Review article

Quetiapine Fumarate Syntheses and Its Determination Methods in the Pharmaceutical Dosage Forms, Human Plasma and Urine by RP-HPLC and Other Analytical Techniques: A Review

Mehdi Rezaei¹, Ali Ramazani⁰, Fahimeh Hokmabadi²

¹ Department of Chemistry, University of Zanjan, P.O. Box: 45195-313, Zanjan, Iran.
² Chemistry and Chemical Engineering Research Center of Iran, P.O. Box 14335-186, Tehran 1496813151, Iran

ARTICLE INFORMATION
Received: 17 November 2017
Received in revised: 18 January 2018
Accepted: 29 January 2018
Available online: 02 April 2018

DOI:
10.22631/chemm.2018.111208.1028

ABSTRACT

Background: Quetiapine fumarate is a dibenzothiazepine derivative and it is classified as a second-generation antipsychotic drug that has been established as an effective therapy for schizophrenia and bipolar disorder. These antipsychotics have a low incidence of extrapyramidal side effects and tardive dyskinesia as compared to older antipsychotics. The advantages of the therapeutic profile of quetiapine have led to increasing the use of the clinical practice encouraging the development of new pharmaceutical preparations. Objective: The goal of this work was to recognize the synthesis and analytical deference methods of quetiapine fumarate. Methods: Generally, A precise, specific, rapid and feasible reversed-phase high-performance liquid chromatographic (RP-HPLC), UV spectrophotometric and reversed phase ultra-performance liquid chromatography (RP-UPLC) methods for the determination of an antipsychotic drug quetiapine fumarate in pharmaceuticals, spiked human urine and plasma sample have been developed and collected in this review. The methods also find applications in clinical, biological and pharmacokinetic studies of quetiapine fumarate.

KEYWORDS
Human plasma
Quetiapine fumarate
RP-HPLC
Spectrophotometry
Synthesis
Graphical Abstract

Introduction

Quetiapine, is described as 2-[2-{4-Dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl}ethoxy]ethanol hemifumarate with molecular formula C_{46}H_{54}N_{6}O_{8}S_{2} and molecular weight 883.092 g/mol (Figure 1).

Figure 1. Molecular structure of quetiapine fumarate

Quetiapine is applied for the treatment of schizophrenia and has recently received food and drug administration approval for treatment of manic depression. Affective and aggressive symptoms in schizophrenia, adolescent schizophrenia, schizoaffective disorder, bipolar affective disorder and mania, affective psychoses, behavior and symptom control in dementia could create secondary indications, but more studies are awaited. The relatively greater ability to reduce negative symptoms as compared to conventional antipsychotics provides an additional indication. Quetiapine fumarate antagonizes serotonin activity mediated by 5-HT1A and 5-HT2 receptors. With a lower affinity, this agent also reversibly binds to dopamine D1 and D2 receptors in the mesolimbic and mesocortical areas of the brain leading to decreased psychotic effects, such as
hallucinations and delusions. In addition, quetiapine fumarate also binds to other alpha-1, alpha-2 adrenergic and histamine H1 receptors [1, 2]. A few analytical methods have been reported for the determination of quetiapine fumarate in pure drug, pharmaceutical dosage forms and biological samples using spectrophotometry [3, 4], liquid chromatography [5-19], high performance thin layer chromatography [20, 21], gas chromatography [22], electrophoresis [23, 24] and polarography [25]. None of the analytical methods can separate all the known related compounds and degradation impurities of quetiapine dosage form. Quetiapine pharmaceutical formulation is also not official in any pharmacopoeia yet. Furthermore, there is no less time-consuming and stability-indicating RPUPLC method reported in the literature that can adequately separate all the substance and accurately quantify quetiapine in solid oral dosage form. Also, the cost of the analysis using LCMS, GC/MSD and LC-MS-MS is very high [26].

Synthesis and Purification

Sarita S. Pawar; Dibenzothiazepine as conjugated heterocyclic ring systems were reported for their wide spectrum of pharmacological activity especially for their psychotherapeutic activities. Successful introduction of quetiapine, tianeptine, clozapine for antipsychotic activity along with its evidence for other biological activity proved potential of dibenzothiazepine moiety. Subsequently, dibenzodiazepine were highlighted as important biologically active scaffolds. The discovery of quetiapine fumarate as psychotropic agents attracted much attention worldwide. The current review article focuses on pharmacological and synthetic profile of dibenzothiazepine. This article mainly outlines some structural modifications done on dibenzothiazepine to offer newer derivatives with potential biological activity. Warawa and Migler (1989) reported the synthesis of 11-[4-[2-(2-Hydroxyethoxy) ethyl]-1-piperazinyl]-dibenzo[b,f][1,4]thiazepine. According to this method, 2-Amino diphenylsulfide and phenyl chloroformate in toluene and alkali were reacted to afford urethane, phenyl 2-(phenylthio)phenylcarbamate which when heated with polyphosphoric acid gave dibenzo [b,f][1,4] thiazepine-11(10-H) one. Dibenzo[b,f][1,4]thiazepine-11(10-H) and POCl₃ were reacted in the presence of N,N-dimethyl aniline to give the imino chloride (92.6%). Piperazine in toluene and 11-chloro-dibenzo[b,f][1,4]thiazepine were added together and refluxed in order to give an oil which was treated with a solution of hydrogen chloride in ethanol to get 11-Piperazinyl dibenzo[b,f][1,4]thiazepine as dihydrochloride salt (88%). This salt, sodium carbonate, sodium iodide and 2-chloroethoxyethanol were combined together in npropanol and N-methyl
pyrrolidone to give oil which was isolated as the hemi-fumarate salt [27, 28].

Figure 2. Quetiapine synthesis of dibenzo[b,f][1,4]thiazepine-11(10-H)-one and POCl₃

Moreover, in another method dibenzo[b,f][1,4]thiazepinone was converted to dibenzo[b,f][1,4]thiazepinone-11(10H)-thione with P₂S₅ which on treatment with alkyl halide get corresponding sulfanyl derivative. This on further reaction with 1-(2-(2-hydroxyethoxy) ethyl) piperazine afforded quetiapine [27-29] (Figure 3).

