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ESTIMATION OF QUETIAPINE IN BULK DRUG AND TABLET DOSAGE FORM

S. S. CHHAJED*, S. S. AGRAWAL[a], V. A. BASTIKAR[b], R. A. GOSAVI, S. H. KUNTE and R. D. WAGH

S. M. B. T. College of Pharmacy, DHAMANGAON, Dist. - Nasik (M. S.) INDIA
[a]H. R. Patel, College of Pharmacy, SHIRPUR – 425405, (M. S.) INDIA
[b]Dr. D. Y. Patil Institute of Biotechnology and Bioinformatics, Belapur (CBD), NAVI MUMBAI (M. S.) INDIA

ABSTRACT

New, simple, cost effective, accurate and reproducible UV-spectrophotometric methods are developed and validated for the estimation of quetiapine fumarate in bulk drug and tablet formulation. Quetiapine was estimated at 239 nm in 0.1N hydrochloric acid (pH 1.2) and at 250 nm in ethanol. Beer's law was obeyed in the concentration range of 1–12 μgmL^{-1} (r^2 = 0.9999) in hydrochloric acid and 1–14 μgmL^{-1} (r^2 = 0.9998) in the ethanol. The apparent molar absorptivity and Sandell's sensitivity coefficient were found to be 4.63×10^4 L mol^{-1} cm^{-1} and 9.5 ng cm^{-2}/0.001A in hydrochloric acid; and 4.08×10^4 L mol^{-1} cm^{-1} and 10.8 mg cm^{-2}/0.001A in ethanol, respectively indicating the high sensitivity of the proposed methods. These methods were tested and validated for various parameters according to ICH guidelines. The detection and quantitation limits were found to be 0.0402, 0.1217 μgmL^{-1} in hydrochloric acid and 0.0384, 0.1163 μgmL^{-1} in ethanol, respectively. The proposed methods were successfully applied for the determination of quetiapine in pharmaceutical formulation (tablets). The results demonstrated that the procedure is accurate, precise and reproducible (relative standard deviation < 2%), while being simple, cheap and less time consuming and hence, can be suitably applied for the estimation of quetiapine in its tablet dosage.

Key words : Quetiapine fumarate, UV Spectrophotometric method, Validation

INTRODUCTION

Quetiapine (Seroquel) (Fig. 1) was introduced in the clinic as a new antipsychotic drug for the treatment of schizophrenia and other psychotic[1,2] or schizoaffective disorders[3]. Chemically, quetiapine is 2-[2-(4-dibenzo [b, f] [1, 4]thiazepin-11-yl-1-piperazinyl)

* Author for correspondence; E-mail- santosh_chhajed@rediffmail.com; Ph: +919766315165

ethoxy]-ethanol fumarate which are classified as "atypical" antipsychotic[4] and do not cause major extra pyramidal side effects. Each is effective in the treatment of schizophrenia, treating both the positive and negative symptoms[1–3]**.** These new antipsychotics have markedly improved the quality of life in many schizophrenic patients and have consequently become first line antipsychotics.

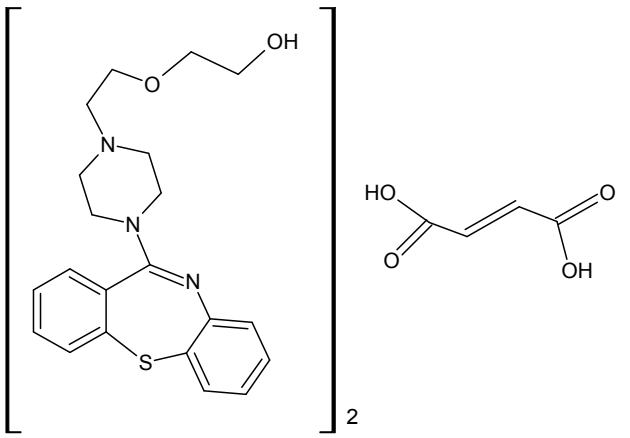

Fig. 1: Chemical structure of quetiapine fumarate

Quetiapine is a new drug and finds place in Merck Index[5]. Literature survey reveals that for quantification of quetiapine in human serum, spectrophotometric method for estimation of quetiapine in human serum[6], analysis of quetiapine in human blood by high performance-liquid chromatography with column-switching[7] methods are reported. The objective of the present study was to develop simple, precise, accurate and validated, economic analytical methods for the estimation of quetiapine in bulk and tablet formulations. Two analytical methods have been developed in different media for estimation of quetiapine. Media used were 0.1 N hydrochloric acid (HCl) (pH 1.2) and ethanol. Quetiapine showed absorption maxima at 239 nm in 0.1N HCl and at 250 nm in ethanol. The developed analytical methods were validated as per ICH guidelines and USP requirements[8, 9]. Statistical tests were performed on validation data[10].

