

## Stress Testing of Quetiapine Fumarate by a Chemometric Assisted Multi-Component Ion-Interaction System

Suryakanta Swain<sup>1\*</sup> and Prafulla Kumar Sahu<sup>2</sup>

<sup>1</sup>College of Pharmacy, Southern Institute of Medical Sciences, Guntur, Andhra Pradesh, India

<sup>2</sup>Department of Pharmaceutical Analysis, Raghu College of Pharmacy, Visakhapatnam, Andhra Pradesh, India

\*Corresponding author: Suryakanta Swain, College of Pharmacy, Southern Institute of Medical Sciences, Mangaldas Nagar, Vijaywada Road, Guntur-522001, Andhra Pradesh, India, Tel: +917702247710; E-mail: swain\_suryakant@yahoo.co.in

Received date: Apr 14, 2017; Accepted date: Apr 27, 2017; Publish date: May 05, 2017

Copyright: © 2017 Swain S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

Classical experimental designs have been popularly employed in establishing robust analytical methods while achieving other advantages, viz., reduction in the number of experiments and hence lower reagent consumption and less laboratory work. To achieve optimum chromatographic condition, a computer-aided Box-Behnken Design (BBD) in ion-pairing stability-indicating RP-HPLC assay of quetiapinefumarate along with its stress related substances has been investigated here, proving to be an invaluable tool in ascertaining a reliable method. The study includes forced degradation of quetiapinefumarate under acidic, alkaline, photo, oxidative and peroxide stress conditions followed by separation of degradation products. Critical factors including buffer pH, % organic phase (acetonitrile) and concentration of hexane sulphonate (ion-pairing reagent) susceptible to influence the separation (critical resolutions) and total analysis time were investigated by response surface methodology. The best optimal separation condition as obtained was observed on an enable C-18 column (250mm x 4.6mm i.d. 5µm particle size) using mobile phase composed of Phosphate buffer (pH 2.0) containing 0.002mM hexane sulphonate and acetonitrile (74.4:25.6 v/v) at a flow rate of 1.00ml/min. The eluents were observed at 220nm using a PDA detector. Further, the method was validated to ensure its reliability and other regulatory criteria are met.

**Keywords:** Quetiapine fumarate; Stability-indicating; HPLC; Chemometry; Box-behnken design; Ion-interaction chromatography

### Introduction

Quetiapine fumarate (Seroquel<sup>®</sup>, ICI204, 636) is a psychotropic compound approved as a therapy to treat schizophrenia [1-6], acute mania [7-10], and acute bipolar depression in adult Patients [11,12]. Chemically, quetiapine is a dibenzothiazepine derivative that is {2-(2-(4-dibenzo [b,f] [1,4] thiazepine-11-yl-1-piperazinyl) ethoxy) ethanol} (Figure 1) [13]. The literature review revealed that only few methods; spectrophotometric, capillary zone electrophoretic [14] and voltammetric [15], were used for the assay of quetiapine in tablet formulations. Several bio-analytical methods are also available. These methods include HPLC with UV detection for the determination of quetiapine either alone [16] or in presence of antipsychotics [17,18], antidepressants [19], its metabolites [20] and its degradants [21]. Also, HPLC-electrospray ionization mass spectrometry [22], UPLC-MS/MS [23], HPLC-MS/MS method [24], and capillary zone electrophoresis [25] methods have been reported recently for quantitative analysis of quetiapine.

All of the above methods based on univariate approach (changing one variable at a time, whilst keeping the others constant); seem to lack systematic statistical optimization and are inefficient and time-consuming. In the last years, there has been an increasing interest in developing chemometric approaches for RP-HPLC determination of all types of analytes. Chemometry on the basis of Design of Experiments (DoE) is an emerging approach used for chromatographic analysis that requires limited experiments, less laboratory work and lower reagent consumption; hence relatively fast

and inexpensive than the traditional procedure. These methods discover and screen the probable sources of variability that could impair the RP-HPLC method performance; and facilitate to find the optimum combination of factors and their levels. In the present work, a HPLC method with PDA detection was employed for the analysis of quetiapine in the presence of its stress degradation products. All the influential HPLC parameters have been optimized to facilitate a rapid and sensitive determination of those drugs with the aid of DoE. This method can be applied for the quality control of quetiapine tablets, as well as for the quantitative estimation of quetiapine in biological samples.

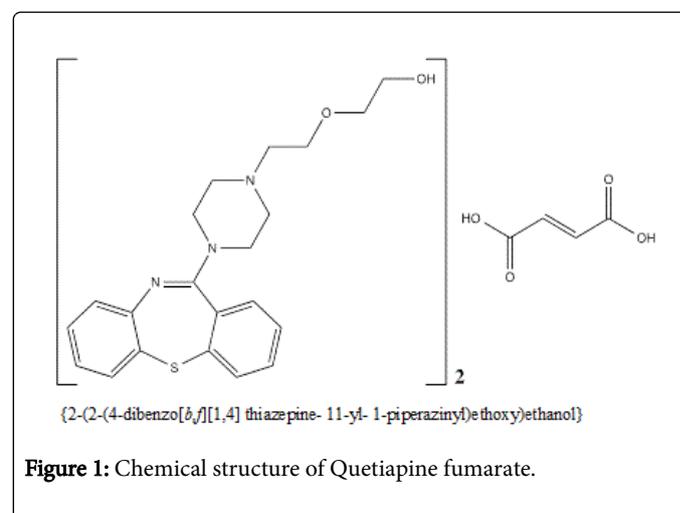


Figure 1: Chemical structure of Quetiapine fumarate.

