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HPLC and Spectrophotometric Determination and Formulation of Quetiapine Fumarate in the Pharmaceutical Dosage Forms

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The aim of this work was to develop and validate of assay and dissolution tests for quetiapine fumarate in the pharmaceutical dosage by 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.

Key Words: HPLC, Quetiapine, Spectrophotometry, Pharmaceutical dosage.

INTRODUCTION

Quetiapine, is described as 2-(2-(4-dibenzo(b,f)(1,4) thiazepine-11-yl-1-piperazinyl)ethoxy)ethanol with molecular formula $C_{21}H_{25}N_3O_2S$ and molecular weight 383.51 (Fig. 1).

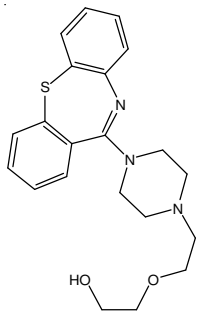

Fig. 1. Molecular structure of quetiapine

Quetiapine is used for the treatment of schizophrenia and recently has received food and drug administration approval for treatment of manic depression[1-6]. Affective and aggressive symptoms in schizophrenia, adolescent schizophrenia, schizoaffective disorder, bipolar affective disorder and mania, affective psychoses, behaviour and symptom control in dementia could form secondary indications, but more studies are awaited. The relatively greater ability to reduce negative symptoms compared to conventional antipsychotics provides an additional indication[7]. In this work, quetiapine fumarate was determined in the pharmaceutical dosage forms by using flow injection assay and dissolution methods.

EXPERIMENTAL

Quetiapine fumarate and potassium dihydrogen phosphate were prepared from Aarti Industries Ltd., India and Merk (K.GaA 64271 Darmstadt, Germany), respectively. HPLC solvents such as acetonitril and methanol were supplied from (KALEDON LABRATORIES LID, Canada). All the other chemical reagents were prepared with suitable analytical grade.

An Agilent series 1200 apparatus was used for HPLC. This Agilent apparatus equipped with a pump (quaternary gradient mode G1311A Quat) and a detector (Agilent 1200 series VWD). Data acquisition was performed by the Chemstation software which operated with a Pentium IV microprocessor. Analysis was carried out at 250 nm wavelength with a Perfectsil target C_{18} column (dimensions of 4.6 mm × 250 mm with inner diameter 5 µm) by using a reversed-phase. The mobile phase consists of buffer (pH: 7 ± 0.05, potassium dihydrogen phosphate), acetonitrile and methanol (2:2:1 v/v). This analysis was done at the room temperature.

Preparation of standard solution: In order to preparation of standard solution, drug stock solution of the quetiapine

