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Reversed Phase High Performance Liquid Chromatographic Method for Determination of Quetiapine Fumarate in Pharmaceutical Formulation and in Spiked Human Urine

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A B S T R A C T

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 mm × 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.

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Introduction

Quetiapine fumarate (QTF), a dibenzothiapine derivative, chemically known as 2-(2-(4-dibenzo [b,f] [1,4] thiazepine-11-yl-1-piperazinyl) ethoxy)ethanol, fumaric acid (1 : 2 salt) (Fig. 1) is one of the most recent "atypical" antipsychotic drugs[1]. It is used in the treatment of schizophrenia and of mania associated with bipolar disorders [2, 3]. It is reported to have affinity for serotonin, histamine, and adrenergic receptors, as well as dopamine D_2 receptors [4].

Several methods have been reported for the quantitative determination of quetiapine in biological samples and include HPLC with UV detection [5-12], chemiluminescence spectrometry [13], electrospray ionization MS [14-17] and tandem MS/MS detection [18-20], UPLC with tandem MS detection [21, 22], GC [23, 24] and voltammetry [25]. QTF is not official in any pharmacopoeia. Methods based on different techniques such as titrimetry[26, 27], potentiometry[28], spectrophotometry[27, 29-33], polarography[34], capillary zone electrophoresis[33, 35], HPTLC[36, 37] and HPLC[38, 39] have earlier been employed for the determination of QTF in pharmaceuticals.

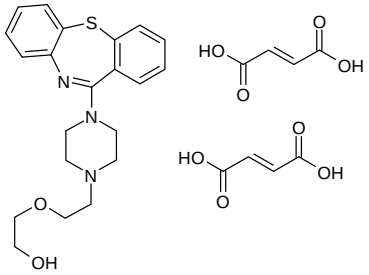

Fig. 1. Structure of QTF

Of the various chromatographic techniques reported for the determination of QTF in body fluids [5-24], only the GC-MS method [24] is devoted to urine sample. The RP-HPLC method developed by Radhakrishnan et al[38], uses a column temperature of 40 °C and limited to the identification of the related substances in QTF. There is only one article dealing with the HPLC assay of QTF in tablets [39], but is less sensitive with a linear range of 10-100 µg/mL QTF. Even the report of Belal *et al* [5] deals with the determination of QTF in human plasma and tablets, thus necessitating feasible method for the quantification of QTF in urine. In this report, development and validation of a reliable assay procedure for QTF in urine and pharmaceutical formulations is described; it uses HPLC with UV detection at 240 nm.

Materials and Methods

Chromatographic analyses were carried out using Alliance Waters HPLC system equipped with Alliances 2657 series low pressure quaternary pump, a programmable variable wavelength UV-visible detector, Waters 2996 photodiode array detector and auto sampler. Data were collected and processed using Waters Empower 2.0 software.

All reagents used were HPLC grade. QTF pure drug was kindly provided by Cipla India Ltd, Bangalore, India, as a gift and used as received. Qutipin-200 and Qutipin-100 (both from Sun Pharmaceuticals Ltd, India) tablets were purchased from local market. Orthophosphoric acid (Rankem, Bangalore, India), acetonitrile (Labscan Asia Co. Ltd, Bangkok, Thailand) and de-ionized water were used in the investigation. Urine sample was obtained from a 34 years old healthy male.

Chromatographic conditions

Phosphate buffer (pH 3.1) was prepared by adding 0.02 M NaOH to 0.1% orthophosphoric acid in water and adjusting the pH using pH meter. The analysis was carried out on a chromatopack ODS column (250 mm × 4.6 mm i.d., 5 µm particle size). A solution containing a mixture of acetonitrile and phosphate buffer of pH 3.1 (40:60) was used as mobile phase. The flow rate was 1 mL/min, the detector wavelength was set at 240 nm and the injection volume was 20 µL.

General Procedures

Procedure for preparation of solutions

A stock standard solution of 200 µg/mL QTF was prepared in diluent solution which is a mixture of acetonitrile and phosphate buffer (pH 3.10) (50:50). Working solutions were prepared by diluting the stock solution with the mobile phase.