Figure 3. Quetiapine synthesis of dibenzo[b,f][1,4]thiazepine-11(10-H)-one and P₂S₅

Venkata Ramana Kandula; Simple one pot synthetic pathway is described for Dibenzo [b,f] [1,4] thiazepin-11[10H]-one as an advanced intermediate in the synthesis of quetiapine (Figure 4). The procedure starts from 2-(phenylthio) aniline and involves two simple insitu steps in one pot to give dibenzo [b,f][1,4] thiazepin-11[10H]-one [30-33].
Kansal et al provided a novel synthesis of quetiapine and pharmaceutically acceptable salts thereof in which an alkali metal halide or silyl halide is involved in the reaction mixture. In one embodiment, the present invention provides a method for preparing quetiapine comprising: reaction of 11-chlorodibenzo[b,f][1,4]-thiazepine with 1-(2-hydroxyethoxyethyl)piperazine in a reaction solvent selected from the group consisting of C5 to C12 saturated or aromatic hydrocarbons, C1 to C4 alcohols, C1 to C4 alkyl esters, C2 to C8 ketones, C2 to C8 linear, branched or cyclic or acyclic ethers, C3 to C10 alkyl esters, and C1 to C4 alkyl nitriles, or mixtures thereof in the presence of at least one organic or inorganic base and an alkali metal halide or a silyl halide in order to obtain quetiapine and recovering the obtained quetiapine. In other words, the present invention relates to a method of preparing a pharmaceutically acceptable salt of quetiapine comprising and combining an acid with the quetiapine prepared according to the process described above, and also recovering the obtained pharmaceutically acceptable salt of quetiapine. Preferably, the pharmaceutically acceptable salt is quetiapine fumarate, and the acid is fumaric acid [35].

Grumann et al; The present invention which reports a process for preparing and purifying crystalline quetiapine hemifumarate explains preparing crystalline quetiapine hemifumarate via a crystalline salt, which is not a salt of fumaric acid. Applicants have discovered that it is possible to improve the purity of quetiapine hemifumarate significantly if it is first crystallized as a different salt and then converted to the hemifumarate. Moreover, the term different salt or first salt is used, here, to refer to any other salt of quetiapine than the salts of fumaric acid.
Preparation of Quetiapine Hydrochloride From Quetiapine Fumarate:

**Method 1:** Crude quetiapine fumarate 10 g which was suspended to ethanol (20 ml) and heated at 60° C. 15 w-% Ethanol-HCl solution (8 ml) was added to the stirred mixture at 60° C. The mixture was stirred until all solid material was dissolved, and then it was stirred at 60° C. for 30 min. The reaction mixture was cooled to 0° C., cooling rate 10° C./h and stirred 1 h at 0° C. Quetiapine hydrochloride crystals were collected by filtration and washed once with cold ethanol. The product 7.95 g was obtained as white crystals having HPLC purity of 99.98%, critical impurity was not detected.

**Method 2:** Crude quetiapine fumarate was suspended to isopropanol (30 ml) and heated at 70° C. It is worth mention that 30 w-% HCl solution (2.5 ml) was added to stirred reaction mixture at 70° C. The mixture was stirred until all solid material was dissolved and stirred at 70° C. for 30 min. The reaction mixture was cooled to 0° C., cooling rate 10° C./h and stirred 1 h at 0° C. Quetiapine hydrochloride crystals were collected by filtration and washed once with cold isopropanol to obtain 8.28 g white crystals having HPLC purity of 99.89%, critical impurity was not detected.

Preparation of Quetiapine Hydrochloride From Quetiapine Free Base:
Quetiapine base 8 g was dissolved to ethanol 16 ml and heated to reflux. Ethanol-HCl solution 15 w-% 5 g was added to hot ethanol quetiapine mixture and allowed to cool to 0° C. Cooling rate was 10° C./h and the mixture was stirred for 1 h at 0° C. The crystals were filtered off and dried. The yield of quetiapine hydrochloride was 6.0 g and HPLC purity 99.65%. Critical impurity was not detected.

Conversion of quetiapine hydrochloride to quetiapine fumarate:
Quetiapine hydrochloride (6 g) was added to a mixture of water (10 ml) and methanol (10 ml). The mixture was stirred for 10 min to dissolve solid material. Toluene 30 ml was added and the pH of the solution was adjusted to 13-14 by addition of 50% NaOH solution. The mixture was heated to 40-50° C. and stirred for 10 min. The toluene phase was separated and washed once with water (10 ml). The toluene solution was evaporated under reduced pressure. The remaining residue was dissolved to 80% ethanol (24 ml) and fumaric acid (0.85 g) was added to the solution. The mixture was heated to reflux for 10 min and cooled to 0° C. The solid material was filtered to give pure white crystals of quetiapine fumarate 4.92 g.

Conversion of Quetiapine Free Base to Quetiapine Tosylate:
Solution of toluenesulfonic acid monohydrate (1.13 g) in acetone (10 ml) was added to quetiapine base (prepared from 2.61 g of hemifumarate HPLC purity 99.40 and the amount of critical impurity was 0.13%) dissolved in toluene (155 ml) under stirring. The formed oily mixture was slightly
warmed to dissolve the oil and left at room temperature for 4 h and then at 0° C. overnight. The precipitate was filtered off to obtain quetiapine tosylate salt in 3.05 g amount [36].

**Analytical Method Oligiesin the Pharmaceutical Doseage Forms:**

Raju Chandra et al; A reliable and reproducible reversed-phase high performance liquid chromatography (RP-HPLC) was developed for the quantitative 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 quantifies UV detector at 359 nm. The retention time of quetiapine fumarate is 5.27 min. A good linearity relation ($r^2=0.999$) was obtained between drug concentration and average peak areas. The limit of detection and limit of quantification of the instrument were calculated 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 international conference harmonization guidelines [37].