EXPERIMENTAL

Material and reagents

Quetiapine fumarate was obtained as gift samples from Enem Nostrum Remedies Ltd. Mumbai, India. Tablets containing quetiapine fumarate S Quitine 50 tablets, labelled to contain 50 mg of quetiapine fumarate per tablet (Sun Pharma Ltd., India), All other

chemicals and reagents used were of analytical grade.

Insrument

A double-beam Shimadzu 1650 UV–vis spectrophotometer, connected to computer and loaded with UV-Probe software was used. For intermediate precision study, a different Shimadzu 1650 UV–vis spectrophotometer connected to computer with UV-PC software was used. Both the instruments have an automatic wavelength accuracy of 0.1 nm and matched quartz cells of 10 mm (1.0 cm) cell path length.

Analytical method development

For selection of media, the criteria employed were sensitivity of the method, ease of sample preparation, solubility of the drug and cost of solvents, applicability and robustness of the method for various purposes. Absorbance of quetiapine in the selected medium at respective wavelength was determined and apparent molar absorptivity and Sandell's sensitivity coefficients were calculated according to the standard formulae (Table 1).

Procedure for calibration curve

Two different stock solutions of 100 μgmL^{-1} of quetiapine fumarate were prepared in 0.1N hydrochloric acid (HCl) (pH 1.2) and ethanol by dissolving 5 mg of quetiapine fumarate in 50 mL of each media. For preparation of different concentrations, aliquots of stock solutions were transferred into a series of 10 mL standard volumetric flasks and volumes were made with the respective media. Five different concentrations were prepared in the range of 1–12 $\mu gmL^{-1}$of quetiapine fumarate in hydrochloric acid. In a similar way, five different concentrations were prepared in the range of 1–14 μgmL^{-1} of quetiapine fumarate in the ethanol for standard curve. Quetiapine fumarate was estimated at 239 nm and 250 nm in 0.1 M hydrochloric acid and ethanol medium, respectively.

Sample preparation

Quetiapine fumarate tablets were powdered and extracted with two media viz. 0.1N HCl and ethanol separately. The solutions were then filtered and suitably diluted to get final concentration of 5 $\mu gmL^{-1.}$

Table 1. Optical characteristics, statistical data of the regression equation and validation parameters of quetiapine fumarate

Parameter	0.1N HCl	Ethanol
Optical characteristics		
Apparent molar absorptivity (L mol^{-1} cm^{-1})	4.63×10^4	4.08×10^4
Sandell's sensitivity (ng cm^{-2}/0.001 A)	9.5	10.8
Regression analysis		
Slope (S. E.[a])	0.1060 (1.12×10^{-4})	0.0925 (8.73×10^{-5})
95% confidence limits of slope	0.1058; 0.1063	0.0923; 0.0927
Intercept (S. E.[a])	−0.0025 (4.30×10^{-4})	0.0029 (3.59×10^{-4})
95% confidence limits of intercept	−0.0035; −0.0015	0.0020; 0.0037
Regression coefficient (r^2)	0.9999	0.9998
Calculated *F*-value (critical *F*-value)[b]	1.649 (2.244)	1.120 (2.244)
Validation parameters		
Specificity and selectivity—t_{cal} (t_{crit})[c]	1.29 (2.31)	1.10 (2.31)
Linearity (μgmL^{-1})	1–12	1–14
Limit of detection (LOD) (μgmL^{-1})	0.0402	0.0384
Limit of quantification (LOQ) (μgmL^{-1})	0.1217	0.1163
Robustness (mean % recovery ± S.D.)	101.03 ± 1.29	100.51 ± 0.97

[a] Standard error of mean

[b] Theoretical value of F is based on one way ANOVA test at p = 0.05 level significance.

[c] t_{cal} is calculated value and t_{crit} is theoretical value (at eight degree of freedom) based on paired t-test at p = 0.05 level of significance.