In the present work, a HPLC method with PDA detection was used for the analysis of quetiapine in the presence of its stress degradation products. Ten degradation products were formed by forced degradation of quetiapine fumarate under acidic, alkaline, photo, oxidative and peroxide stress conditions. However, all the degradants were difficult to resolve and tend to co-elute with each other. Ion-pairing reagents improve resolution thereby affecting the retention times of analytes due to their distinct hydro-affinity [26,27]. Influence of hexane sulphonic acid as ion-pairing reagent, buffer pH and mobile phase composition was investigated on the DoE platform to facilitate an optimal separation and sensitive determination of the analyte and its related substances. This method can be applied for the quality control of quetiapine tablets, as well as for the quantitative determination of quetiapine in biological matrices.

## Experimental

### Apparatus

A binary gradient HPLC system equipped with two LC-20AD pumps, a SPD-M20A diode array detector with a manual injector (all from Shimadzu, Kyoto, Japan) was used throughout the experiment. Reverse-phase Enable C18 G (P/N: A8-ST5 C18G 120-98; S/N: J12-052) analytical column (250 × 4.6mm; 5µm) was used for chromatographic separation of the Quetiapine fumarate and degradation related impurities.

### Materials and reagents

Quetiapine fumarate was procured from Sris Pharmaceuticals, Hyderabad, Telangana, India. HPLC grade water was used throughout the study (acquired from Nanopure, Bransted, USA). All other solvents, chemicals and reagents used were of HPLC grade (all from Merck, Mumbai, India).

### Preparation of standard solutions

Stock solution (standard) was prepared by suspending 100 mg of Quetiapine fumarate in 100 ml of acetonitrile. Further dilution to stock solution was made to get the working standard solution of 100µg/ml.

### Preparation of buffer

The aqueous phase of the HPLC solvent system consists of an equimolar mixture of sodium dihydrogen o-phosphate dihydrate and disodium hydrogen o-phosphate dihydrate buffer (10mM). Different amount of hexane sulphuric acid (0.001-0.003M) as ion-pair reagent was added according to the study designs. The final volume was made up with HPLC grade water to get the desired buffer following pH adjustment to 2.0 and 4.0 with orthophosphoric acid. The prepared buffer was filtered through 0.25µm membrane filter and degassed for 30min in an ultrasonic bath.

### Calculations and software

Chromatographic data analysis and simulation was done by LC-Solution software (Shimadzu, Kyoto, Japan). The experiment was designed employing design-expert software (version: 9.0.3; Stat-Ease Inc.). Execution of experimental trial runs and subsequent statistical evaluation of factorial effects were performed according to the software. MS-Excel was utilized for construction of a calibration plot

and other calculations like mean, standard deviation (SD), %RSD during validation.

### Method optimization

Use of experimental designs (DOE) and their benefits in HPLC method development is very well known. In contrast, traditional (One Factor at a Time (OFAT)) strategy in HPLC is not only exaggerated in terms of time, money, and labour, but also critical to fix true optimal conditions. As mentioned, the main objective of this study is to use DOE for HPLC optimization and separation of quetiapine fumarate from its degradation products. During optimization, the critical method parameters whose variability is known to influence the separation were identified. As in this case, a Response Surface Method (RSM) based BBD was employed to evaluate the impact of three critical variables (buffer pH, % organic phase (acetonitrile) and concentration of hexane sulphonate) on critical resolutions and total analysis time. During RSM computations, polynomial models were generated and factorial effects from interaction and quadratic terms for all the responses were evaluated using Multiple Linear Regression (MLR) analysis (Eqn. 1).

$$Y = \hat{a}_0 + \hat{a}_1X_1 + \hat{a}_2X_2 + \hat{a}_3X_1X_2 + \hat{a}_4X_1^2 + \hat{a}_5X_2^2 + \hat{a}_6X_1X_2^2 + \hat{a}_7X_1^2X_2 \quad (1)$$

Where,  $\hat{a}_0$  is the intercept representing the average of quantitative results of all the experimental runs;  $\hat{a}_1$  to  $\hat{a}_7$  are the coefficients from the observed response values of Y;  $X_1$  (buffer pH),  $X_2$  (%ACN) and  $X_3$  (HSA concentration) are the independent variables; and the terms  $X_1X_2$ ,  $X_1X_3$ ,  $X_2X_3$  and  $X_i^2$  (i=1-3) represent the interaction and quadratic terms, respectively.

