

Original article

Sensitive ultraviolet spectrophotometric determination of quetiapine fumarate in pharmaceuticals

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Abstract:

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⁻¹ QTF for both the methods with apparent molar absorptivity values of 6.21 × 10⁴ and 5.93 × 10⁴ L mol⁻¹cm⁻¹ for method A and method B, respectively. Sandell sensitivity, limits of quantification (LOQ) and detection (LOD) are also reported. The methods were validated in accordance with the current ICH guidelines. The precision results, expressed by intra-day and inter-day relative standard deviation values, are satisfactory (RSD ≤ 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%.

Keywords: Determination; Pharmaceuticals; Quetiapine fumarate; Spectrophotometry

Introduction

Quetiapine fumarate (QTF) is chemically known as 2-(2-(4-dibenzo[b,f] [1, 4] thiazepine-11-yl-1-piperazinyl)ethoxy)ethanol fumaric acid (1 : 2 salt) (Figure 1). QTF was introduced in the clinic as a new antipsychotic drug for the treatment of schizophrenia and other psychotic [1, 2] or schizoaffective disorders [3]. QTF belongs to the same family as clozapine and olanzapine, which are classified as “atypical” antipsychotics [4] and do not cause major extrapyramidal side effects. QTF is effective in the treatment of schizophrenia, treating both the positive and negative symptoms [1-3].

Many methods have been used to determine QTF in biological materials including HPLC with UV [5-12], chemiluminescence [13], electrospray ionization MS [14-17], tandem MS/MS [18-20], UPLC with tandem MS [21, 22], GC [23, 24] and voltammetry [25]. QTF is not official in any pharmacopoeia. Methods based on different techniques such as polarography [26], capillary zone electrophoresis [27, 28], HPTLC [29, 30], HPLC [31-33] and UV spectrophotometry [27, 34] have earlier been employed for the determination of QTF in pharmaceuticals.

Pucci *et al.* [27] have reported a spectrophotometric method for the determination of QTF after converting the drug into its free base by using 50 mM phosphate buffer (pH 2.5) as diluent. The assay was carried out by measuring the absorbance of quetiapine free base solution at 246 nm. The linearity was observed in the range of 5-25 $\mu\text{g mL}^{-1}$ QTF. The UV spectrophotometric method developed by Fursule *et al.* [34] involved the

measurement of QTF at 290 nm in water and Beer's law was obeyed in the range, 6-54 $\mu\text{g mL}^{-1}$. Both the reported spectrophotometric methods [27, 34] were less sensitive.

The aim of our work was to develop simple and sensitive spectrophotometric methods for the quantitative determination of QTF in bulk drug and in tablets. 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). The methods were optimized in accordance with the current ICH guidelines [35].

Materials and Methods

Instrument

The spectrophotometric measurements were carried out using Shimadzu Pharmaspec 1700 UV/Visible spectrophotometer (Shimadzu Scientific Instruments Ltd, Japan). Chromatographic analysis was carried out using Alliance Waters HPLC system equipped with Alliances 2657 series low pressure quaternary pump, a programmable variable UV-visible detector, photodiode array detector and autosampler.

Materials

All chemicals used were of analytical reagent grade. QTF pure drug (certified to be 99.85% pure) was kindly provided by Cipla Ltd, Bangalore, India, as a gift and used as received. Qutipin-200[®] (200 mg QTF; Batch No. AD82847) and Qutipin-100[®] (100 mg QTF; Batch No. AD90376) were manufactured from Sun Pharmaceuticals Ltd, India, and were purchased from a local market.