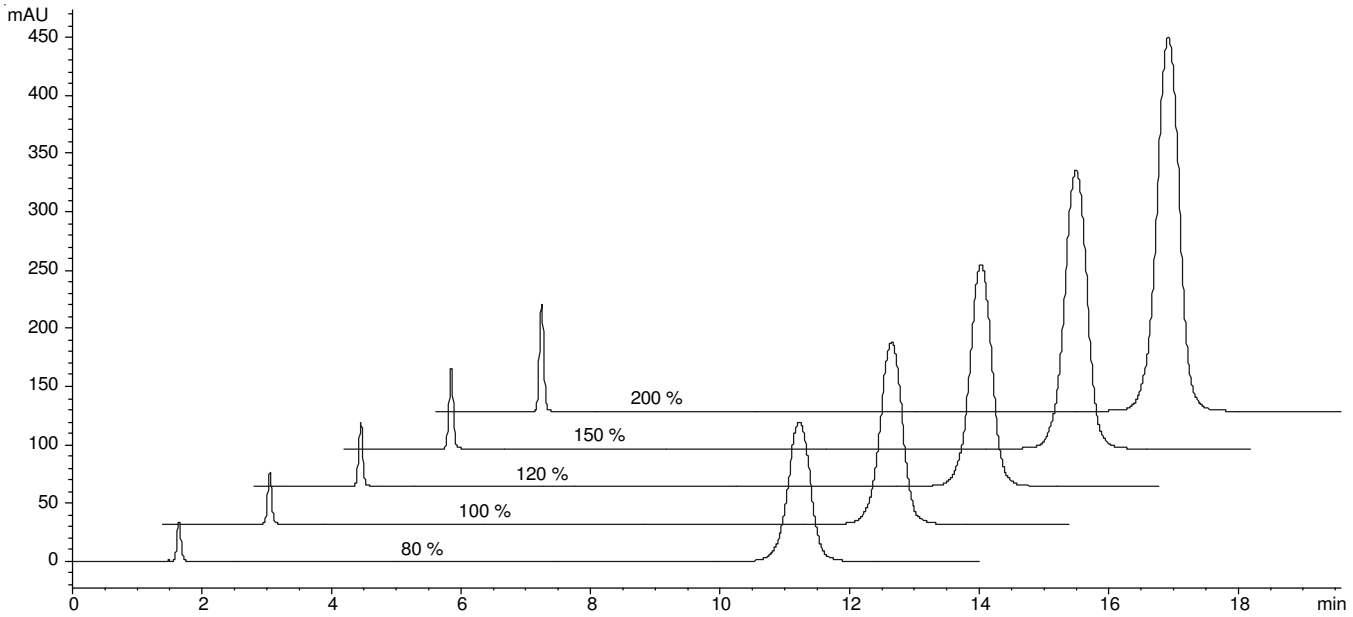

Fig. 2. Chromatograms of quetiapine (from top to bottom)

fumarate was prepared by dissolving 125 mg of the quetiapine fumarate in 250 mL of the mobile phase (final concentration 0.500 mg/mL). Dilute solution (0.100 mg/mL) was freshly produced from this stock standard solution during the analysis day.

Preparation of sample solution: In order to preparation of sample solution as well as to estimate the dosage form of the quetiapine fumarate, 20 tablets of each batch were randomly selected and powdered. Then, an accurately weighed quantity of the powdered tablets, equivalent to 25 mg of quetiapine fumarate, was transferred to a 50 mL volumetric flask. 30 mL of the mobile phase was added to the flask and this mixture was shaked intensively for 15 min until the drug was completely solved. The mobile phase was used to increase the volume to 50 mL and then the mixture was centrifuged at 4500 rpm for 0.5 h (Sigma 10l, Germany). 2 mL of the clear supernatant was taken and diluted with the mobile phase to 10 mL. The used concentration for quality control of the samples was 100 µg/mL. 20 µL of this solution was injected to the HPLC analyzer.

Procedure of assay: Assay method was analyzed by using HPLC. For HPLC analysis, volumes equal to 20 µL of the centrifuged quetiapine fumarate sample and the standard solution were separately injected to the chromatograph which records the chromatograms. Then, the response areas of major peaks which correspond to quetiapine were measured. Calculate the quantity (mg) of quetiapine in the portion of tablets taken by the following formula:

mg of quetiapine = $AUC_{Sam}/AUC_{St} \times LC \times P_{St} /100 \times 0.868$

where AUC_{Sam} = Area under curve of sample; AUC_{St} = Area under curve of standard; LC = Label claim of quetiapine in mg; PS_t = Purity of standard.

Validation of assay method: Validation of method was divided into linearity (calibration curve), accuracy and precision studies. The details of each section were followed.

Linearity (calibration curve): The Linearity and/or calibration curve were generated with five various concentrations of solution including the limit of quantification in the range of 80 to 200 µg/mL (Table-1). Chromatograms of quetiapine (from top to bottom) indicated that the various standard solutions of quetiapine elutes approximately at 11 min (Fig. 2). The linear dependence of this method was evaluated by the linear regression analysis, which was calculated by the least square regression method (Fig. 3).

Accuracy studies: The accuracy of this developed method was checked through the determination of the interference of the formulation additives. The analytical recovery experiments were carried out by the standard methods. The percentage of the recovery from the total amount of the drug was calculated. The results were reported in the Table-2.

TABLE-1
AREA UNDER CURVE (AUC) FOR QUETIAPINE IN DIFFERENT CONCENTRATIONS BY HPLC

Linearity of quetiapine F.C. tablets				
Concentration of quetiapine fumarate (mg/mL)	Mean	1	2	3
0.08	2974.41	2957.48	2972.09	2993.67
0.10	3812.77	3821.88	3808.64	3807.80
0.12	4628.89	4623.39	4623.49	4639.78
0.15	5886.43	5895.18	5882.11	5882.00
0.20	7896.15	7903.09	7890.79	7894.57

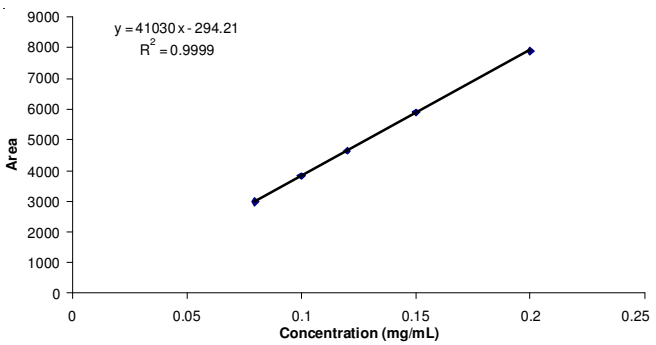

Fig. 3. Calibration curve of quetiapine by HPLC

TABLE-2
ACCURACY OF QUETIAPINE FOR VALIDATION TEST BY HPLC

Concentration of quetiapine fumarate (ppm)	AUC Quetiapine				Exact concentration	% of accuracy
	Mean	1	2	3		
80	2974.4	2957.5	2972.1	2993.7	79.664	99.580
120	4628.9	4623.4	4623.5	4639.8	119.988	99.990
200	7896.2	7903.1	7890.8	7894.6	199.619	99.809