### Developing the experimental design

Preliminary experiments by OFAT approach were conducted to check the criticality of the factors on the desired separation. From this investigation, the critical (upper and lower) levels of the variables were finalized. Subsequently, an efficient design space was chosen that could award the optimal condition with minimum experiments. In optimization study, a 33 BBD experimental design was used for evaluation of  $\Delta$ buffer pH ( $3 \pm 1$ ),  $\Delta$ % organic phase ( $30 \pm 5\%$ ) and  $\Delta$ hexane sulphonate concentration ( $0.002 \pm 0.001$ mM) under a set of 17 experimental runs. BBD allowed different combinations of the three factors to bring significant changes in critical resolutions ( $R_{S1-R_{S10}}$ ) and total analysis time. The coded levels of the three factors are portrayed in Table 1. The experiment runs were processed on the chromatographic system and the second order polynomial equation was generated by ANOVA to present the response surface. The p-value of less than 0.05 was regarded as statistically significant.

Variables	Levels		
	-1	0	1
Buffer pH	2	3	4
% ACN	25	30	35
% HSA	0	0	0

Table 1: Coded levels of variables and their values.

### Method validation

To check its suitability for routine use, the method was validated for various parameters as per ICH guideline at the optimal combination of the factor levels (obtained from the mathematical model). A series of dilutions (0.1-100ppm) of the standard solution was chromatographed so as to ascertain the linearity and range of the method. The resulted peak areas were plotted against their corresponding concentrations to obtain the calibration curve. In the precision study, three individual QC samples (10, 50 and 100ppm) within the linearity range were analyzed in triplicate. Method sensitivity was determined by analysing standard solutions ranging from 0.01-20ppm and Limit of Detection (LOD) and Limit of Quantification (LOQ) were calculated from signal to noise ratio (S/N).

### Forced degradation studies

Stock solution of 1mL was used to perform all stress degradation studies. For acid and alkaline hydrolysis, the drug solution was heated in 1mL each of HCl and NaOH (1N) at 60°C for 30min. Stress testing under neutral condition was studied by heating the drug dissolved in water at 60°C for 6h. For study in oxidative condition, the drug solution was kept at 60°C in 1mL of 20% hydrogen peroxide for 30min. For photolytic study, the drug solution was exposed to UV Light (200-Watt hours/m<sup>2</sup>) for 7 days. Additionally, the drug solution was exposed to dry heat at 105°C for 6h in a hot air oven to perform the thermal degradation study. After the stipulated time, equal quantity of samples from each stress conditions was mixed, filtered, sonicated and subjected to HPLC analysis soon after suitable dilution (100µg/mL) and neutralize.

## Results and Discussion

### Method goals

The primary goal of developing the RP-HPLC method is to improve the separation efficiency, which ensures that the method is capable of separating all the analytes with good resolution ( $R_S > 1.5$ ). Other significant necessities for instance short analysis time (<30min) and good peak shapes were also taken into consideration.

### BBD-aided method optimization

The BBD aided set of 17 experimental runs was executed to evaluate the significant impact of different combinations of the said 3-leveled factors in critical separation (resolutions ( $R_S$ 1- $R_S$ 10) and total analysis time. The chromatographic data was depicted in Table 2 and resulted chromatograms in Figure 2.

#### Formation of the second order model and analysis of variance (ANOVA)

The corresponding chromatographic responses from the 17 runs were subjected to statistical analysis by ANOVA (analysis of variance). The regression model was found significant and valid for each response since the p-values for all variables are less than 0.05. The resulted p-values and degree of freedom were enumerated in Table 3. The insignificant terms were excluded. The magnitudes of effects of the three variables and their interactions on each response were studied from the polynomial regression Eqn. 2-5.

$$R_{S1} = +11.84 + 3.11A + 0.98B + 1.65C + 2.17AB + 2.81AC + 0.65BC - 1.56A^2 - 0.08B^2 - 5.98C^2 \quad (2)$$

$$R_{S8} = +2.82 + 0.36A - 0.41B - 1.02C + 0.45AB - 1.44 AC - 0.56 BC - 0.59 A^2 - 1.13 B^2 + 0.77C^2 \quad (3)$$

$$R_{S10} = +1.26 - 1.63A - 0.094B - 1.26C - 3.76AB - 0.25AC - 0.055BC + 5.64A^2 - 0.39 B^2 + 1.93C^2 \quad (4)$$

$$TAT = +20.15 + 2.41A - 8.39B + 2.01C - 0.60AB + 1.16 AC - 3.22 BC + 0.91A^2 + 1.39B^2 - 0.84C^2 \quad (5)$$

Where, A is buffer pH, B is % acetonitrile and C is hexane sulphonate concentration in the mobile phase.

The values of the coefficients define the magnitude of factorial effects and the positive and negative sign on them describe the kinds of effects (positive: synergistic; negative: antagonistic) on the related response. Eqn. 2-5 concludes that buffer pH (variable-A) had the most profound effect on  $R_S$  1 and  $R_S$  10, whereas  $R_S$  8 varies significantly due to factor C (HSA concentration). Unlike others, factor B (% ACN) had a significant effect on total analysis time.