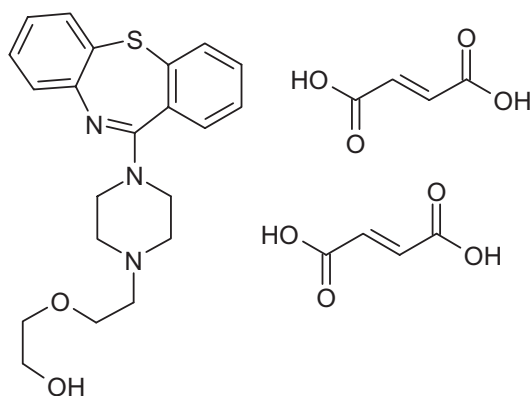


Figure 1 Chemical structure of quetiapine fumarate (QTF)

Reagents and solutions

Hydrochloric acid (0.1 N) was prepared by successive dilutions of appropriate volume of concentrated acid (S.D. Fine Chem, Mumbai, India, sp. gr. 1.18) in water. Methanol AR (S.D. Fine Chem, Mumbai, India) was used as solvent in the present study.

Standard drug solution

Standard drug solutions of $25 \mu\text{g mL}^{-1}$ QTF in 0.1 M HCl and methanol were prepared separately and used for assay in method A and method B, respectively.

Recommended procedures

Calibration curves

Method A

Varying aliquots (0.2, 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 mL) of working standard solution corresponding to 0.5-12.5 $\mu\text{g mL}^{-1}$ QTF were taken in a series of 10 mL volumetric flasks and volume was made upto mark with 0.1 N HCl. The absorbance of each solution was measured at 209 nm against 0.1 N HCl.

Method B

Into a series of 10 mL calibration flasks, aliquots of QTF standard solution ($25 \mu\text{g mL}^{-1}$) equivalent to 1.25-12.5 $\mu\text{g mL}^{-1}$ QTF were accurately transferred and volume was made upto mark with methanol. The absorbance of each solution was measured at 208 nm against methanol.

In both cases, calibration curves were prepared and the concentration of the unknown was read from the respective calibration curve or computed from the regression equation derived using the Beer's law data.

Procedure for tablets

Method A

Weighed amount of tablet powder equivalent to 10 mg of QTF was transferred into a 100-mL volumetric flask. The content was shaken well with about 50 mL of 0.1 N HCl for 20 min. The mixture was diluted to the mark with the same acid. It was filtered using Whatman No. 42 filter paper. First 10 mL portion of the filtrate was discarded and a subsequent portion was diluted to get

a working concentration of $25 \mu\text{g mL}^{-1}$ and subjected to analysis by taking 3 or 4 mL and following the procedure described earlier.

Method B

Tablet powder equivalent to 10 mg of QTF was transferred into a 100 mL volumetric flask. The content was shaken well with about 50 mL of methanol for 20 min and diluted to the mark with the same solvent. It was filtered using Whatman No. 42 filter paper. First 10 mL portion of the filtrate was discarded and subsequent portion was analyzed after dilution to $25 \mu\text{g mL}^{-1}$ QTF with methanol.

Reference HPLC method

A quantity of tablet powder containing 25 mg QTF was dissolved ultrasonically and diluted to 50 ml with methanol. The solution was filtered through a $0.45 \mu\text{m}$ filter membrane and a 1 ml portion of the filtrate was diluted to 10 ml with methanol. A $10 \mu\text{L}$ portion of the above solution was injected and analyzed on a $5 \mu\text{m}$ Hypersil ODS-C18 column (25 cm x 4.6 mm i.d.), with methanol and 0.5% triethylamine (39:11, pH 7-8) as mobile phase at a flow rate of 1 mL min^{-1} and UV detection was made at 254 nm.

Results and Discussion

Spectral characteristics

QTF dissolved in 0.1 N HCl exhibited an absorption maximum at 209 nm whereas the methanolic solution was peaked at 208 nm (Figure 2), and the corresponding blank solutions had insignificant absorbance.

