA. Simultaneous analysis of classical neuroleptics, atypical antipsychotics and their metabolites in human plasma. Anal Bioanal Chem 2007;388:235-43.
56. Saracino MA, Mercolini L, Flotta G, Albers LJ, Merli R, Raggi MA. Simultaneous determination of fluvoxamine isomers and quetiapine in human plasma by means of high-performance liquid chromatography. J Chromatogr B 2006;843:227-33.
57. Belal F, Elbrashy A, Eid M, Nasr JJ. Stability-indicating HPLC method for the determination of quetiapine: Application to tablets and human plasma. J Liq Chromatogr Rel Tech 2008;31(9):1283-98.
58. Lin S, Chang Y, Moody DE, Foltz R. 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. J Analy Toxicol 2004; 8: 443-8.

59. Tu J, Xu P, Xu D, Li H. UPLC–MS–MS analysis of quetiapine and its two active metabolites, 7-Hydroxyquetiapine and 7-Hydroxy-*N*-dealkylquetiapine, in rat plasma and cerebrospinal fluid. Chromatographia 2008;68(7-8):525-32.
60. Hasselstrom J, Linnet K. Fully automated on-line quantification of quetiapine in humanserum by solid phase extraction and liquid chromatography. J Chromatogr B 2003;798:9-16.
61. Frahnert C, Rao ML, Grasmader K. Analysis of eighteen antidepressants, four atypical antipsychoticsand active metabolites in serum by liquid chromatography: a simple tool for therapeutic drug monitoring. J Chromatogr B 2003;794:35-47.
62. Kirchherr H, Kuhn-Velten WN. Quantitative determination of forty-eight antidepressants and antipsychotics in human serum by HPLC tandem mass spectrometry: A multi-level, single-sample approach. J Chromatogr B 2006;843:100-13.
63. Sachse J, Koller J, Sebastian Hartter S, Hiemke C. Automated analysis of quetiapine and other antipsychotic drugs in human blood by high performance-liquid chromatography with column-switching and spectrophotometric detection. J Chromatogr B 2006;830:342-8.
64. Atanasov VN, Kanev KP, Mitewa M. Detection and identification of atypical quetiapine metabolite in urine. Cent Eur J Med 2008;3(3):327-31.
65. Kanakapura VB, Hosakere RD. Spectrophotometric determination of quetiapine fumarate in pharmaceuticals and human urine by two charge-transfer complexation reactions.
66. Nagaraju R, Kanakapura B, Kanakapura VB. Extractive spectrophotometric determination of quetiapine fumarate in pharmaceuticals and human urine using calmagite as an ion-pair reagent. Chem Ind Chem Eng Q 2011;17(3):259-67.
67. Nagaraju R, Kanakapura B, Kanakapura VB. Extractive spectrophotometric determination of quetiapine fumarate in pharmaceuticals and spiked human urine. Croat Chem Acta 2012; 85(1):9-17.
68. Bellomarino SA, Brown AJ, Conlan XA, Barnett NW. Preliminary evaluation of monolithic column high-performance liquid chromatography with tris(2,2'-bipyridyl)ruthenium(II) chemiluminescence detection for the determination of quetiapine in human body fluids. Talanta 2009;77:1873-6.

69. Ozkan SA, Dogan B, Uslu B. Voltammetric Analysis of the Novel Atypical Antipsychotic Drug Quetiapine in Human Serum and Urine. Microchim Acta 153, 27–35 (2006).
70. Saar E, Gerostamoulos D, Drummer O, Beyer J. Assessment of the stability of 30 antipsychotic drugs in stored blood specimens Forensic Sci Int 2012;215:152-8.
71. Loralie J, Langman T, Henry A. Kaliciak, and Sheila Carlyle. Fatal overdoses associated with quetiapine. J Analy Toxicol 2004;28:520-525.
72. Flarnmia DD, Valouch T, Venuti S. Tissue distribution of quetiapine in 20 cases in Virginia. J Analy Toxicol 2006;30:287-92.
73. Hopenwasser J, Mozayani A, Danielson TJ, Harbin J, Narula HS, Posey DH et al. Postmortem distribution of the novel antipsychotic drug quetiapine. J Analy Toxicol 2004;28:264-68.
74. Wise S, Jenkins AJ. Disposition of quetiapine in biological specimens from postmortem cases. J Forensic Sci 2005;50(1):1-6.
75. Anderson DT, Fritz KL. Quetiapine (Seroquel®) concentrations in seven postmortem cases. J Anal Toxicol 2000;24(4):300-4.