Run	Factors			Responses			
	A:pH	B:% ACN	C:HSA Concentration	$R_{S1}$	$R_{S8}$	$R_{S10}$	TAT
1	3	30	0.002	11.63	2.82	1.167	20.2
2	3	30	0.002	10.9	2.85	1.272	20.01
3	3	30	0.002	11.47	2.8	1.184	20.23
4	2	25	0.002	7.966	1.97	4.066	27.97
5	3	35	0.003	6.382	0.28	0.681	11.88
6	2	30	0.001	8.633	1.68	11.17	17.58
7	3	25	0.001	0.479	3.5	4.797	23.08
8	4	30	0.001	2.995	6.41	9.699	20.13
9	2	30	0.003	8.042	2.47	8.463	17.98
10	4	25	0.002	7.453	0.66	7.024	33.96
11	4	35	0.002	10.78	1.12	1.434	15.73
12	3	35	0.001	4.106	3.39	2.602	13
13	2	35	0.002	2.63	0.65	13.52	12.13
14	3	30	0.002	11.89	2.78	1.338	20.11
15	4	30	0.003	14.22	1.44	5.982	25.17
16	3	30	0.002	13.34	2.83	1.324	20.19
17	3	25	0.003	0.156	2.64	3.097	34.83

**Table 2:** Experimental runs as said by BBD for the two variables (3 levels) and their observed responses.

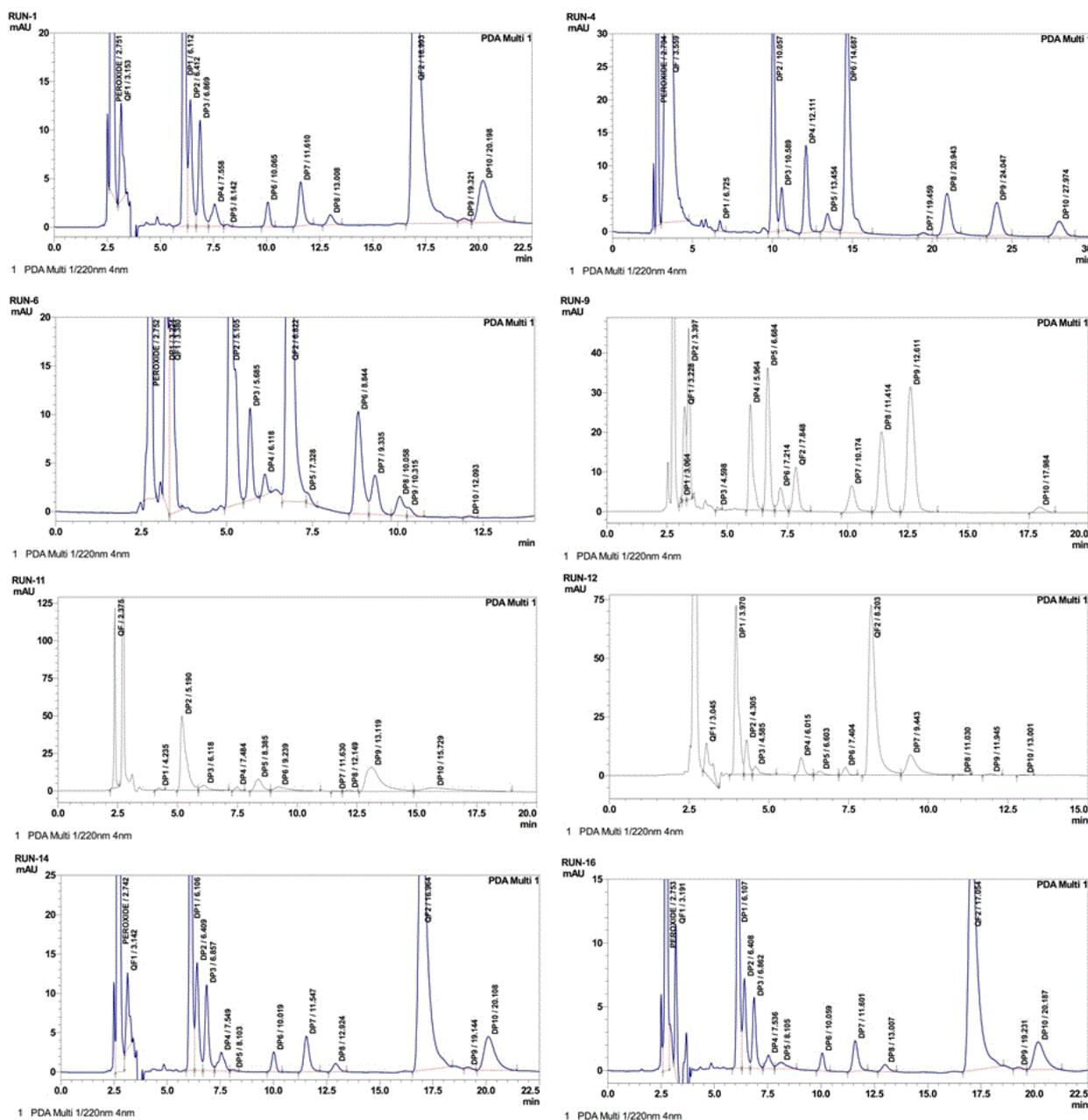


Figure 2: Represented chromatograms obtained from the investigated trial runs.