Table 2

Level	Predicted conc. ($mgmL^{-1}$)			Mean % recovery (± S. D.)	Accuracy (%)[b]
	Range	Mean ± S. D.	% RSD		
0.1 N HCl					
LC ($2\ \mu gmL^{-1}$)	1.98-2.02	2.005 ± 0.013	0.66	100.25 ± 0.658	0.25
IC ($5\ \mu gmL^{-1}$)	4.97-5.03	4.996 ± 0.018	0.35	99.92 ± 0.353	-0.08
HC ($10\ \mu gmL^{-1}$)	9.95-10.07	10.007 ± 0.037	0.37	100.07 ± 0.366	0.07
Ethanol					
LC ($2\ \mu gmL^{-1}$)	1.98-2.02	1.996 ± 0.011	0.55	99.82 ± 0.544	-0.18
IC ($8\ \mu gmL^{-1}$)	7.99-8.11	8.070 ± 0.040	0.49	100 ± 0.498	0.87
HC ($13\ \mu gmL^{-1)}$	12.95-1.05	12.995 ± 0.039	0.3	99.96 ± 0.298	-0.04

[a] Predicted concentration of quetiapine was calculated by linear regression equation

[b] Accuracy is given in % relative error (= 100×{predicted conc. – nominal conc. }/ nominal conc.

Analytical method validation

Specificity and selectivity

Quetiapine fumarate ($5\ \mu gmL^{-1}$) were prepared in both the selected media along with and without common excipients (lactose, microcrystalline cellulose, magnesium stearate, talc, HPMC, iron oxide red, titanium dioxide) separately. All the solutions were scanned from 450 to 200 nm at a speed of 400 nm min^{-1} and checked for change in the absorbance at respective wavelengths. In a separate study, drug concentration of $5\ \mu gmL^{-1}$ was prepared independently from pure drug stock solution in selected media and analyzed (n = 9). Paired t-test at 95% level of significance was performed to compare the means of absorbance (Table 1).

Accuracy

To determine the accuracy of the proposed methods, different levels of drug concentrations—lower concentration (LC), intermediate concentration (IC) and higher concentration (HC) (in both media) were prepared from independent stock solutions and analyzed (n = 9). Accuracy was assessed as the percentage relative error and mean % recovery (Table 2). To provide an additional support to the accuracy of the developed assay method, standard addition method was employed, which involved the addition of different concentrations of pure drug (1, 2 and 5 μgmL^{-1}in HCl medium; 2, 6 and 8 μgmL^{-1} in the ethanol medium) to a known pre-analyzed formulation sample and the total concentration was determined using the proposed methods (n = 9). The % recovery of the added pure drug was calculated as, % recovery = $[(C_t - C_s)/C_a]\times 100$, where C_t is the total drug concentration measured after standard addition; C_s, drug concentration in the formulation sample; C_a, drug concentration added to formulation (Table 3).

Precision

Repeatability was determined by using different levels of drug concentrations (same concentration levels taken in accuracy study), prepared from independent stock solutions and analyzed (n = 9) (Table 2). Inter-day, intra-day and interinstrument variation were studied to determine intermediate precision of the proposed analytical methods. Different levels of drug concentrations in triplicates were prepared three different times in a day and studied for intra-day variation. Same procedure was followed for three different days to study inter-day variation (n = 27). One set of different levels of the concentrations was re-analyzed using Shimadzu 1650 UV–vis spectrophotometer connected to computer with UV-Probe software, by proposed methods to study inter-instrument variation (n = 3). The percent relative standard deviation (% R. S. D.) of the predicted concentrations from the regression equation was taken as precision (Table 4). Precision studies were also carried out using the real samples of quetiapine fumarate tablets in a similar way to standard solution to prove the usefulness of method.

Linearity

To establish linearity of the proposed methods, nine separate series of solutions of quetiapine fumarate (1–12 μgmL^{-1} in 0.1 N hydrochloric acid and 1–14 μgmL^{-1}in ethanol) were prepared from the stock solutions and analyzed. Least square regression analysis was done for the obtained data. One-way ANOVA test was performed based on the absorbance values, observed for each pure drug concentration during the replicate measurement of the standard solutions (Table 1).

Limit of detection (LOD) and limit of quantitation (LOQ)

The LOD and LOQ of quetiapine fumarate by the proposed methods were determined using calibration standards. LOD and LOQ were calculated as 3.3 σ/S and 10 σ/S, respectively, where S is the slope of the calibration curve and σ is the standard deviation of y-intercept of regression equation (n = 9) (Table 1).