P. Nagaraju; A simple, rapid, accurate and precise RP-HPLC method was developed for the determination of quetiapine fumarate in tablet dosage forms. Separation of the drug was performed on isocratic Shimadzu prominence HPLC instrument on a Waters Xterra C18 column (250 × 4.6 mm, 5μ). The method showed a linear response for concentration in the range of 50–150 μg/ml using buffer (9.2 ± 0.05) and acetonitrile in the ratio of 51:49 v/v with detection at 254 nm with a flow rate of 1.0 ml/min and retention time was 6.588 min. The method was statistically validated for linearity, accuracy, precision and selectivity. Quantitative and recovery studies of the dosage form were also carried out and analyzed, the %RSD from recovery studies was found to be less than 1.0 [38].

Sawsan et al; Two chromatographic methods were developed for determination of quetiapine fumarate in the presence of three related compounds; namely quetiapine N-oxide, des-ethanol quetiapine and quetiapine lactam, in pure form and pharmaceutical preparation. The first method depended on densitometric thin layer chromatography in which the separation was achieved using silica gel 60F$_{(254)}$ plates as stationary phase and toluene:1,4-dioxane:dimethylamine (5:8:2, v/v/v) as a mobile phase. The second method utilized the reverse phase high performance liquid chromatographic technique, using C18 column and methanol, acetonitrile, and phosphate buffer (pH 5.3) in a ratio (19:40:41, v/v/v) as a mobile phase. The flow rate was 1.0 ml/min and UV-detection was at wavelength 220 nm. The validation parameters of the developed methods were
calculated and the obtained results were statistically compared to those of the HPLC manufacturer method [39].

Zarna Ronak; The objective of the current study was to develop a validated stability indicating assay method for quetiapine fumarate after subjecting it to forced decomposition under hydrolysis, oxidation, photolysis and thermal stress conditions. The liquid chromatographic separation was achieved on a symmetry achieved on a C18 column (250 × 4.6 mm i.d., 5 μm) using methanol, acetonitrile, and water (67:16:17) at a flow rate of 1 ml/min at ambient temperature with retention time 5.35 min. at 220 nm detection wavelength. The method was linear in concentration range 10-50 μg/ml ($r^2 = 0.998$) with a limit of detection and quantitation of 3.27 μg/ml and 9.92 μg/ml, respectively. The method was validated with respect to linearity, precision (including intermediate precision), accuracy and specificity. The %RSD values for inter-day and intra-day precision studies were < 1.15 % and < 1.02 %, respectively. The recovery of the drug ranged 99.68 ± 1.67 % to 100.37 ± 1.34 % from pharmaceutical dosage form. Degradation products resulting from the stress studies did not interfere with the detection of quetiapine fumarate and the assay is thus stability-indicating [40].

Kumar et al; This study was designed to develop and validate a simple, sensitive, precise, and specific stability indicating reverse phase high-performance liquid chromatographic (HPLC) method for estimation of quetiapine fumarate in bulk and tablet dosage form. The HPLC separation was carried out by reverse phase chromatography on Thermo column Symmetry C18 (4.6 × 150 mm, 5 μm) with a mobile phase composed of sodium dihydrogen phosphate and the pH adjusted to 4.0 by orthophosphoric acid & Methanol in the ratio of 35:65 v/v in isocratic mode at a flow rate of 1.0 ml/min. The run time was maintained for 6 mins. The detection was monitored at 290 nm. The calibration curve for quetiapine fumarate was linear from 20 to 60 μg/ml. The inter-day and intra-day precision was found to be within the limits. The proposed method was adequate sensitive, reproducible, and specific for the determination of quetiapine fumarate in bulk and its tablet dosage forms. The limit of detection (LOD) and limit of quantification (LOQ) for quetiapine fumarate were found to be 0.01 μg/ml and 0.03 μg/ml respectively. The accurate recoveries were 100.0-100.4% and reproducibility was found to be satisfactory. The bulk active pharmaceutical ingredient was subjected to thermal, photolytic, hydrolytic (acidic and basic) and oxidative stress conditions and stressed samples were analyzed by the proposed method. The method was validated in terms of linearity, precision, accuracy, specificity and robustness. All the validation was done as per ICH guidelines. The proposed method was simple, fast, accurate, and precise for the
quantification of quetiapine fumarate in the dosage form, bulk drugs and also for routine analysis in quality control [41].

Macharla Gouthami et al; A simple, specific, accurate, rapid, inexpensive isocratic Reversed Phase-High Performance Liquid Chromatography (RP-HPLC) method was developed and validated for the quantitative determination of quetiapine fumarate in pharmaceutical tablet dosage forms. RP-HPLC method was developed using Welchrom C18 Column (4.6 × 250 mm, 5 µm), Shimadzu LC-20AT Prominence Liquid Chromatograph. The mobile phase was composed of 10 mM Phosphate buffer (pH 3.0, adjusted with triethylamine): acetonitrile (50:50 v/v). The flow rate was set to 1.0 ml/min with the responses measured at 230 nm using Shimadzu SPD-20A Prominence UV-Vis detector. The retention time of quetiapine fumarate was found to be 3.260 minutes. Linearity was established for quetiapine fumarate in the range of 2-10 µg/ml with correlation coefficient 0.9999. The validation of the developed method was carried out for specificity, linearity, precision, accuracy, robustness, limit of detection, and limit of quantitation. The developed method can be used for routine quality control analysis of quetiapine fumarate in pharmaceutical tablet dosage form [42].