TABLE-3
REPEATABILITY TEST FOR QUETIAPINE BY HPLC

Quetiapine 25 mg F.C. Tablets						
Intermediate between day precision						
Concentration of quetiapine base (mg/mL)	Mean Day 1	Mean Day 2	Mean Day 3	Mean	SD	RSD %
0.08	4019.477	4032.730	4027.577	4026.595	6.681	0.166
0.10	5034.107	5067.383	5097.033	5066.174	31.480	0.621
0.12	6077.370	6095.540	6141.980	6104.963	33.320	0.546
Mean						0.444

TABLE-4
REPEATABILITY TEST FOR QUETIAPINE BY UV SPECTROPHOTOMETRY

Quetiapine 25 mg F.C. Tablets						
Intermediate Between day Precision						
Concentration of quetiapine base (mg/mL)	Mean Day 1	Mean Day 2	Mean Day 3	Mean	SD	RSD %
0.005	0.151	0.150	0.150	0.150	0.001	0.384
0.010	0.303	0.302	0.302	0.302	0.001	0.191
0.015	0.460	0.461	0.461	0.461	0.001	0.125
Mean						0.233

Precision test: Precision test showed the similarity degree of results, compared with each other, when the method was performed on a number of samples from a homogenate substance, which included following two steps.

Precision determining in a single day method (inter-day): In such method, three concentrations of sample in the range between 70 %- 130 % was prepared and each one was analyzed three times.

Precision determining between days method (intra-day): In such method, three concentrations of sample was prepared and analyzed in three separate days each day three concentrations was analyzed each one for three times (Tables 3 and 4).

Stability of tablets: The stability of the drug solution was determined by using the quality contron samples for short-term stability by keeping samples at the room temperature for 36 h and then analyzing them. The long-term stability was determined by keeping samples at 45 ºC and 75 % relative humidity (RH) for 180 days. The samples (n = 3) were taken out after 30, 90 and 180 days and the drug content and their physical parameters such as colour change, friability, hardness and disintegration were evaluated.

Dissolution of the drug: For dissolution studies, an USP Type 2 dissolution apparatus was used. The dissolution was carried out in 900 mL of water. The dissolution medium was thermostatically controlled with the water bath which maintained at 37 ± 0.5 ºC. The paddle was lowered so that the lower end of the stirrer was 25 mm above the beaker bottom. The pre-weighed tablet was then introduced into the dissolution jar and the paddle was rotated at 50 rpm. At different time intervals, 15 mL of the sample was taken. The solution was passed through whatman filter paper no. 42. Then, 5 mL of the filtrated solution was transferred to a 50 mL volumetric flask and the volume was increased with distilled water. The sample evaluated by the spectrophotometer at the wavelength of 250 nm (Fig. 4). The validation method is as same as the assaying method (Fig. 5 and Tables 5 and 6).

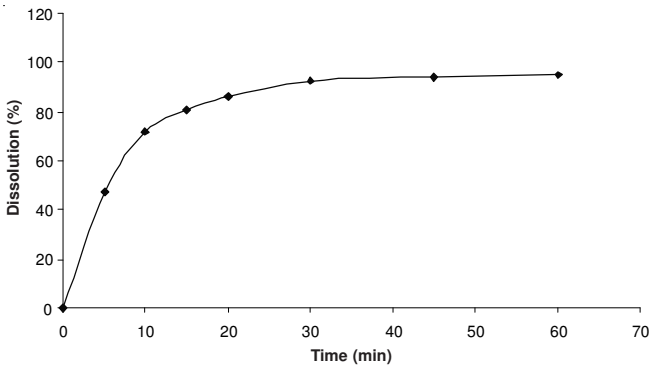

Fig. 4. Release of quetiapine in the tablets by dissolution rate

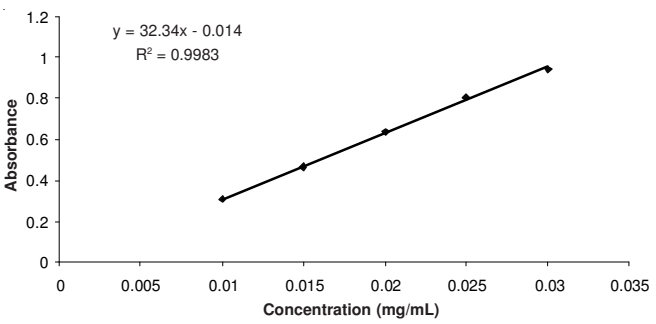

Fig. 5. Calibration curve of quetiapine by UV spectrophotometry

TABLE-5
ABSORBANCE FOR QUETIAPINE IN DIFFERENT CONCENTRATIONS BY UV SPECTROPHOTOMETRY

Concentration of quetiapine base (mg/mL)	Abs	%T
0.010	0.305	49.5
0.015	0.468	34.0
0.020	0.639	22.9
0.025	0.809	15.5
0.030	0.943	11.4