Table 3.Standard addition method (n = 9)

Method	Dug in formulation (µg mL^{-1})	Pure drug added (µg mL^{-1})	Total drug found µgmL^{-1} (± S. D.)	% Recovery (± S. D.)
0.1 N HCl	5.4	1	6.39 ± 0.032	99.87 ± 0.494
	5.4	2	7.44 ± 0.045	100.50 ± 0.612
	5.4	5	10.41 ± 0.075	100.12 ± 0.719
Ethanol	5.4	2	7.39 ± 0.042	99.84 ± 0.539
	5.4	6	11.50 ± 0.061	100.89 ± 0.539
	5.4	8	13.42 ± 0.085	100.15 ± 0.634

Table 4. System precision study (n = 9)

Conc. (µgmL^{-1})	Intra-day repeatability			Inter-day repeatability	Intrainstrument repeatability
	% R. S. D			%RSD (n = 27)	%RSD (n = 6)
	Day 1	Day 2	Day 3		
0.1 N HCl					
2	0.817 (1.279)	1.056 (0.993)	0.748 (1.003)	0.873 (0.819)	1.233 (1.103)
5	0.734 (0.655)	0.451 (0.689)	1.031 (0.965)	0.739 (0.844)	0.887 (0.654)
11	0.419 (0.813)	1.031 (0.965)	0.956 (1.083)	0.781 (0.329)	0.645 (0.773)

Cont…

Conc. (μgmL^{-1})	Intra-day repeatability			Inter-day repeatability	Intrainstrument repeatability
	% R. S. D			%RSD (n = 27)	%RSD (n = 6)
	Day 1	Day 2	Day 3		
Ethanol					
4	1.245 (0.971)	1.387 (0.995)	0.763 (0.538)	1.131 (0.911)	1.719 (1.281)
8	0.338 (0.409)	0.906 (1.372)	1.353 (0.984)	1.131 (0.911)	1.719 (1.281)
13	0.633 (0.576)	1.062 (1.118)	1.320 (1.220)	1.005 (1.237)	0.663 (0.572)

Values in parenthesis shows the values of % R. S. D. for real samples of quetiapine fumarate tablets

Robustness

Robustness of the proposed method was determined by (a) changing pH of the media by ±0.1 units and (b) stability of the quetiapine fumarate in both the selected media at room temperature for 24 h. Three different concentrations (LC, IC and HC) were prepared in both the media with different pH and mean % recovery was determined (Table 1).

Estimation from tablet formulation

Twenty tablets were weighed and pulverized. Amount of the powder equivalent to 10 mg of quetiapine fumarate was taken and extracted with both media separately for 30 min. These solutions were diluted suitably to prepare a 100 μgmL^{-1} concentration in respective media. Finally solutions were filtered through Whatman filter paper number 40 and the filtrate was suitably diluted to prepare a 5 μgmL^{-1} concentration in both the media separately and the samples were analyzed using proposed analytical methods (Table 5).

Table 5. Application of spectrophotometric method to the determination of quetiapine fumarate from tablets (*n* = 9)

Formulation	0.1 N HCl		Ethanol	
	Amount found[b]	% assay	Amount found[b]	% assay
S Qutine 50 Tablets (50 mg)	50.23 ± 0.69	101.06 ± 0.42	50.54 ± 0.25	100.84 ± 0.56
t[a]	1.75 (2.31)			
f[a]	0.51 (2.36)			

[a] The values in parenthesis are the tabulated values of *t* and *F* at *P* = 0.05.

[b] Amount found is represented as average ± S. D.

RESULTS AND DISCUSSION

Quetiapine fumarate exhibits the λ max at 239 nm and 250 nm in the 0.1 M hydrochloric acid and ethanol, respectively. Beer's law was obeyed in the concentration range of 1–12 µg/mL in hydrochloric acid and 1–14 μgmL^{-1} in the ethanol. The apparent molar absorptivity and Sandell's sensitivity coefficient were found to be 4.63×10^4 L mol^{-1} cm^{-1} and 9.5 $ngcm^{-2}$/0.001A in HCl; and 4.08×10^4 L mol^{-1} cm^{-1} and 10.8 ng cm^{-2}/0.001A in ethanol, respectively indicating the high sensitivity of the proposed methods. The UV-spectrum of quetiapine fumarate was not changed in the presence of common excipients used in the formulation of quetiapine fumarate tablets, in both the selected media. Absorption spectrum of pure drug sample was matching with the formulation samples in both the selected media. The calculated *t*-values were found to be less than that of the tabulated *t*-values, indicating that statistically there was no significant difference between the mean absorbance of solutions prepared from pure drug sample and the formulation samples (Table 1). Therefore, proposed analytical methods are specific and selective for the drug.

CONCLUSION

The proposed analytical methods are simple, rapid, accurate, precise and inexpensive and hence, these can be used for the routine analysis of quetiapine in bulk,

pharmaceutical formulations and for dissolution samples of formulations. The sample recovery from tablet formulations was in good agreement with their respective label claim, which suggested non-interference of formulations excipients in the estimation. Moreover, the present method is fast with respect to analysis time as compared to sophisticated chromatographic techniques and no expensive laboratory technique is needed, they can be used for routine analysis in quality control laboratories.

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