Method Validation

Linearity, sensitivity, limits of detection and quantification

A linear correlation was found between absorbance at λ_{max} and concentration of QTF in the ranges given in Table 1. The graphs are described by the regression equation:

$$Y = a + bX$$

,where Y = absorbance of 1-cm layer of solution; a = intercept; b = slope and X = concentration in $\mu\text{g mL}^{-1}$. Regression analysis of the Beer's law data using

the method of least squares was made to evaluate the slope (b), intercept (a) and correlation coefficient (r) for each system and the values are presented in Table 1. A plot of log absorbance versus log concentration yielded straight lines with slope equal to 0.960 and 1.01 for method A and method B, respectively, further establishing the linear relation between the two variables. The optical characteristics such as Beer's law limits, molar absorptivity and Sandell sensitivity

values [36] of both the methods are also given in Table 1. The limits of detection (LOD) and quantitation (LOQ) calculated according to ICH guidelines [35] using the formulae: $LOD = 3.3 S/b$ and $LOQ = 10 S/b$, where S is the standard deviation of blank absorbance values, and b is the slope of the calibration plot, are also presented in Table 1. The high values of molar absorptivity (ϵ), low values of Sandell sensitivity and LOD indicated the high sensitivity of the proposed methods [35, 36].

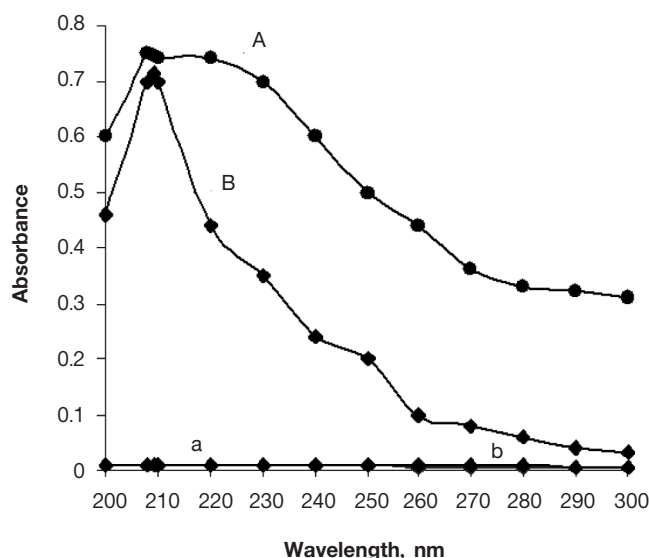


Figure 2 Absorption spectra of A: $7.5 \mu\text{g mL}^{-1}$ QTF in 0.1 N HCl; B: $7.5 \mu\text{g mL}^{-1}$ 1QTF in methanol; a: 0.1 N HCl and b: methanol.

Table 1 Sensitivity and regression parameters

Parameter	Method A	Method B
λ_{max} , nm	209	208
Linear range, $\mu\text{g mL}^{-1}$	1.25-12.5	1.25-12.5
Molar absorptivity(ϵ), $\text{L mol}^{-1} \text{cm}^{-1}$	6.21×10^4	5.93×10^4
Sandell sensitivity*, $\mu\text{g cm}^{-2}$	0.0099	0.0104
Limit of detection (LOD), $\mu\text{g mL}^{-1}$	0.02	0.02
Limit of quantification (LOQ), $\mu\text{g mL}^{-1}$	0.07	0.07
Regression equation, Y^{**}		
Intercept (a)	0.0199	-0.0050
Slope (b)	0.0971	0.0972
Standard deviation of a (S_a)	0.0111	0.0092
Standard deviation of b (S_b)	0.0014	0.0012
Variance (S_a^2)	1.23×10^{-4}	8.5×10^{-5}
Regression coefficient (r)	0.9997	0.9998

*Limit of determination as the weight in μg per mL of solution, which corresponds to an absorbance of

A = 0.001 measured in a cuvette of cross-sectional area 1 cm^2 and $l = 1 \text{ cm}$

** $Y = a + bX$, where Y is the absorbance, X is concentration in $\mu\text{g mL}^{-1}$, a is intercept, b is slope

Precision and accuracy

The assays described under “general procedures” were repeated seven times within the day to determine the repeatability (intra-day precision) and five times on five different days to determine the intermediate precision (inter-day precision) of the methods. These assays were performed for three levels of analyte. The results of this study are summarized in Table 2. The percentage relative standard deviation (%RSD) values were $\leq 1.98\%$ (intra-day) and $\leq 2.50\%$ (inter-day) indicating high precision of the methods. Accuracy was evaluated as percentage relative error (RE) between the measured mean concentrations and taken concentrations for QTF. Percent relative error (%RE) values of $\leq 2.50\%$ demonstrated the high accuracy of the proposed methods.