### Appraisal of response sensitiveness by perturbation plots

Perturbation plots generated by the model elucidate the factorial effect on a specific response, when the others kept constant at a reference point. A steepest slope or curvature analogous to a particular factor indicates that it has significant influence on the response. The plots show and concludes that buffer pH (variable-A) had the most profound effect on  $R_{S1}$  and  $R_{S10}$ , whereas,  $R_{S8}$  varies significantly due to factor C (HSA concentration). Unlike others, factor B (% ACN) had a significant effect on total analysis time (Figures 3a-3d).

### Formation of 3D response surface plots

Three-dimensional (3D) response surface plots allow visual interpretation of the model. The 3D plots were formed to assess the factor-response relationship and changes in the response surface. Figure 4 shows the collective influence of the three variables on the responses  $R_{S1}$ ;  $R_{S8}$ ;  $R_{S10}$  and total analysis time (min). Since, some of the observed response surfaces formed hillsides with tiny or no curvatures; both the factors appeared to have an independent contribution towards the elution of the compounds.

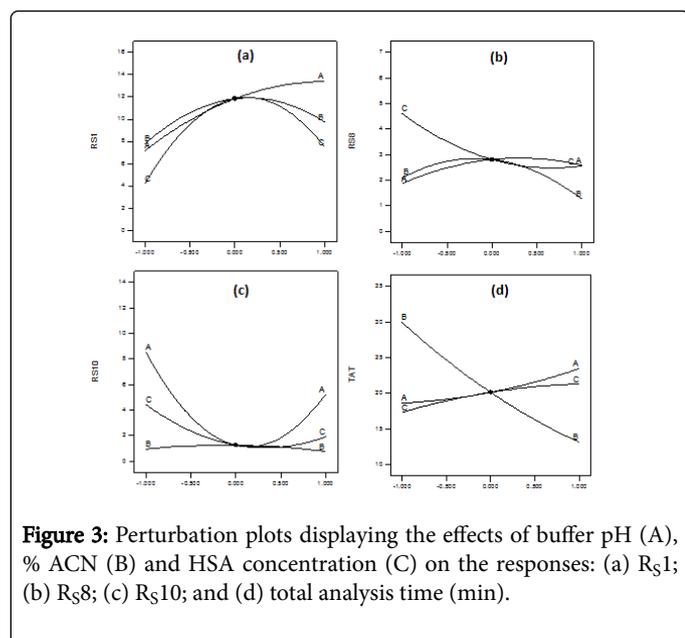
Source	R <sub>S1</sub>		R <sub>S8</sub>		R <sub>S10</sub>		TAT	
	F Value	p-value	F Value	p-value	F Value	p-value	F Value	p-value
		Prob>F		Prob> F		Prob> F		Prob> F
Model	6.78	0.0097	8.1	0.0058	14.35	0.001	155.1	< 0.0001
A-pH	12.54	0.0095	2.48	0.1594	11.23	0.0122	92.36	< 0.0001
B-% CAN	1.25	0.3005	3.31	0.1115	0.037	0.8532	1115.47	< 0.0001
C-HSA Concentration	3.52	0.1026	20.04	0.0029	6.63	0.0368	64.01	< 0.0001
AB	3.05	0.1243	1.92	0.2082	29.71	0.001	2.82	0.1367
AC	5.11	0.0582	20.13	0.0028	0.13	0.7257	10.66	0.0138
BC	0.27	0.6166	3.05	0.124	6.41E-03	0.9384	82.05	< 0.0001
A2	1.66	0.2388	3.49	0.1041	70.46	< 0.0001	6.88	0.0343
B2	6.48	0.0383	13.09	0.0085	0.34	0.5795	16.21	0.005
C2	24.49	0.0017	6.03	0.0438	8.22	0.0241	5.89	0.0456

\*Values closer to 1 show perfect fit to quadratic mathematical model for the three independent factors.  
\*\*Adequate precision (signal to noise ratio) greater than 4 indicates adequate signal and the model is useful to navigate the design space.