Procedure for preparation of calibration curves

Working solutions equivalent to 0.09-18.0 µg/mL QTF were prepared by serial dilutions of aliquots of the stock solution. Aliquots of 20 µL were injected

(triplicate) and eluted with the mobile phase under the reported chromatographic conditions. The average peak area versus the concentration of QTF in µg/mL was plotted. Alternatively, the corresponding regression equation was derived using mean peak area-concentration data and the concentration of the unknown was computed from the regression equation.

Procedure for analysis of dosage forms

Twenty tablets were accurately weighed, finely pulverized using a mortar and pestle. An amount of tablet powder equivalent to 20 mg QTF was weighed and transferred into a 100 mL volumetric flask, 50 mL of diluent solution was added and was sonicated for 20 min in an ultrasonic bath to complete dissolution of the QTF, and the mixture was then diluted to the mark with the diluent, mixed well and filtered through Whatman No. 42 filter paper. Aliquots of this solution were successively diluted with the mobile phase and then subjected to analysis as per the general procedure described for the calibration curve. The nominal content of the tablets was obtained from the calibration graph or from the regression equation.

Procedure for analysis of spiked human urine

Ten milligrams of pure QTF was taken in a 50 mL volumetric flask containing 5 mL of drug free urine, 5 mL of diluent solution and 25 mL of acetonitrile. The content was mixed well and the volume was brought up to mark with water. The solution was filtered through Whatman No. 42 filter paper. A 20 µL aliquot was injected in triplicate and eluted with the mobile phase under the reported chromatographic conditions. The concentration of QTF was found using the area versus concentration plot or regression equation and the percentage recovery of QTF was calculated.

Results and Discussion

The proposed method permits the quantitation of QTF in commercial tablets and in human urine. In order to obtain good linearity, sensitivity and selectivity, the method was optimized and validated according to the Guidance of Bioanalytical Method Validation [40]. Figure 2 shows a chromatogram indicating good peak of QTF (t_R = 3.828 min) under the optimized conditions.

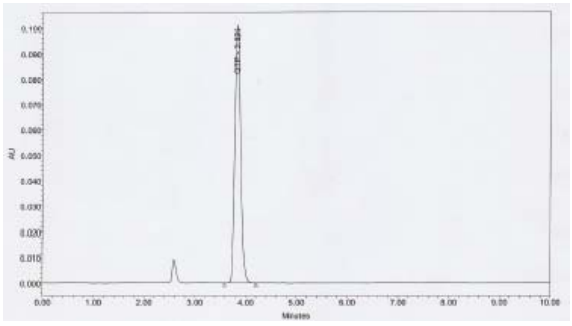

Fig. 2. A chromatogram showing QTF from pure drug (14 µg/mL)

Method Optimization

A well defined symmetrical peak and good results were obtained upon measuring the response of eluent under the optimized conditions after thorough experimental trials that could be summarized as follows:

Mobile phase composition

Several modifications in the mobile phase compositions were made in order to study the possibilities of changing the selectivity of the chromatographic system. These modifications included the change of the type and ratio of organic modifier, the pH and strength of phosphate buffer. The results obtained are shown in Table 1.

Table 1. Effect of ratio of organic modifier, pH and ionic strength of buffer on the number of theoretical plates

Ratio (A/B)[a]	Number of theoretical plates (N)	pH of the medium	Number of theoretical plates (N)	$\%H_3PO_4$	Number of theoretical plates (N)
60/40	3562	2.0	5162	0.050	2576
50/50	4361	2.5	5432	0.075	3896
45/55	5714	3.0	5611	0.100	5796
40/60	5796	3.1	5793	0.125	5798
30/70	1706	3.2	5714	0.150	5795
-	-	3.5	4361	0.200	5786
-	-	4.0	2717	0.250	5780

[a]A. acetonitrile and B. phosphate buffer

Ratio of organic modifier

The effect of ratio of organic modifier on the selectivity and retention time of the test solute was investigated using mobile phases containing 30-60% acetonitrile. Table 1 shows that 40% acetonitrile was the best, giving well defined peak with more number of theoretical plates.