Selectivity

A systematic study was performed to determine the effect of matrix by analyzing the placebo blank and synthetic mixture containing QTF. A placebo blank of the composition: starch (10 mg), acacia (15 mg), hydroxyl cellulose (10 mg), sodium citrate (10 mg), talc (20 mg), magnesium stearate (15 mg) and sodium alginate (10 mg) was made and its solution was prepared as described under ‘tablets’, and then subjected to analysis. The absorbance of the placebo solution in each case was almost equal to the absorbance of the blank which revealed no interference. To assess the role of the inactive ingredients on the assay of QTF, a synthetic mixture

was separately prepared by adding 10 mg of QTF to the placebo mentioned above. The drug was extracted and solution prepared as described under the general procedure for tablets. The solutions after appropriate dilution were analyzed following the recommended procedures. The absorbance values resulting from 2, 6 and $10 \mu\text{g mL}^{-1}$ QTF solution in both the methods had nearly the same as those obtained for pure QTF solutions of identical concentrations. (The percentage recovery values of QTF obtained from this study were in the range from 99.32 to 102.54). This unequivocally demonstrated the non-interference of the inactive ingredients in the assay of QTF. Further, the slopes of the calibration plots prepared from the synthetic mixture solutions were about the same as those prepared from pure drug solutions.

Ruggedness

Method ruggedness was demonstrated having the analysis done by four analysts, and also by a single analyst performing analysis on four different instruments in the same laboratory. Intermediate precision values (%RSD) in both instances were in the range 1.65-2.89% indicating acceptable ruggedness [35]. The results are presented in Table 3.

Analysis of pharmaceutical formulations

The proposed methods were applied for the quantification of QTF in commercial tablets. The results

Table 2 Evaluation of intra-day and inter-day accuracy and precision

Method	QTF taken, $\mu\text{g mL}^{-1}$	Intra-day accuracy and precision (n=7)			Inter-day accuracy and precision (n=5)		
		QTF found, $\mu\text{g mL}^{-1}$	%RE	%RSD	QTF found, $\mu\text{g mL}^{-1}$	%RE	%RSD
A	2.00	2.03	1.50	1.23	2.04	2.00	2.50
	6.00	6.05	0.83	0.99	5.89	1.83	2.30
	10.00	9.95	0.50	1.10	9.81	1.90	1.85
B	2.00	2.03	1.50	1.98	2.05	2.50	1.32
	6.00	5.93	1.17	1.56	6.12	2.00	2.12
	10.00	9.90	1.00	1.25	10.16	1.60	1.22

RE = relative error, RSD = relative standard deviation (CL = confidence limits calculated from $\text{CL} = \pm tS/\sqrt{n}$. The tabulated value of t is 2.45 and 2.77 for six and four degrees of freedom respectively, at the 95% confidence level; S = standard deviation; n = number of measurements)

were compared with those obtained using a published reference method [33]. The reference method is a liquid chromatography where QTF has been detected using UV detector at 254 nm. The assay was performed for two different brands of tablets containing 200 and 100 mg of active ingredient (Quitipin-200[®] and Quitipin-100[®]) as described in the chromatographic procedure for tablets. The percentage recovery of QTF was evaluated and it was found to be in the range 97.30-104.60. Statistical analysis of the results did not detect any significant difference between the performance of the proposed methods and reference method with respect to accuracy and precision as revealed by the Student's t-value and variance ratio F-value [37]. The results of this study are presented in Table 4.