**Table 3:** Analysis of variance for the screened chromatographic responses (insignificant terms are excluded).

It was observed that R<sub>S1</sub> varied in a curvilinear order due to %ACN and nonlinearly ascending due to buffer pH. R<sub>S8</sub> was observed to have negligible impact by AB interaction. R<sub>S10</sub> varies in an ascending linear order by %ACN while the effect was curvilinear due to buffer pH. Total analysis time also varied in a linearly descending manner by %ACN, whilst linearly descending order by buffer pH.

critical pair of peaks, and (ii) minimum analysis time. Desirability criteria for optimizing individual responses including upper and lower limits were mentioned in Table 4. The optimal method condition was predicted using a mathematical method (Eqn. 6). Condition among the three checkpoint solutions with least prediction error denotes the optimal combination of variables for desired separation.



**Figure 3:** Perturbation plots displaying the effects of buffer pH (A), % ACN (B) and HSA concentration (C) on the responses: (a) R<sub>S1</sub>; (b) R<sub>S8</sub>; (c) R<sub>S10</sub>; and (d) total analysis time (min).

**Optimization**

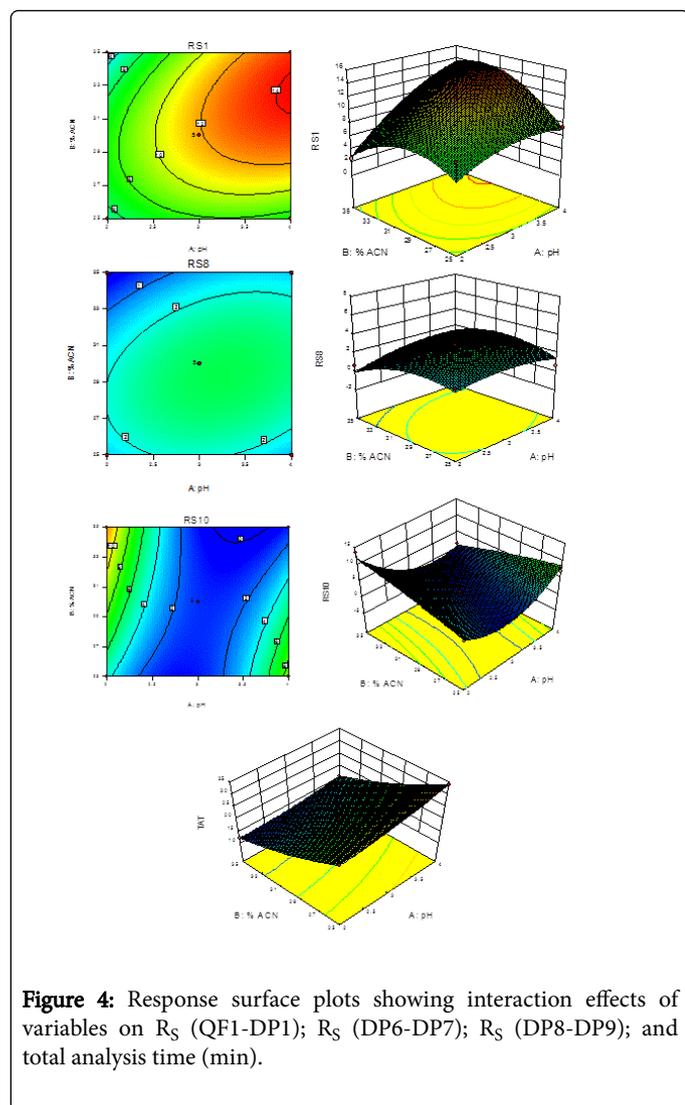
The optimum HPLC condition was accomplished based on the following desired separation criteria: (i) maximum resolution between

$$\text{Percentage prediction Error (P.E.)} = \frac{\text{Observed} - \text{Predicted}}{\text{Predicted}} \times 100 \quad (6)$$

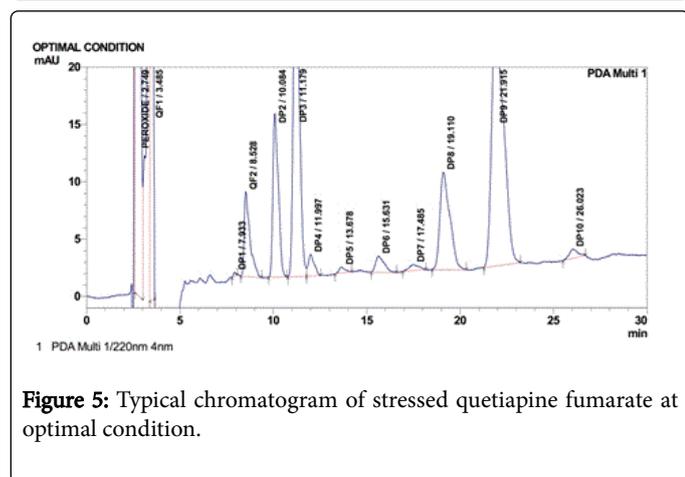
Consequently, phosphate buffer (pH 2.0) containing 0.002mM hexane sulphonate and acetonitrile (25.6: 74.4v/v) at a flow rate of 1.00mL/min was considered as optimal HPLC condition to achieve the desirable responses. In this condition, R<sub>S1</sub> of 17.839, R<sub>S8</sub> of 1.611, R<sub>S10</sub> of 4.344 and total analysis time of 26.023 were observed. The chromatogram obtained from the above condition is revealed in Figure 5.