TABLE-6
ACCURACY OF QUETIAPINE FOR DISSOLUTION STUDY BY UV SPECTROPHOTOMETRY

Accuracy of quetiapine				
Concentration of quetiapine base (ppm)	Absorbance		Exact concentration	% of accuracy
	Abs.	T (%)		
10	0.305	49.5	9.86	98.64
20	0.639	22.9	20.19	100.96
30	0.943	11.4	29.60	98.64

RESULTS AND DISCUSSION

Both, HPLC and UV spectrophotometric methods were found to be the simple, accurate, economic and rapid methods for routine estimation of the quetiapine in the tablet dosage forms.

In the HPLC method, the conditions were optimized to obtain an adequate amount of the eluted compounds. Initially, it would be tried to separate the various mobile phase compositions. The mobile phase and flow rate selection was chosen based on the peak parameters (such as height, tailing, theoretical plates and capacity factor) and run times. A system consisted of a buffer [pH: 7 (±0.05), potassium dihydrogen phosphate], acetonitrile and methanol (2 : 2 : 1 v/v) was used. The flow rate of 1 mL/min is quite robust. Typical chromatograms for the quetiapine are shown in the Fig. 6. The optimum wavelength for detection was found to be 250 nm which led to better detector response for the drugs. To ascertain its effectiveness, the system suitability tests were carried out on freshly prepared stock solutions. The slope and intersept value for calibration curve were obtained y = 41030x - 294.21 (R^2 = 0.9999). The low RSD value (0.444 < 3 %) indicates that this method is precise and accurate (Table-3).

The inter day precision and accuracy were evaluated by using three samples of three different concentrations which were prepared and analyzed at the same day. The intraday precision was assessed by using three concentrations analyzed on three different days over a period of 2 weeks.

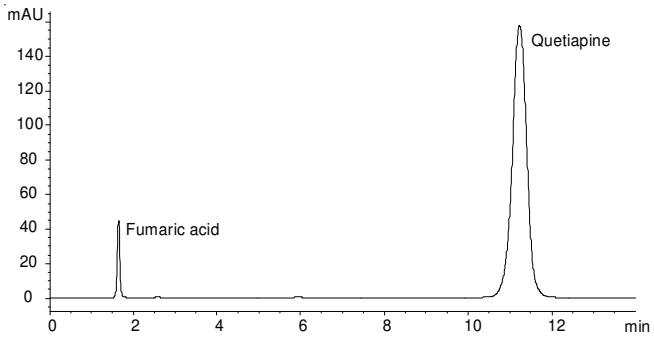

Fig. 6. Chromatogram of quetiapine and fumaric acid

These results show the accuracy and repeatability of the assay. Thus, it was concluded that there was no significant difference on the assay which was tested on an intraday and inter day basis.

The percentage of the RSD values, reported in Table-3, show that the proposed method provides acceptable intraday and inter day variations of quetiapine.

For the UV spectrophotometric method, the linear dependence for quetiapine was obtained in the concentration range between 10-30 µg/mL. The slope and intersept value for calibration curve were obtained y = 32.34x - 0.014 (R^2 = 0.9983). The value of the standard deviation and relative standard deviation (R.S.D) in the recovery were found to be 0.233 < 3 % which supported the higher precision of this method (Table- 4).

The proposed methods are accurate, simple, rapid and selective for the estimation of the quetiapine in the tablet dosage form.

Hence, it can be conveniently adopted for the routine quality control analysis. The low time consumption of this method allows analysis of numerous samples with low mobile phase which leads to higher cost efficiency. Although, the spectrophotometric method for dissolution is so time consuming. The HPLC-UV method can be used for the routine drug analysis. The assay could be attractive to this clinical analysis because the run time for the quantification of the drug is approximately 11 min per sample and no interferences are currently known.

Conclusion

Both, UV spectrophotometric and HPLC methods were found to be the simple, accurate, economic and rapid methods for routine estimation of the quetiapine in the tablet dosage forms. In the HPLC method, the low R.S.D value (0.444) also indicates the precise and accuracy of this method. The assay should be attractive to this clinical analysis. However, it was concluded that there was no significant difference on the assay which was tested on an intraday and inter day basis. For the UV spectrophotometric method, the linear dependence for quetiapine was obtained in the concentration range between 10-30 µg/mL with R.S.D of 0.233 which supported the higher precision of this method. Thus, the HPLC-UV method can be useful for this drug analysis.

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