Effect of pH and ionic strength of buffer

The effect of pH of the mobile phase on the selectivity and retention time of the test solute was investigated using mobile phases of pH ranging from 2.0-4.0. The results (Table 1) revealed that pH 3.10 was most appropriate and giving well defined peak with more number of theoretical plates. At lower and higher pH non-symmetrical peak and smaller number of theoretical plates were observed. Therefore, pH 3.1 was fixed as optimum. The same trend was observed after making alteration in the ionic strength of the buffer and 0.1% phosphate buffer was used as working buffer throughout the investigation. The results of these observations are also presented in Table 1.

Validation of the Method

Linearity

Working standard solution of QTF (200 µg/mL) was appropriately diluted with the diluent to obtain 0.09-18 µg/mL QTF. A 20 µL of each solution was injected in triplicate onto the column under the operating chromatographic conditions described above. The least squares method was used to calculate the slope, intercept and the correlation coefficient (r) of the regression line. The relation between mean peak area Y (n=3) and concentration, X expressed by the equation Y = 49249.47 X + 4530.54 (r^2 = 0.9999), was linear. A plot of log peak area *versus* log concentration was a straight line with the slope of 1.1135 and this coupled with a high value of the correlation coefficient (r>0.999) indicated excellent linearity between mean peak area and concentration in the range 0.09-18.0 µg/mL QTF. Statistical data are presented in Table 2.

Table 2. Regression and Sensitivity parameters

Parameters	Value
Linearity range, µg/mL	0.09-18.0
Regression (Y^* = a + bX)	
Slope (b)	49249.47
Intercept (a)	4530.54
Standard deviation of intercept (S_a)	3889.90
Standard deviation of Slope (S_b)	224.76
Correlation co-efficient (r)	0.9999
Limit of detection (LOD, µg/mL)	0.03
Limit of quantification (LOQ, µg/mL)	0.09
Variance (Sa^2)	1.512×10^7
$\pm tS_a / \sqrt{n}$	4081.27
$\pm tS_b / \sqrt{n}$	235.82

*Y = a+bX, where Y is the area and X concentration in µg/mL.

$\pm tS_a / \sqrt{n}$ =confidence limit for intercept, $\pm tS_b / \sqrt{n}$ =confidence limit for slope.

Limits of quantification (LOQ) and detection (LOD)

The LOD and LOQ were calculated using signal-to-noise ratio method which in according to Guidance of Bioanalytical Method Validation [40]. LOD was taken as the concentration of the analyte where the signal-to-noise ratio was 3, and it was found to be 0.03 µg/mL. LOQ defined as the analyte concentration at a signal-to-noise ratio of 10 and it was 0.09 µg/mL.

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. Figure 3, a chromatogram obtained for placebo solution does not show any interference from the above substances. 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 procedure. The peak area value resulting from 14 µg/mL QTF solution had nearly the same as that obtained for pure QTF solutions of identical concentration. 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. Method selectivity was checked by comparing the chromatograms obtained for placebo blank (Fig 2), pure QTF solution (Fig 3), synthetic mixture and tablet solution. An examination of the chromatograms of the above solutions revealed the absence of peaks due to additives present in tablet preparations.

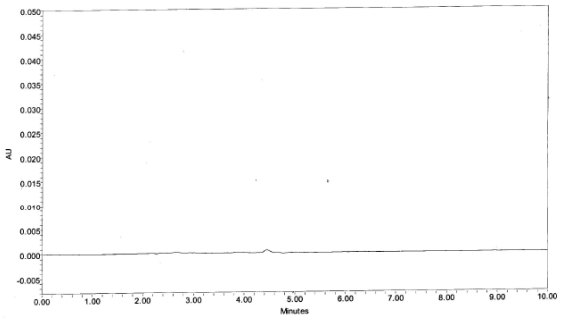

Fig. 3. A chromatogram obtained from placebo blank

Precision and Accuracy

Method precision was evaluated from the results of seven independent determinations of QTF at three different concentrations, 5.0, 10.0 and 15.0 µg/mL on the same day. The inter-day and intra-day relative standard deviation (RSD) values for peak area and retention time for the selected concentration of QTF were less than 2.52 and 2.4%, respectively. The method accuracy, expressed as relative error (%RE) was determined by calculating the percent deviation found between concentrations of QTF injected and concentrations found from the peak area. This study was performed by taking the same three concentrations of QTF used for precision estimation. The intra-day and inter-day accuracy (expressed as %RE) was less than 4% and the values are compiled in Table 3.

