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Isocratic ultra-performance liquid chromatographic assay of quetiapine fumarate in pharmaceuticals

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ABSTRACT

An isocratic and reversed phase ultra-performance liquid chromatographic (RP-UPLC) method has been developed for the determination of quetiapine fumarate (QTF) in bulk drug and in its tablets. The method was developed using AQUITY UPLC HSS T3 (2.1 × 50 mm, 1.8 μm) column with mobile phase consisting of 30:70 (v/v) mixture of potassium dihydrogen phosphate and dipotassium hydrogen phosphate (pH was adjusted to 6.5 with orthophosphoric acid) (mobile phase A) and methanol (mobile phase B). The UV detection of the eluted compound was made at 252 nm. The flow rate of the mobile phase was adjusted at 1.0 ml min^{-1}. The injection volume of operation was set at 5.0 μL. A linear calibration curve was obtained for the concentration range 1.0-15.0 μg ml^{-1} QTF with regression coefficient (r) value of 0.9999. The limit of detection and quantification were found 0.04 and 0.1 μg ml^{-1}, respectively, and which is at signal to noise ratio of 3 and 10. Three quality control concentrations of 7.5, 10, and 12.5 μg ml^{-1} QTF were subjected to study of accuracy and precision of the assay, and the results were satisfactory. Both within day and between days RSD were <3%. The validation of the developed method was done in accordance with the ICH guidelines. The method was successfully applied to the determination of QTF in pharmaceuticals, and no interference was observed from common pharmaceutical adjuvants in tablets. Statistical comparison of the results with those of an official method showed an excellent agreement and indicated no significant difference in precision. The stability-indicating ability of the method was studied by exposing QTF to acid and base hydrolysis, oxidation, heat, and light. The results revealed that the drug is amenable to slight degradation under oxidant-induced stress conditions but remained intact under other conditions.

INTRODUCTION

Quetiapine hemifumarate (QTF), chemically known as 1-[2-(2-hydroxyethoxy)-ethyl] -4-(dibenzo[b,f] [1,4]thiazepin-11-yl)-piperazinium hemifumarate (Figure 1), is one of the dibenzothiazepine derivatives. It is used as an atypical antipsychotic drug and is prescribed for the treatment of schizophrenia and bipolar disorders [1-3].

QTF has no official Pharmacopoeia monograph of analytical procedure for its assay in pure form and in dosage forms. However, there are many analytical methods were reported by different workers for its determination in pure form, formulations and in biological materials. Ultra-performance liquid chromatographic high-performance liquid chromatographic (UPLC) [4-11], UPLC with tandem MS detection [12,13], chemiluminescence [14], electrospray ionization MS [12,15-17], tandem MS/MS [18-21] detection, gas chromatographic [22,23], and voltammetric [24] techniques were used for assay of QTF in body fluids. QTF was assayed before by polarography [23], capillary zone electrophoresis [24,25], HPTLC [26-28], HPLC [29-33],and spectrophotometry [24,34-40] in pharmaceuticals.

UPLC is an innovative technique and which is mostly preferred technique for analysis nowadays because of decreased sample run times, lesser solvent, and significantly improved productivity than HPLC. The replacement of standard 5 μm particles in conventional HPLC column with sub 2 μm particles in UPLC has resulted in significant improvements in resolution, sensitivity, speed, and minimized band spreading.

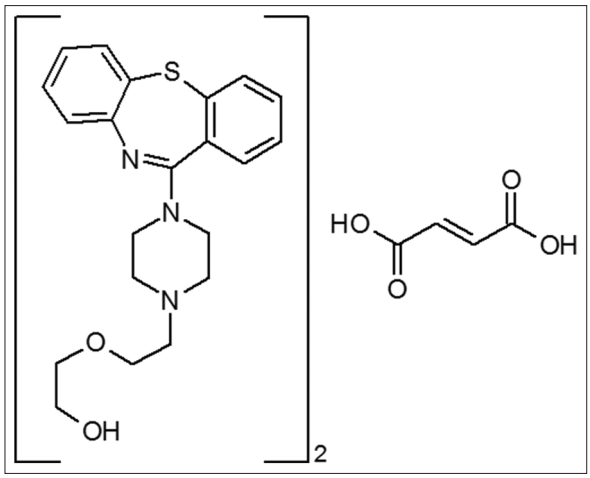

Figure 1: Structure of quetiapine fumarate

It is revealed by the literature presented above that no UPLC procedures reported so far for the assay of QTF in pharmaceuticals.