Lakshmi et al; A new simple, sensitive, precise and accurate high performance liquid chromatography method has been established and validated for analysis of quetiapine fumarate in bulk and tablet dosage form. This study was designed to develop and validate high performance liquid chromatographic method for estimation of quetiapine fumarate from bulk and tablet dosage form. The separation was achieved on a C18 column using a mixture of phosphate buffer, acetonitrile and methanol in the ratio 50:40:10 v/v/v with a flow rate of 1 ml/min and detection wavelength at 245 nm. The method was validated for linearity, accuracy, precision and specificity as per ICH guidelines. The developed and validated method was successfully used for the quantitative analysis of commercially available dosage form. The retention time of quetiapine fumarate was found to be at 5.08 min. Linearity of the method was found to be in the concentration range of 10-80 µg/ml with correlation coefficient of 0.999. Limit of detection and limit of quantification for quetiapine were found to be 18.815 and 57.016 µg/ml respectively. The high percentage of recovery and low percentage of relative standard deviation confirm the suitability of the method for the estimation of quetiapine in bulk and tablet dosage form [43].

Pramod L. Ingale et al; A new, simple, specific, sensitive, rapid, accurate and precise RP-HPLC method was developed for the estimation of quetiapine fumarate in bulk and pharmaceutical formulations. Quetiapine fumarate was chromatographed on Microsorb-MV 100-5 C-18 (250 × 4.6 mm, 5 µm) column using UV detector. The mobile phase consisted of acetonitrile and phosphate buffer (pH 3.0) in the ratio of 50:50 (v/v) at a flow rate of 1.0 ml/min with detection at 292 nm. The
method was validated according to the ICH guidelines with respect to specificity, linearity, accuracy, precision and robustness [44].

Nesrin K. Ramadan et al; Five accurate, precise and sensitive methods were developed for the determination of quetiapine fumarate (QF) in the presence of its degradation product. Method (A) was based on second derivative spectrophotometry \( ^2 \text{D} \), then measured by the amplitude at 266 nm. Method (B) depended on measuring the peak amplitudes of the first derivative of the ratio spectra \( ^1 \text{DD} \) at 244, 285 and 344 nm. Method (C) was based on the separation of the drug from its oxidized degradation product followed by densitometric measurement of the intact drug band at 302 nm. The separation was carried out on Fluka TLC plates of silica gel 60 F254 using ethyl acetate/methanol/10% ammonium hydroxide (8.5:1:0.5 by volume) as a mobile phase. Method (D) was a high performance liquid chromatographic one; separation by HPLC was achieved using an Eclipse XDB C18RP-column and methanol / water in a ratio of 80:20 (v/v) as a mobile phase. The flow rate was 1 ml/min. Method (E) was based on the reaction of QF with P-Chloranilic acid (PCA) in presence of its degradation product. Linearities were obtained in concentration range 10-60 µg/ml in case of methods (A) and (B). While in case of methods (C) and (D), linearities were obtained in concentration range of 4-20 µg/band and 1-20 µg/ml respectively. While in method (E), the linearity was achieved in the range of 40-400 µg/ml. In method (A), the mean percentage recovery was 99.9 ± 0.6%. In method (B) the mean percentage recoveries were 99.9 ± 0.4%, 99.2 ± 0.8% and 99.4 ± 0.8% at 244, 285 and 344 nm respectively. Method (C) showed percentage mean recovery of 99.9 ± 0.7%, while in methods (D) and (E) were 99.8 ± 0.7% and 99.9 ± 0.4% respectively. The degradation product was obtained in oxidative stress condition, separated, and identified by IR and MS spectral analysis, from which the degradation product was confirmed, and the degradation pathway was suggested. The five methods were found to be specific for QF in presence of different concentration % of its degradation product. The proposed methods were validated according to ICH guidelines Q2 (R1). The five proposed methods were successfully applied for the determination of QF in Seroquel tablets. Statistical comparison between the results obtained by these methods and that obtained by the manufacturer method for the determination of the drug was done, and it was found that there was no significant differences between them [45].

Manal A. El-Shal; Cyclic voltammetry and differential pulse voltammetry were used to explore the diffusion behavior of two antipsychotic drugs at a glassy carbon electrode. A well-defined oxidation peak was obtained in Britton-Robinson (BR) buffer (pH 2.0). The response was evaluated as a function of some variables such as the scan rate, and pH. A simple, precise, inexpensive and sensitive voltammetric method has been developed for the determination of the cited drugs
olanzapine (OLZ) and quetiapine fumarate (QUT). A linear calibration was obtained from $3 \times 10^{-8}$ M to $4 \times 10^{-6}$ M and $2 \times 10^{-8}$ M to $5 \times 10^{-6}$ M, with RSD being 1.6 % and 1.2 % for OLZ and QUT, respectively. The limit of detection was $1 \times 10^{-8}$ M, while the limit of quantification was $3 \times 10^{-8}$ M. The method was applied to the determination of investigated drugs in urine and serum samples and dosage forms [46].

Vessali et al; The aim of this work was to develop and validate assay and dissolution tests for quetiapine fumarate in the pharmaceutical dosage using HPLC and spectrophotometric analyses. The assay method with HPLC analysis was found to be linear in the concentration range of 80 to 200 μg/ml. The validation included linearity, accuracy and precision. In addition, drug stability in medium was demonstrated. Moreover, a simple and precise UV spectrophotometric technique was used for the determination in dissolution analysis. Linear dependency of UV spectrophotometric method lies in the concentration range of 10 to 30 μg/ml. These proposed methods were sensitive, accurate, repeatable and useful for the routine determination of quetiapine in the tablets [1].