Table 3. Intra-day and Inter-day Accuracy and Precision

QTF Injected, µg/mL	Intra-day accuracy and precision				Inter-day accuracy and precision			
	QTF found[a], µg/mL	%RE	%RSD[b]	%RSD[c]	QTF found[a], µg/mL	%RE	%RSD[b]	%RSD[c]
5.00	5.09	1.85	1.70	1.26	5.19	3.80	2.26	1.81
10.00	10.09	0.95	1.63	2.41	10.13	1.30	1.92	0.98
15.00	15.35	2.34	2.52	2.68	15.42	2.80	2.40	1.06

[a]Mean value of seven determinations
[b]Based on peak area
[c]Based on retention time

Robustness

To determine the robustness of the method small deliberate changes in the chromatographic conditions like detection wavelength and column temperature were made, and the results were compared with those of the optimized chromatographic conditions. For each varied parameter and respective values of area, %RSD values were evaluated. The results indicated that changing the detection wavelength (±1 nm) had little effect on the chromatographic behavior of QTF with RSD value of 1.42. However, the alteration in the column temperature (±1 °C) had no significant effect.

Method Application

Application to dosage forms

The developed and validated method was successfully applied to the assay of QTF in commercial tablets. The average percent recoveries of different concentrations were based on the average of three replicate determinations. The results were statistically compared with the reference method [32] which is a UV spectrophotometric method for the determination of QTF in water at 290 nm. Student-t test and variance ratio F-test [41] were used to evaluate the accuracy and precision, respectively, and the results are in good agreement. Therefore, the proposed method can be adopted as a routine quality control procedure for the assay of QTF.

Application to spiked human urine sample

The developed and validated method was successfully applied to determine QTF in spiked urine sample with satisfactory recovery. The recovery of QTF from urine sample was measured under the procedure as described above. The recovery for QTF in spiked human urine analysis was calculated at three concentrations (2.0 µg mL^{-1}, 9.0 µg mL^{-1} and 16.0 µg mL^{-1}). The recovery for QTF-spiked human urine sample was in the range of 95.66 – 103.1% with standard deviation values of less than 3%.

Recovery study

To further assess the accuracy and reliability of the method, recovery studies *via* standard addition procedure was performed. To the pre-analyzed tablet

powder, pure QTF was added at three levels and the total was found by the proposed method. Each test was triplicated. When the test was performed on 200 and 100 mg tablets, the percent recovery of pure QTF was in the range of 97.20 – 103.4 with standard deviation values of 0.52 -1.25. The results indicated that the method is very accurate and common excipients in tablet preparations did not interfere. The results are complied in Table 4.

Table 4. Results of recovery study by standard addition procedure

Tablet	QTF in tablet, µg/mL	Pure QTF added, µg/mL	Total found, µg/mL	Pure QTF recovered*, Percent ± SD
Qutipin 200	5.0	2.5	7.62	99.6±0.52
	5.0	5.0	10.21	101.6±1.02
	5.0	10.0	15.47	103.4±1.25
Qutipin 100	5.0	2.5	7.36	97.60±0.60
	5.0	5.0	9.88	99.20±0.56
	5.0	10.0	14.93	100.1±1.02

*Mean value of three determinations

Conclusions

The proposed method for the determination of quetiapine fumarate based on the use of liquid chromatography with UV detection was shown to be reliable, simple, sensitive and accurate and precise. Moreover the method is fast and feasible. The proposed method uses a simple mobile phase compared to the multi-component mobile phase in many reported methods. The separation and determination was achieved at an ambient temperature. This, itself offers the advantages of low column back pressure, good peak shape, improved column efficiency, higher theoretical plates and consistent retention time. The proposed procedure was successfully applied for the assay of QTF in spiked human urine without any interference from other products present in the urine and it seems to be very promising for the therapeutic drug monitoring of patients undergoing chronic treatment with quetiapine.

Conflict of interest

Authors certify that no actual or potential conflict of interest in relation to this article exists.

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