Hence, a modest attempt was made to develop and validate a sensitive, accurate and precise, and stability-indicating UPLC method for the determination of QTF in bulk drug and in its tablets.

EXPERIMENTAL

Materials

Pure (99.5% w/w) pharmaceutical grade QTF was gifted by Cipla India Ltd., Bengaluru, India. It was used without further purification. Qutipin-200 and Qutipin-100 (both from Sun Pharmaceuticals Ltd, India) tablets were purchased from local commercial sources. HPLC grade methanol was purchased from Merck India Pvt. Ltd., Mumbai, India. Potassium dihydrogen phosphate, dipotassium hydrogen phosphate, and orthophosphoric acid were from Qualigens Fine Chemicals. Mumbai, India. Doubly distilled water was used throughout the investigation.

Mobile Phase

A 1.52 g of potassium dihydrogen phosphate and 2.41 g of dipotassium hydrogen phosphate were dissolved in 1000 ml of water, and the pH was adjusted to 6.5 by adding orthophosphoric acid (mobile phase A). A 300 ml portion of this resulting buffer was mixed with 700 ml of methanol, shaken well, and filtered through 0.22 μm nylon membrane filter.

Chromatographic Conditions and Equipment

UPLC analysis was performed using a Waters Acquity system equipped with binary solvent delivery pump, an autosampler, and tunable UV detector. The output signal was monitored and processed using Empower 2 software. The chromatographic column used was Acquity UPLC HSS T3 (2.1 × 50 mm, 1.8 μm).

Chromatographic Operation

The isocratic flow rate of mobile phase was maintained at 1.0 ml min^{-1}. The column temperature was adjusted to 35°C. The injection volume was set as 5.0 μL. Eluted sample was monitored at 252 nm and the run time was 0.8 min. Under these conditions, the retention time (R_T) of the sample was found at 0.48 min.

Standard Stock QTF Solution

A 100 μg ml^{-1} stock standard solution of QTF was prepared in mobile phase, and this was subsequently diluted to 10 μg ml^{-1} in the same solvent and used for assay.

Procedures

Preparation of calibration curves

Suitable aliquots of standard stock solution were serially diluted with mobile phase to get 1 to 15 μg ml^{-1} QTF. A 5 μL volume of each was injected (six injections) and eluted with the mobile phase under the reported chromatographic conditions, and the area of the each chromatographic peak was recorded. The values of average peak area were plotted as the function of concentration of QTF in μg ml^{-1}. The regression equation was also derived using mean peak area concentration data to read out the concentration of the unknown.

Preparation of tablet extracts and assay procedure

About 20 tablets were weighed and transferred into a clean, dry mortar, and powdered. A portion of the powdered tablet equivalent to 100 mg of QTF was transferred into a 100 ml volumetric flask, and 60 ml of the mobile phase was added. The content was sonicated for 20 min to achieve complete dissolution of QTF, and the solution was then diluted to volume with the mobile phase to yield a concentration of 1000 μg ml^{-1} and filtered through q 0.22 μm nylon membrane filter. The filtrate was then subsequently diluted with the mobile phase to get 15 μg ml^{-1} solution. The solution obtained was injected to the UPLC column.