Rosa et al; A simple and sensitive high performance liquid chromatographic method has been developed for the determination of assay quantitative of related compounds and quetiapine hemifumarate in raw material and tablets. Quetiapine hemifumarate is used for the treatment of schizophrenia and there are some generic medicines available in brazilian marketing pharmaceutical, it’s significant to mention that evaluation of the quality control of raw material was used in the production. Efficient chromatographic separation was carried out on a C18 stationary phase with mobile phase consisting of a mixture of phosphate buffer pH 6.6:Acetonitrile:Methanol (45:40:15), flow rate of 1.0 ml/min, injection volume of 20 μL, temperature of 25°C and ultraviolet detection at 220 nm. All of the chromatographic parameters were attended with resolution greater than 2.9 and between quetiapine hemifumarate and impurities. The HPLC method was validated according to ICH guidelines, evaluating selectivity, limits of detection and quantification, linearity, accuracy, precision and robustness. The relative retention times were about 0.58, 0.69 and 0.88 to related compounds, piperazine, lactam and ethanol compound, respectively. Impurities were found < 0.1 % in samples and the assay of quetiapine hemifumarate was > 98.15%. The method can be used for the routine analysis of the impurities in quetiapine hemihumarate (QH) without any interference [47].

R.Valarmathi et al; Quetiapine fumerate (QTF) (bis [2-[(2-[(2-[4-(dibenzo [b,f][1,4]thiazepin-11-yl]ethoxy) ethanol]fumarate] is the most recent agent introduced on the drug market for the treatment of psychotic disorders. Spectrophotometric analytical methods for the quality control of quetiapine fumarate in two different commercial marketed tablet dosage which form (BRAND A &
BRAND B) of same strength 25 mg have been developed. The absorbance data was obtained by the measurements at selected wavelength of 290 nm using Methanol and water in the ratio 50:50v/v as solvent. Beers Lambert’s law obeyed at concentration range 15.99 - 24.09 µg/ml and concentration range of quetiapine for spectrophotometric methods at selected wavelength. The proposed method gave satisfactory results in terms of precision and repeatability for both the brands i.e. 100.41% and 99.77% respectively. Also, accuracy values were very good for both brands i.e.100 % and 99.83 % which are drawn out by recovery studies and were found to be satisfactory. The spectroscopic method have excellent linearity and range \((r^2=0.9997)\). The procedures do not require any separation step. These methods were successfully applied to any solid dosage form containing same drug and was found to be utter, swift, simple, fast, reliable, sensitive, specific and efficient for their estimation from pharmaceuticals [48].

Kiran B. Venkata et al; A rapid, specific, and accurate isocratic HPLC method was developed and validated for the assay of quetiapine fumarate in pharmaceutical dosage forms. The assay 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 in the ratio of 50:50 (v/v). The wavelength of detection is 294 nm. The method showed good linearity in the range of \(2.0-50.2 \times 10^{-3} \) g/Lt the runtime of the method is 5 mins. The developed method was applied to directly and easily 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. The excipients did not interfere in the analysis. The results showed that this method can be used for rapid determination of quetiapine fumarate in pharmaceutical tablet with precision, accuracy, and specificity [49].

Onur et al; Simple and selective-extractive spectrophotometric methods for the determination of quetiapine hemifumarate (QF) were developed and validated. The methods were based on the formation of yellow ion-pair complexes between QF and acidic dyes namely bromcresol purple (BCP) and bromcresol green (BCG) at room temperature in phosphate buffer (pH 3.0). The formed complexes were extracted with chloroform and the absorbances were measured at 406.5 nm for BCP and at 416 nm for BCG complexes. The compositions of the ion-pairs were found as 1:1 by mole-ratio method. The reaction conditions such as concentration, pH, color formation time, temperature and chromogen stability were optimized. Good linear relationship was obtained between the absorbance and the concentration of QF in the range of 0.5 - 20 µg/ml for both BCP and BCG \((r > 0.9974)\). LOD values were found as 0.12 and 0.16 µg/ml for BCP and BCG complexes,
respectively. Intra-day precisions were found less than 1% in the methods. The developed methods were applied successfully to the determination of QF in tablets marketed in Turkey [50].

Pant & Khatri; A simple, rapid, accurate and precise RP-HPLC method has been developed for estimation of quetiapine fumarate from tablet dosage form. Assay method was developed using Zorbax ODS C18, 150 mm x 4.6 mm, 5.0 μm 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. All the validation were done as per ICH guidelines [51].

Basavaiah et al; Quetiapine fumarate (QTF) is a selective monoaminergic antagonist with high affinity for the serotonin Type 2 (5HT2), and dopamine type 2 (D2) receptors. 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 μg/ml. 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 4.25×104 L mol⁻¹cm⁻¹ and the Sandell sensitivity was 0.0145 μg cm⁻². The limits of detection and quantification calculated as per the ICH guidelines were 0.07 and 0.21 μg/ml, 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. The methods have demonstrated to be simple and easy to apply in routine usage and do not need any costly instrumentation. Therefore, the proposed procedures are advantageous and can be adopted in routine quality control laboratories in the developing or under developed countries [52].

Raju et al; An LC method has been developed and subsequently validated for the determination of quetiapine fumarate and its related substances in bulk and pharmaceutical formulation. Separation was achieved in gradient mode using Kromasil 100, C18, 30 × 3.0 mm, 3.5 μm 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 1.0 ml/min. UV detection was performed at 240 nm. The method is simple, selective and stability indicating. The described method is accurate and linear over a range of about 0.052 μg/ml to 3.289 μg/ml. The method precision for the determination of related impurities was below 3.5% RSD. The Percentage recoveries of known related impurities from dosage forms ranged from 96.7 to 106.920%. LOD and LOQ of all related impurities of quetiapine fumarate was established and ranged from 0.017 μg/ml - 0.027 μg/ml for LOD and 0.052 μg/ml – 0.086 μg/ml for LOQ. The method is useful in the quality control of bulk manufacturing and also in pharmaceutical formulations [53].

Prasanth et al; A simple, sensitive, selective, economical and reproducible UV spectrophotometric method has been developed 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 in ethanol at 207 nm. Beer’s law is obeyed over the linear range 1-5 μg/ml of QTF for the method with apparent molar absorptivity value of 1434.41281 L mol⁻¹ cm⁻¹. Limits of quantification and detection are also reported. The methods were validated in accordance to 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. The Method has excellent linearity and range \( r^2 =0.998 \) [54].