**Method validation**

The summary of method validation data is shown in Table 5. From the system suitability test results, it has been confirmed that the system was found to be suitable as it complies with the limits of peak parameters. Resolution (>2) and peak asymmetry (<1.4) for all the analytes confirm the good selectivity of the method. Peak areas for drug samples were precisely linear in the concentration range between 25-200µg/mL. The data were analyzed by least squares linear regression indicating good linearity for quetiapine fumarate (R<sup>2</sup>=0.999). The obtained LOD (1.47µg/mL) and LOQ (4.45µg/mL) results demonstrate that the method is adequately sensitive. The data attained from precision study for intra-and inter-day precision experiments.



**Figure 4:** Response surface plots showing interaction effects of variables on  $R_S$  (QF1-DP1);  $R_S$  (DP6-DP7);  $R_S$  (DP8-DP9); and total analysis time (min).



**Figure 5:** Typical chromatogram of stressed quetiapine fumarate at optimal condition.

The calculated % R.S.D. values for inter-day and intra-day precision study were <2.0% proving that the method was suitably precise. The mean percentage recovery from the accurate study was calculated for fortified and unfortified solutions. Excellent recoveries were obtained (>99.62%) at each added concentration.

Responses	Goal	Lower Limit	Upper Limit
$R_{S1}$	Maximize	0.865	2.038
$R_{S8}$	Maximize	1.602	2.286
$R_{S10}$	Maximize	0.878	1.545
Total analysis time	In range	15.553	27.387

**Table 4:** Desirability criteria for optimizing individual responses.

Parameters	Quetiapine fumarate
<b>System suitability</b>	
RT (min)	3.485
$A_s$	0.984
N	4563
<b>Linearity</b>	
Range ( $\mu\text{g/mL}$ )	25-200
$R^2$	0.9989
Slope (mean $\pm$ SD)	4295.4 $\pm$ 34.34
Intercept (mean $\pm$ SD)	5261.4 $\pm$ 9.32
<b>Sensitivity<sup>b</sup></b>	
LOD ( $\mu\text{g/mL}$ )	1.47
LOQ ( $\mu\text{g/mL}$ )	4.45
<b>Precision (%RSD)<sup>a</sup></b>	
Intra-day	0.42
Inter-day	0.93
<b>Accuracy</b>	
<b>At 50 % level<sup>b</sup></b>	
Amount added ( $\mu\text{g/mL}$ )	50
%Recovery (mean $\pm$ SD; %RSD)	99.73 $\pm$ 0.3458; 0.346
<b>At 100 % level<sup>b</sup></b>	
Amount added ( $\mu\text{g/mL}$ )	100
%Recovery (mean $\pm$ SD; %RSD)	99.62 $\pm$ 0.260; 0.261
<b>At 150 % level<sup>b</sup></b>	
Amount added ( $\mu\text{g/mL}$ )	150
%Recovery (mean $\pm$ SD; %RSD)	99.7 $\pm$ 0.193; 0.193

<sup>a</sup>Average of the three determinations. <sup>b</sup>Average of six determinations. RT: Retention time;  $A_s$ : Tailing factor; N: Number of the theoretical plates;  $r^2$ : Correlation coefficient.

**Table 5:** Method validation summary.

## Conclusion

A chemometric design of experiment was exercised for isocratic RP-HPLC determination of Quetiapine fumarate and its related substances. A response surface methodology with the aid of Box-Behnken design was employed to study the factorial influence on desired separation criteria. Phosphate buffer (pH 2.0) containing 0.002 mM hexane sulphonate and acetonitrile (74.4:25.6 v/v) at a flow rate of 1.0mL/min was recognized as the optimal condition to facilitate the desired chromatographic elution of the drug along with its degradation products. As a consequence, it will be a valuable tool for routine quality control of the analyte.