Recovery study

To further assess the accuracy of the methods, recovery experiments were performed by applying

the standard-addition technique. The recovery was assessed by determining the agreement between the measured standard concentration and added known concentration to the sample. The test was done by spiking the pre-analyzed tablet powder with pure QTF at three different levels (50, 100 and 150%) of the content present in the tablet powder (taken) and the total was found by the proposed methods. Each test was repeated three times. In all the cases, the recovery percentage values ranged between 101.50 and 108.25% with relative standard deviation in the range 0.37-1.12%. Closeness of the results to 100% showed the fairly good accuracy of the methods. The results are shown in Table 5.

Conclusion

Two simple, sensitive UV-spectrophotometric methods for the determination of quetiapine fumarate in bulk drug and in pharmaceutical dosage forms were

Table 3 Method ruggedness expressed as intermediate precision (%RSD)

Method	QTF taken, $\mu\text{g mL}^{-1}$	Inter-analysts, (%RSD) (n=4)	Inter-instruments, (%RSD) (n=4)
A	2.00	2.58	2.89
	6.00	2.66	2.56
	10.00	1.98	2.06
B	2.00	1.65	2.25
	6.00	1.98	2.33
	10.00	2.05	2.10

Table 4 Results of analysis of tablets by the proposed methods and statistical comparison of the results with reference method [33]

Tablet brand name	Nominal amount, (mg QTF/tablet)	Found* (Percent of label claim \pm SD)		
		Reference Method [33]	Proposed methods	
Quitipin-200 [®]	200	98.40 \pm 0.62	99.40 \pm 1.18	97.30 \pm 0.86
			t = 1.62	t = 2.41
			F = 3.62	F = 1.92
Quitipin-100 [®]	100	103.30 \pm 0.76	102.50 \pm 0.92	104.60 \pm 0.82
			t = 1.50	t = 2.60
			F = 1.47	F = 1.16

*Mean value of 5 determinations

Tabulated t-value at the 95% confidence level and for four degrees of freedom is 2.77

Tabulated F-value at the 95% confidence level and for four degrees of freedom is 6.39

Table 5 Results of recovery study via standard-addition method

Tablets studied	Method A				Method B			
	QTF in tablet, $\mu\text{g mL}^{-1}$	Pure QTF added, $\mu\text{g mL}^{-1}$	Total found, $\mu\text{g mL}^{-1}$	Pure QTF recovered (percent \pm SD*)	QTF in tablet, $\mu\text{g mL}^{-1}$	Pure QTF added, $\mu\text{g mL}^{-1}$	Total found, $\mu\text{g mL}^{-1}$	Pure QTF recovered (percent \pm SD*)
Qutipin-200 [®]	3.98	2.00	6.05	103.50 \pm 0.64	4.00	2.00	6.10	105.00 \pm 0.68
	3.98	4.00	8.19	105.25 \pm 0.85	4.00	4.00	8.33	108.25 \pm 0.47
	3.98	6.00	10.10	102.00 \pm 0.38	4.00	6.00	10.40	106.67 \pm 0.72
Qutipin-100 [®]	4.10	2.00	6.16	103.00 \pm 0.73	4.18	2.00	6.21	101.50 \pm 1.03
	4.10	4.00	8.26	104.00 \pm 1.12	4.18	4.00	8.43	106.25 \pm 0.76
	4.10	6.00	10.30	103.33 \pm 0.85	4.18	6.00	10.40	103.67 \pm 0.37

*Mean value of three determinations.

developed and validated for accuracy, precision, linearity and ruggedness. The proposed methods have better linear dynamic ranges and sensitivity compared to the reported uv spectrophotometric methods [27, 34]. The methods have the advantages of simplicity without involving heating or extraction step and high sensitivity. No interference due to co-formulated substances was observed when applied to the determination in tablets. Hence, the proposed methods could be adopted for quality control in pharmaceutical industries.

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