Sravan kumar. et al; A simple, sensitive, rapid, robust and reproducible method for the determination of quetiapine fumarate in bulk and pharmaceutical formulation (Tablets) was developed using reverse phase high performance liquid chromatographic method (RP-HPLC). The RP-HPLC analysis was performed isocratically on XTERRA C18 (4.6 × 150 mm), analytical column using a mobile phase consisting of buffer and acetonitrile in the Ratio of 40:60v/v, with a flow rate of 0.8 ml/min. The analyte was monitored with UV detector at 294 nm. The developed method quetiapine fumarate elutes at a retention time of 2.839 min. The proposed method has linearity in the concentration range from 10 to 50 μg/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. The proposed method can be readily utilized for bulk drug and pharmaceutical formulations [55].
R. K. Trivedi and M. C. Patel; The present work reports a stability indicating reversed phase ultra-performance liquid chromatography (RP-UPLC) method for the quantitative determination of quetiapine in pharmaceutical dosage form. The chromatographic separation is performed on an Agilent Eclipse Plus C18, RRHD 1.8 μm (50 mm × 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 [56].

K. Basavaiah et al; Two direct, simple, sensitive and rapid extraction-free spectrophotometric methods have been developed for the determination of quetiapine fumarate (QTF) 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 in method A and method B with apparent molar absorptivities of 2.97 × 10⁴ and 1.97 × 10⁴ L mol⁻¹ cm⁻¹, respectively. The Sandell sensitivity values, limits of detection (LOD) and quantification (LOQ) values have also been reported for both the methods. The stoichiometry of the reaction in both cases was accomplished adopting the limiting logarithmic method and was found to be 1:2 (drug:dye). The accuracy and precision of the methods were evaluated on intra-day and inter-day basis; the relative error (%RE) was ≤ 3.5% and the relative standard deviation (RSD) was < 3%. The methods were successfully applied to the determination of drug in tablets without interference by the common co-formulated substances. Statistical comparison of the results with the reference method showed good concurrence and indicated no significant difference in accuracy and precision [57].

K.B. Vinay et al; Quetiapine (QTF) is a potent serotonin and dopamine receptor antagonist used to treat major depressive disorders and schizophrenia. A simple, precise, accurate and cost effective 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 ≤ 1.2%). The accuracy was satisfactory as well (RE ≤ 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%.

K. Basavaiah et al; Quetiapine fumarate (QTF) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives indicated for the treatment of schizophrenia. It is a selective monoaminergic antagonist with high affinity for the serotonin type 2 (5HT2), and dopamine type 2 (D2) receptors. 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 μg/ml QTF 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, 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 ≤ 2.50%). The accuracy is also satisfactory (RE ≤ 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 ≤ 1.12%.

Bagade S.B.et al; Simple, fast and reliable derivative Spectrophotometric methods were developed for determination of quetiapine fumarate in pharmaceutical formulation. Second order derivative ultraviolet spectrophotometric methods were developed. Spectrophotometrically, quetiapine fumarate was determined by measuring the 2D-values at 254.76 nm with 0.1 N HCl as background solvent. Analytical Calibration curves were linear within a concentration range from 10 to 30 μg/ml. The developed method was applied to directly and easily to the analysis of the pharmaceutical tablet preparations. RSD 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. The results showed that this method can be used for rapid determination of quetiapine fumarate in pharmaceutical tablet with precision, accuracy and specificity [60].

S. Radha Krishna et al; A simple and accurate reverse phase liquid chromatographic method was developed for the determination of related substance and degradants of quetiapine Fumarate bulk drug used as antipsychotic agent for the management of the manifestations of schizophrenia. 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, 150 × 4.6 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 and 80 ng/ml, for Impurity-3 was 14 ng/ml and 40 ng/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. The proposed method was found to be suitable and accurate for the quantitative determination related substances and degradants during quality control of quetiapine fumarate active pharmaceutical ingredient [61].

Aanlytical Method Ligies the Human Plasma and Urine:
Khanvilkar Vineeta V et al; A simple high-performance liquid chromatographic (HPLC) method for the analysis of the antipsychotic drug quetiapine fumarate in human plasma has been developed. Zolpidem tartrate was employed as the internal standard (IS). Biological samples were pretreated by liquid-liquid extraction (LLE) technique using tert-butyl methyl ether (TBME). Separation was performed on a HiQSil C18HS (250 × 4.6 mm, 5μm) column. The mobile phase used was acetonitrile-ammonium acetate buffer (pH 3.5, 10 mM) (40:60 v/v) pumped at a flow rate of 1 ml/min. Samples were injected by means of an autosampler via a variable loop and detected using UV detector at a wavelength of 254 nm. A good linearity was found in the concentration range of 100-2000 ng/ml. Within and between batch precision and accuracy of the proposed method were evaluated by percent relative standard deviation (% RSD) and percent relative error (% RE) respectively; both being within the acceptable limits. The method was also validated for recovery,
carry-over and stability. Freeze and thaw stability, short term stability and long term stability were evaluated for the developed bioanalytical method. The described method can be applied for quantitation of quetiapine in real clinical samples [62].

Vinay et al; A precise and feasible reversed-phase high-performance liquid chromatographic method for the determination of an antipsychotic drug quetiapine fumarate (QTF) in pharmaceuticals and spiked human urine sample has been developed and validated. The analysis was carried out using a ODS (250 × 4.6 mm i.d., 5 μm particle size) chromatopack column. Mobile phase containing a mixture of acetonitrile and 0.1% phosphate buffer (pH: 3.1) (40:60) was pumped at a flow rate of 1 ml/min with UV detection at 240 nm at ambient column temperature (25 ºC). The method showed good linearity in the range of 0.09 – 18 μg/ml QTF with limits of detection (LOD) and quantification (LOQ) values of 0.03 and 0.09 μg/ml, respectively. The suggested method was successfully applied for the analysis of QTF in bulk drug, tablets and human urine with average recoveries of 100.06, 100.26 and 98.83%, respectively. The intra- and inter-day RSD values were less than 5%. The method is accurate, precise, sensitive and selective for routine analysis in quality control laboratories [63].