## References

1. Arvanitis LA, Miller BG (1997) Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry* 42: 233-246.
2. King DJ, Link CG, Kowalczyk B (1998) A comparison of bd and tid dose regimens of quetiapine (Seroquel) in the treatment of schizophrenia. *Psychopharmacology* 137: 139-146.
3. Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CG (1997) Quetiapine in patients with schizophrenia. A high- and low-dose double-blind comparison with placebo. *Arch Gen Psychiatry* 54: 549-557.
4. Peuskens J, Trivedi J, Malyarov S, Brecher M, Svensson O, et al. (2007) Prevention of schizophrenia relapse with extended release quetiapine fumarate dosed once daily: a randomized, placebo-controlled trial in clinically stable patients. *Psychiatry* 4: 34-50.
5. Kahn RS, Schulz SC, Palazov VD, Reyes EB, Brecher M, et al. (2007) Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 68: 832-842.
6. Lindenmayer JP, Brown D, Liu S, Brecher M, Meulien D (2008) The efficacy and tolerability of once-daily extended release quetiapine fumarate in hospitalized patients with acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled study. *Psychopharmacol Bull* 41: 11-35.
7. Bowden CL, Grunze H, Mullen J, Brecher M, Paulsson B, et al. (2005) A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry* 66: 111-121.
8. McIntyre R, Brecher M, Paulsson B, Huizar K, Mullen J (2005) Quetiapine or haloperidol as monotherapy for bipolar mania: a 12-week, double-blind, randomized, parallel-group, placebo-controlled trial. *Eur Neuropsychopharmacol* 15: 573-585.
9. Sachs G, Chengappa KN, Suppes T, Mullen JA, Brecher M, et al. (2004) Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. *Bipolar Disord* 6: 213-223.
10. Vieta E, Mullen J, Brecher M, Paulsson B, Jones M (2005) Quetiapine monotherapy for mania associated with bipolar disorder: combined analysis of two international, double-blind, randomized, placebo-controlled studies. *Curr Med Res Opin* 21: 923-934.
11. Calabrese JR, Keck PE, Macfadden W, Minkwitz M, Ketter TA, et al. (2005) A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry* 162: 1351-1360.
12. Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, et al. (2006) Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol* 26: 600-609.
13. Indian Pharmacopoeia (2010) Indian Pharmacopoeia Commission (7th edn). Ministry of Health and Family Welfare, Government of India.
14. Pucci V, Mandrioli R, Ferranti A, Furlanetto S, Raggi MA (2003) Quality control of commercial tablets containing the novel antipsychotic quetiapine. *J Pharm Biomed Anal* 32: 1037-1044.
15. Ozkan SA, Dogan B, Uslu B (2006) Voltammetric Analysis of the Novel Atypical Antipsychotic Drug Quetiapine in Human Serum and Urine. *Mikrochimica Acta* 153: 27-35.
16. Mandrioli R, Fanali S, Ferranti A, Raggi MA (2002) HPLC analysis of the novel antipsychotic drug quetiapine in human plasma. *J Pharmaceutic Biomed Anal* 30: 969-977.
17. Frahnert C, Rao ML, Grasmader K (2003) Analysis of eighteen antidepressants, four atypical antipsychotics and active metabolites in serum by liquid chromatography: a simple tool for therapeutic drug monitoring. *J Chromatogr B Analyt Technol Biomed Life Sci* 794: 35-47.
18. Sachse J, Koller J, Harter S, Hiemke C (2006) Automated analysis of quetiapine and other antipsychotic drugs in human blood by high performance-liquid chromatography with column-switching and spectrophotometric detection. *J Chromatogr B Analyt Technol Biomed Life Sci* 830: 342-348.
19. Saracino MA, Mercolini L, Flotta G, Albers LJ, Merli R (2006) Simultaneous determination of fluvoxamine isomers and quetiapine in human plasma by means of high-performance liquid chromatography. *J Chromatogr B Analyt Technol Biomed Life Sci* 843: 227-233.
20. Hasselstrom J, Linnet K (2003) Fully automated on-line quantification of quetiapine in human serum by solid phase extraction and liquid chromatography. *J Chromatogr B Analyt Technol Biomed Life Sci* 798: 9-16.
21. Belal F, Elbrashy A, Eid M, Nasr JJ (2008) Stability-Indicating HPLC Method for the Determination of Quetiapine: Application to Tablets and Human Plasma. *J Liquid Chromatography Related Technol* 31: 1283-1298.
22. Zhou Z, Li X, Li K, Xie K, Cheng Z, et al. (2004) Simultaneous determination of clozapine, olanzapine, risperidone and quetiapine in plasma by high-performance liquid chromatography-electrospray ionization mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 802: 257-262.
23. Li KY, Zhou YG, Ren HY, Wang F, Zhang BK, et al. (2007) Ultra-performance liquid chromatography-tandem mass spectrometry for the determination of a typical antipsychotics and some metabolites in in vitro samples. *J Chromatogr B Analyt Technol Biomed Life Sci* 850: 581-585.
24. Barrett, Holcapek B, Huclova M, Borek-Dohalsky J, Fejt V, et al. (2007) Validated HPLC-MS/MS method for determination of quetiapine in human plasma. *J Pharm Biomed Anal* 44:498-505.
25. Hillaert S, Snoeck L, Bossche VD (2004) Optimization and validation of a capillary zone electrophoretic method for the simultaneous analysis of four atypical antipsychotics. *J Chromatogr A* 1033: 357-362.
26. Furuki K, Toyo'oka T (2017) Retention of glycopeptides analyzed using hydrophilic interaction chromatography is influenced by charge and carbon chain length of ion-pairing reagent for mobile phase. *Biomed Chromatogr*.
27. Sviben D, Forcic D, Ivancic-Jelecki J, Halassy B, Brgles M (2017) Recovery of infective virus particles in ion-exchange and hydrophobic interaction monolith chromatography is influenced by particle charge and total-to-infective particle ratio. *J Chromatogr B Analyt Technol Biomed Life Sci* 1054: 10-19.