Procedure for stress study

All stress testing studies were performed at an initial drug concentration of 10 μg ml^{-1} in mobile phase. Acid and base hydrolysis were performed with 1M HCl and 1 M NaOH, respectively, in 10 ml volumetric flasks at 80°C for 2 h. Oxidative degradation was carried out at 80°C in 5% hydrogen peroxide for 2 h. The flasks were cooled, acid or base neutralized with NaOH or HCl as the case may be. All the solutions were diluted to the mark with the mobile phase, and chromatographed. For photolytic degradation, pure drug in solid state was exposed to 1.2 million lux hours in a photostability chamber. In addition, the drug powder was exposed to dry heat at 105°C for 3 h. Sample in each case was cooled and used to prepare 10 μg ml^{-1} solutions in the mobile phase and chromatographed.

Procedure for method validation

Accuracy and precision

To determine the accuracy and intraday precision, pure QTF solutions at three different concentrations were analyzed in seven replicates during the same day. The mobile phase was

injected as blank solution before sample injection, and the RSD (%) values of peak area and R_T were calculated.

Limits of detection (LOD) and quantification (LOQ)
The LOD and LOQ were obtained by signal to noise (S/N) ratio method. LOQ and LOD were obtained by a series of dilutions of the QTF stock solution. The precision study was performed at LOQ level also. LOQ solution was injected seven times (n=7) and calculated the % RSD values for the obtained peak area and R_T.

Linearity
Linearity solutions were prepared from LOQ level to 150% of the actual sample concentration. A total of five concentrations of the solutions (1.0, 2.5, 5.0, 10.0, 12.5, and 15.0 μg ml^{-1} levels) were made separately and injected in triplicate.

Robustness and ruggedness
To determine the robustness of the method the experimental conditions were deliberately changed. The flow rate of the mobile phase (1.0±0.04 ml min^{-1}), column oven temperature (35±5°C), mobile phase composition (40:60, 30:70, 50:50, and 60:40; mobile phase A: Mobile phase B v/v), and detection wavelength (252±1 nm) were the varied parameters. In each case, the %RSD values were calculated for the obtained peak area and R_T. The number of theoretical plates and tailing factors were compared with those obtained under the optimized conditions. Three different columns of same dimensions were used for the analyses. The study was performed on the same day and on three different days by three different analysts for three different concentrations of QTF (triplicates injections). The area obtained from each concentration was compared with that of the optimized one. The relative standard deviation values were evaluated for each concentration.

RESULTS AND DISCUSSION

Method Development

Different chromatographic conditions were experimented to achieve better efficiency of the chromatographic system. Parameters such as mobile phase composition, wavelength of detection, column, column temperature, pH of mobile phase, and diluents were optimized. Several proportions of buffer and solvents (water, methanol, and acetonitrile) were evaluated to obtain a suitable composition of the mobile phase. Choice of R_T, tailing, theoretical plates, and run time were the major tasks while developing the method. Alternate combinations of gradient and isocratic methods were also performed to obtain a suitable peak. Finally, isocratic method was found better to use for the assay.

When QTF solutions were injected with methanol and acetonitrile solvent mobile phases individually, the resultant peak showed either tailing or much shortened R_T factor. As the buffer ratio increased, peaks eluted with abnormal shape. Among -Acquity UPLC HSS T3 (2.1 × 50 mm, 1.8 μm), Acquity BEH C18 (50 mm × 2.1 mm, 1.7 μm), and phenyl (100 mm × 2.1 mm, 2 μm) columns used for the elution acquity UPLC HSS T3 (2.1 × 50 mm, 1.8 μm) found suitable for elution and better results were obtained. With other columns, the experiment ended with inconsistent R_T and peak fronting. The column temperature was varied from 20°C to 45°C in a 5°C increment with the same column; the peak shape was found unaltered. Buffer and methanol solvents ratio were changed and ended up with less number of theoretical plates. Different buffers such as mixture of potassium dihydrogen phosphate, dipotassium hydrogen phosphate and orthophosphoric acid (mobile phase A), sodium dihydrogen orthophosphate, dipotassium hydrogen orthophosphate, and disodium hydrogen orthophosphate of different pH were tried, and the results revealed that the use of former buffer (mobile phase A) was found most suitable. The pH of the mobile phase was varied from 2 to 9. At pH >6.5, the peak eluted very early and resulted in less number of theoretical plates. At lower and higher pH non elution of peak and inefficiency of the system, respectively, were observed. Under these optimized conditions (30:70- mobile phase A: Mobile phase B v/v, Acquity UPLC HSS T3 (2.1 × 50 mm, 1.8 μm) column, 35°C, detection at 252 nm), the system was found more suitable for the validation study with the tailing <1.2, number of theoretical plates >2000 and % RSD for peak area <1.0. Under these optimized experimental conditions, the typical UPLC chromatogram obtained for pure QTF is depicted in Figure 2.