Vineeta Khanvilkar et al; A simple, selective and economical bioanalytical method was developed and validated for estimation of quetiapine fumarate, an antipsychotic drug using High Performance Thin Layer Chromatography from human plasma. Drug was separated from plasma using liquid-liquid extraction technique and quantitated by High performance thin layer chromatography using Zolpidem tartrate as an internal standard. Separation was performed on Silica gel 60 F254 precoated aluminium plates as stationary phase with mobile phase consisting of Ethyl acetate: Toluene: Methanol (7:2:2 v/v/v). Densitometric detection was performed at 292 nm. The method was found to be linear in the range of 300 ng/ml to 8700 ng/ml. The method was validated for linearity, accuracy, precision, recovery and selectivity and the results obtained were found to be within acceptable limits. This simple and selective method can be used for accurate and precise determination of quetiapine fumarate in clinical samples and can be applied for therapeutic drug monitoring and pharmacokinetic studies [64].

Pan et al; A sensitive and selective liquid chromatography–tandem mass spectrometry (LC–MS-MS) method for the determination of quetiapine was developed and validated over the linearity range 1– 1500 ng/ml with 0.1 ml of plasma using clozapine as the internal standard. Detection was performed on a triple-quadrupole tandem mass spectrometer using positive electrospray ionization and quantification was performed by selected reaction monitoring mode. The MS-MS ion transitions monitored were m/z 384.1 →253.1 and 327.0 →270.0 for quetiapine and clozapine,
respectively. The between- and within-run precision was less than 7.44% and accuracy was less than 10.2%. The lower limit of quantification was 1 ng/ml. The extraction recoveries of quetiapine were over 90%. The method is proved to be accurate and specific, and was applied to the pharmacokinetic study in healthy Chinese volunteers [65].

N. Rajendraprasad et al; A simple, sensitive and selective extractive spectrophotometric method for the determination of quetiapine fumarate (QTF) in bulk drug, tablets and spiked human urine sample is described. The method is based on the formation of a chloroform extractable yellow ion-pair complex between basic nitrogen of the drug (QTF) and the dye quinoline yellow (QY) in acetate-hydrochloride buffer (pH 2.56) medium. The formed ion-pair complex exhibited an absorption maximum at 420 nm. Beer’s law is followed over the concentration range 2.5–25 μg/ml with an apparent molar absorptivity value of 2.02 × 10^4 L mol⁻¹ cm⁻¹. The Sandell sensitivity, limits of detection (LOD) and quantification values are also reported. The composition of the ion-pair was established by Job’s continuous variations method and it was found to be 1:1 (QTF:QY). The proposed method was successfully applied for the determination of QTF in bulk drug, tablets and spiked human urine without any interference [66].

F.E. Estevez-Carrizo et al; Quetiapine is a dibenzothiazepine derivative that has been established as an effective therapy for schizophrenia and bipolar disorder. A new extended-release (XR) solid formulation of quetiapine was developed in the United Kingdom and a Uruguayan company has developed a branded generic version of the innovator. The goal of the present study was to evaluate the relative bioavailability of a new XR formulation of quetiapine 300 mg versus the XR reference product after the administration of a high-fat breakfast as required to assume bioequivalence according to the Uruguayan regulatory authority. This was a randomized-sequence, openlabel, 2-period crossover study performed in healthy Uruguayan volunteers with a washout period of 7 days. One tablet of quetiapine XR 300 mg (test and reference formulations) was administered as a single oral dose, and blood samples were collected over 36 hours. Plasma quetiapine concentration was measured by using HPLC. Plasma concentration-time curves were plotted for each volunteer, and AUC from 0 to 36 hours (AUC₀₋₃₆), AUC₀₋∞ C max and T max were calculated. A priori bioequivalence requirements were set to require a 90% CI of the test/reference ratios for AUC and C max values that were between 0.80 and 1.25. Adverse events were determined using clinical assessment, laboratory test results, and monitoring of vital signs throughout the study. Study subjects were asked to report any adverse events at any time during the study. Twenty-four healthy volunteers (12 men, 12 women) were enrolled and completed the study (mean [SD] age, 31 [65] years; weight, 68 [12] kg; height, 1.69 [0.09] m; body mass index, 23.7 [3.2] kg/m²). Arithmetic
Quetiapine Fumarate Syntheses...

mean (SD) of $AUC_{0-36}$, $AUC_{0-\infty}$, $C_{\text{max}}$, and $T_{\text{max}}$ were 3279 (1169) ng/ml/h, 3731 (1332) ng/ml/h, 341.5 (108.3) ng/ml, and (median [range]) 5.0 (1.5–12.0) hours, respectively, for the test formulation and 3528 (1308) ng/ml/h, 3546 (1350) ng/ml/h, 365.9 (136.4) ng/ml, and (median [range]) 5.0 (2.5–10.0) hours, respectively, for the reference formulation. The geometric mean (90% CI) for the test/reference ratio of the log-transformed $AUC_{0-36}$, $AUC_{0-\infty}$, and $C_{\text{max}}$ values were: 0.99 (0.91–1.07), 1.06 (0.95–1.18), and 0.94 (0.84–1.05), respectively. The frequency of reported adverse events was: hypotension (27%), dry mouth (27%), dizziness (10%), headache (7%), and nausea (7%). The difference between formulations was not statistically significant ($P > 0.05$). This single-dose study found that the test and reference formulations of quetiapine met the regulatory criteria for bioequivalence among healthy male and female volunteers who took the medicines after a high-fat breakfast. Both products were generally well tolerated [67].

Mahatthanatrakul et al; Quetiapine is an atypical antipsychotic indicated for the treatment of schizophrenia and related psychoses. Uses of generic drugs are essential due to economic reason. Interchangeability of drugs is determined by bioequivalence studies. We aim to study the bioequivalence of a generic quetiapine (Ketipinor®, Orion Corporation, Finland) and the innovator product (Seroquel®, AstraZeneca, UK). The study was a randomized, two-way crossover design with a two-week washout period in 24 healthy Thai male volunteers. After a single 200-mg oral dosing, serial blood samples were collected at appropriate interval up to 48 h. Plasma quetiapine concentrations were determined by using a validated LC-MS/MS method. Pharmacokinetic parameters were estimated using the WinNonlin® software with noncompartment model analysis. The mean ± SD of maximum plasma concentration ($C_{\text{max}}$), the area under the plasma concentration-time curve from 0 to 48 h ($AUC_{0-\text{last}}$) and the area under the plasma concentration-time curve from 0 to infinity ($AUC_{0-\infty}$) of Ketipinor® v.s. Seroquel® were 632.27 ± 304.43 v.s. 638.83 ± 214.49 ng/ml; 2625.21 ± 972.14 v.s. 2511.82 ± 704.21 ng.h/ml and 2640.25 ± 979.10 v.s. 2526.45 ± 704.37 ng.h/ml, respectively. The time to reach $C_{\text{max}}$ ($T_{\text{max}}$) of Ketipinor® and Seroquel® were 1.34 ± 1.11 and 1.01 ± 0.63 h., respectively. The $T_{\text{max}}$ of Ketipinor® was within the acceptance range of ±20% of the median $T_{\text{max}}$ of the reference product. The 90% confidence interval of the ratios of the log-transformed data of $C_{\text{max}}$, $AUC_{0-\text{last}}$ and $AUC_{0-\infty}$ were 80.75 - 102.60%, 91.32 - 108.42% and 88.47 - 106.77%, respectively, which were within the acceptance range of 80.00 - 125.00%. Power of the test for $C_{\text{max}}$, $AUC_{0-\text{last}}$ and $AUC_{0-\infty}$ were 92.16%, 96.34% and 95.96%, respectively. In conclusion, Ketipinor® was bioequivalent to Seroquel® in terms of both the rate and extent of absorption under fasting condition [68].
B. Barrett et al; A validated, highly sensitive and selective 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 were 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 (RSD) and the percentage of deviation, respectively; both were lower than 8%. The developed method was employed in the pharmacokinetic study of quetiapine [69].

KY Li et al; a high performance liquid chromatography-electrospray mass spectrometry (HPLC-MS/ESI) method for simultaneous determination of quetiapine and its sulfoxide-, 7-hydroxy-, 7-hydroxy-N-dealkyl-metabolites in human plasma was developed. The HPLC separation of the compounds was performed on a Kromasil C18, (250 × 4.6 mm i.d., 5 μm particle size) column, using water (formic acid: 1.70 mmol/L, ammonium acetate: 5.8 mmol/L)-acetonitrile (65:35) as mobile phase, with a flow-rate of 0.95 ml/min. The compounds were ionized in the electrospray ionization (ESI) ion source of the mass spectrometer and detected in the selected ion recording (SIR) mode. The samples were extracted using solid-phase extraction columns. The calibration curves were linear in the ranges of 10-2000 microg/L for quetiapine, 1-200 microg/L for its metabolites, respectively. The average extraction recoveries for all the four samples were above 85 %. The methodology recoveries were much higher than 95 %. The intra-day and inter-day RSD are less than 15 %. The method is accurate, sensitive, and simple for study of pharmacokinetics and metabolic mechanism of quetiapine in patients at therapeutic dose [11].

Conclusion
In the first part in this paper synthesis and purification of quetiapine fumarate are explained and in the second section, all of the routine techniques for determination of quetiapine fumarate in pharmaceutical, human plasma and urine were studied. Proposed methods found to be the simple, accurate, economic and rapid for routine estimation of the quetiapine. The methods can also be use in clinical, biological and pharmacokinetic studies of quetiapine fumarate.

References
[18]. Vijaya Kumar M., Muley P. INDIAN DRUGS-BOMBAY-, 2004, 41:272
[24]. Pucci V., Mandrioli R., Ferranti A., Furlanetto S., Raggi M.A. *Journal of pharmaceutical and biomedical analysis*, 2003, **32**:1037


[26]. ICH, “Validation of Analytical Procedure, Text and Methodology” Q2(R1), International conference on Harmonization, IFPMA, Geneva, Switzerland, **2005**.

[27]. Pawar S.S. *Int J Pharm Bio Sci*, 2013, **4**:68


[34]. Kandula V.R. *Hetero letters.*, 2014, **4**:331


[37]. Chandra R., Sanghi A., Kumar D., Kumar Bharti Bhart A. *Journal of Chemical and Pharmaceutical Research*, 2016, **8**:142

[38]. Nagaraju P. *Pharm Methods*, 2015, **6**:105

[39]. Sawsan M., Hesham S., Marianne N., El-Maraghy M. *Journal of Chromatography & Separation Techniques*, 2015, **6**:1


[41]. Debnath M., Rao J., Kumar S.A. *Journal of Drug Delivery and Therapeutics*, 2013, **3**:62

[42]. Gouthami M., Karthikeyan R., Babu P.S. *Int. Res. J. Pharm.*, 2013, **4**:89

[43]. Sivasubramanian L. *Int. J. Pharm. Pharm. Sci.*, 2013, **5**:269
[46]. El-Shal M.A. Advanced pharmaceutical bulletin, 2013, 3:339
[55]. Trivedi H.K., Patel M.C. Scientia pharmaceutica, 2012, 80:393
[67]. Estevez-Carrizo F.E., Parrillo S., Ercoli M.C., Estevez-Parrillo F.T. *Clinical therapeutics*, 2011, **33**:738

[68]. Mahatthanatrakul W., Pradabsang C., Sriwiriyajan S., Ridtitid W., Wongnawa M. *Basic & Clinical Pharmacology & Toxicology*, 2011, **109**:117