Validation of the Method

The described method for the assay of QTF has been validated as per the current ICH Q2 (R1) Guidelines [41].

Analytical parameters

A calibration curve was obtained for QTF from 50% to 150% of its stock solution. A linear correlation was obtained between the peak area and the concentration in the range of 1.0-15 μg ml^{-1} QTF from which the linear regression equation was computed and found to be:

Y=mC+a, (r=0.9999)

Where Y is the mean peak area, C is the concentration of QTF in μg ml^{-1} and r is the correlation coefficient. The LOD and LOQ values, slope (m), y-intercept (a), and their standard deviations are evaluated and presented in Table 1. These results confirm the linear relation between the concentration of QTF and the peak areas as well as the sensitivity of the method.

Accuracy and precision

The percent relative error which is an index of accuracy is ≤2.5 and is indicative of high accuracy. The calculated percent relative standard deviation (%RSD) can be considered to be

Table 1: Linearity and regression parameters

Parameter	Value
Linear range, μg ml^{-1}	1.0-15
LOQ, μg ml^{-1}	0.10
LOD, μg ml^{-1}	0.04
Regression equation	
Slope (m)	107543.80978
Intercept (a)	−55901.87561
Correlation coefficient (r)	0.9999

LOQ: Limits of quantification, LOD: Limits of detection

satisfactory. The peak area based and R_T based RSD values were <3%. The results obtained for the evaluation of precision and accuracy of the method is compiled in Tables 2 and 3.

Robustness and ruggedness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage. At the deliberate varied chromatographic conditions (flow rate, temperature, and mobile phase composition), the analyte peak %RSD, tailing factor, and theoretical plates remained near to the actual values. The RSD values ranged from 0.1% to 1.2% resumes the robustness of the proposed method. In method ruggedness, different columns (same lot) at different day by different analyst were performed.

Application to tablet

A 10 μg ml^{-1} solution of tablets was prepared as per "preparation of tablet extracts and assay procedure" and injected in triplicate to the UPLC system. The mean peak area of the tablets extract was found to be equivalent to the pure drug, and the results were compared with those of a reference method [28]. In the reference method, the absorbance of the methanolic solution of QTF was measured at 246 nm. Statistical analysis of the results did not detect any significant difference in the performance of the proposed method to the reference method with respect to accuracy and precision as revealed by the Student's *t*-value and variance ratio *F*-value [42]. The results of this study are given in Table 4. The *t*-and *F*-values at 95% confidence level did not exceed the tabulated values and this further confirms that there is no significant difference between the reference and proposed methods.

Specificity

Specificity is the ability to respond to analyte even in the presence of its potential impurities. Forced degradation studies were performed to demonstrate the stability indicating capability of the proposed UPLC method. Significant degradation was not observed when QTF was subjected to

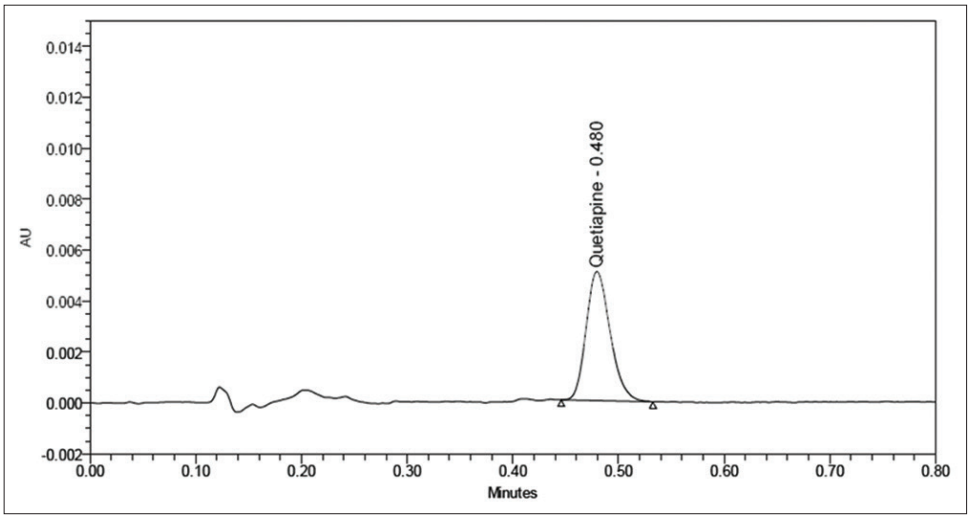

Figure 2: Ultra-performance liquid chromatographic chromatogram of quetiapine fumarate (R_T=0.480 min, run time 0.8 min)

Table 2: Results of accuracy study (*n*=7)

Concentration of QTF injected, μg ml^{-1}	Intra-day		Inter-day	
	Concentration of QTF found, μg ml^{-1}	RE[a], %	Concentration of QTF found, μg ml^{-1}	RE, %
5.0	5.11	2.20	5.12	2.49
10.0	9.88	1.19	10.25	2.50
15.0	15.13	0.87	15.22	1.44

[a]Relative error

Table 3: Results of precision study

Concentration injected μg ml^{-1}	Intra-day precision (*n*=7)			Inter-day precision (*n*=5)		
	Mean area	RSD%[a]	RSD%[b]	Mean area	RSD%[a]	RSD%[b]
5.0	2706422	1.38	2.38	2697635	1.32	2.56
10.0	5344217	2.76	0.85	5339877	1.24	2.54
15.0	8073493	2.47	1.37	8076876	1.67	2.64

[a]Relative standard deviation based on peak area, [b]Relative standard deviation based on R_T

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

Formulation brand name	Nominal amount, mg	% QTF found[a]±SD		*t*	*F*
		Reference method	Proposed method		
Quetipin 100	100.0	100.8±0.68	99.86±0.52	2.45	1.71

[a]Mean value of five determinations. Tabulated *t*-value at 95% confidence level is 2.78; tabulated *F*-value at 95% confidence level is 6.39

Table 5: Results of recovery study by standard addition method

Tablet studied	QTF in tablet, μg ml^{-1}	Pure QTF, μg ml^{-1}	Total found, g ml^{-1}	Pure QTF recovered %±SD
Quetipin 100				
	5.0	2.5	7.44	97.56±0.68
	5.0	5.0	10.02	100.3±0.86
	5.0	10.0	15.26	102.6±0.58

acid, alkali, thermal, hydrolytic, and UV conditions. It was found to undergo slight degradation (12.5%) to oxidative stress condition.

Recovery study

A standard addition procedure was followed to further evaluate the accuracy of the method. The solutions were prepared by spiking pure drug into a pre-analyzed tablet powder at three different levels and injected to chromatographic column. The recovery of the known amount of added analyte was computed. The percentage recovery of QTF from pharmaceutical dosage forms ranged from 97.56% to 102.6%. The results were given in Table 5 and reveal acceptable accuracy of the proposed method.

CONCLUSIONS

The developed rapid, isocratic reversed phase (RP-UPLC) method for quantitative analysis of QTF in pharmaceutical dosage forms is precise, accurate, linear, robust, and specific. The stability study of drug inferred that it will undergo slight degradation to oxidative stress. Satisfactory results were obtained from validation of the method. The R_T obtained (0.48 min) enables rapid determination of the drug which is important in routine analysis. The method exhibited an excellent performance in terms of sensitivity and speed. The method can be used for routine analysis of production samples and can be used for the assay of QTF either in pure drug or in pharmaceutical formulations.

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