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Original article

## Ion-pair titrimetric assays of quetiapine fumarate in pharmaceuticals using sodium tetraphenylboron and sodium lauryl sulphate

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### Abstract:

Two simple, rapid, precise and accurate titrimetric methods employing sodium tetraphenylboron (STPB) and sodium lauryl sulphate (SLS) as titrants are described for the quantitative determination of quetiapine fumarate (QTF) in bulk drug and tablets. The proposed methods are based on the solvent extraction-titration of QTF with STPB (method A) and SLS (method B) using tetrabromophenolphthalein ethyl ester (method A) and dimethyl yellow (method B) as indicators. In method A, the titration was performed in the presence of sodium acetate and 1, 2-dichloroethane whereas in method B, the titration was carried out in the presence of dilute sulphuric acid and dichloromethane. The methods were applicable over the ranges of 4.0-18.0 and 5.0-25.0 mg of QTF for method A and method B, respectively. The proposed methods yielded the reaction stoichiometries of 1:1 and 1:2 for method A and method B, respectively. The methods were applied successfully to the determination of QTF in tablets. The precision results, expressed by intra-day and inter-day relative standard deviation values, were satisfactory ( $RSD \leq 1.56\%$ ). The accuracy was satisfactory as well ( $RE \leq 2.2\%$ ). The percentage recoveries were in the range 97.37-104.1% with standard deviation values 0.47-1.26%.

**Keywords:** Quetiapine fumarate; Assay; Dimethyl yellow; Tetrabromophenolphthalein ethyl ester; Pharmaceuticals

## Introduction

Quetiapine fumarate (QTF), chemically known as 2-(2-(4-dibenzo[b,f][1,4]thiazepine-11-yl-1-piperazinyl)ethoxy) ethanol, fumaric acid (1:2 salt; formula  $C_{29}H_{33}N_3O_{10}S$ ; molecular weight: 615.66) (Figure 1), is an atypical antipsychotic drug [1] used for the treatment of schizophrenia, acute manic bipolar disorder. Recently, it was approved by the FDA for the treatment of depressive episodes associated with Bipolar I (Bipolar II) disorder as a monotherapeutic agent [2].

A number of analytical methods for the quantitative determination of QTF are known. HPLC with UV [3-10], chemiluminescence [11], electrospray ionization MS [12-15], tandem MS/MS [16-18] detection, UPLC with tandem MS detection [19,20], GC [21,22] and voltammetry [23] have been reported for biological fluids. QTF is not official in any pharmacopoeia. Methods based on different techniques such as polarography [24], capillary zone electrophoresis [25,26], HPTLC [27,28], HPLC with UV detection [29-31] and UV spectrophotometry [25,32,33] have been used for the determination of QTF in pharmaceuticals. However, most of these methods except UV methods [25,32,33], require expensive instrumental set up and well trained personal to handle the instrument. In addition, these methods neither involve pre-extraction procedures nor consume longer time.

Two phase titrations (ion-pair extraction titrations or ion association titrations) employing indicators for visual end-point detection are already well established for the determination of surfactants [34-38], amines [39-41], ammonium compounds [39-42] and pharmaceutical

substances [39,40,43-48]. The characteristic of the ion association titration methods consists in the use of a two-phase (water-organic solvent) system. The end point detection is based on the stabilities of the ion-pairs formed between the determined substance with the titrant and with the indicator [43].

There is no titrimetric procedure ever reported for the determination of QTF in pharmaceuticals which is very simple technique adoptable to determine the drug content in milligram level in the quality control laboratories across the developing countries where modern and expensive instruments are not available. Therefore, this paper presents two ion association titration methods for the determination of QTF in pharmaceuticals. In method A, the titrant was sodium tetraphenylboron (STPB) and the titration was done in the presence 1, 2-dichloroethane with tetrabromophenolphthalein ethyl ester (TBPE) as indicator. Method B uses sodium lauryl sulphate (SLS) as the titrant and the titration was carried out in the presence of sulphuric acid ( $pH\ 1.60 \pm 0.01$ ) and dichloromethane using dimethyl yellow (DMY) as indicator. The proposed methods are simple, rapid, and easy to apply in routine usage and do not need any costly instrumentation.

## Experimental

### Instrument

Elico LI 610 digital pH meter provided with a combined glass-SCE electrode system was used to record the pH and Equip-Tronics magnetic stirrer model EQ-770 was used to stir the solution during titration.

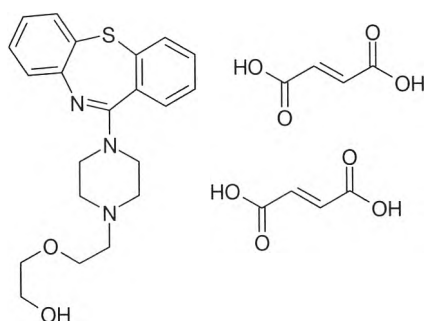


Figure 1 Chemical structure of quetiapine fumarate (QTF)

### Chemicals

1, 2-Dichloroethane (DCE) and dichloromethane (DCM) (Merck, Mumbai, India) (spectroscopic grade) and absolute ethanol were used without any purification. All chemicals used were of analytical reagent grade and distilled water was used throughout the investigations. A  $4 \times 10^{-3}$  M solution of tetraphenylborate was prepared by dissolving required amount of sodium tetraphenylboron (S.D. Fine Chem., Mumbai, India, assay 99.5%) in 100 ml of water and diluting to 250 ml with 0.001 N sodium hydroxide solution; a 0.2% (w/v) potassium salt of tetrabromophenolphthalein ethyl ester (TBPE) (Sigma-Aldrich, Inc., USA) was prepared in absolute ethanol and 1 M sodium acetate (NaOAc) (S. D. fine Chem Ltd., Mumbai, India) was prepared in water.

A 0.01 M sodium lauryl sulfate (LOBA Chemie PVT. Ltd., Mumbai, India) was prepared in water and a 0.01% (w/v) dimethyl yellow (DMY) (Rolex Laboratory Reagent, Mumbai, India) was prepared in absolute ethanol. A 0.1 M sulphuric acid was prepared by appropriately diluting concentrated sulfuric acid (Merck, Mumbai, India, Sp. gr. 1.84) with water. QTF pure drug was kindly provided by Cipla Ltd, Bangalore, India, as a gift and used as received. Qutipin-200 and Qutipin-100 tablets (both from Sun Pharmaceuticals Ltd, India) were purchased from local market.

### Standard drug solution

Stock standard solutions containing 2.0 mg/ml and 2.5 mg/ml QTF were prepared in 0.1 M  $\text{H}_2\text{SO}_4$  and used in method A and method B respectively.

### General analytical procedures

#### Method A (using STPB as titrant)

Different aliquots (2.0-9.0 ml; 2 mg/ml) of pure QTF solution were accurately transferred into a 50 ml beaker and the volume was adjusted to 10 ml with 0.1 M  $\text{H}_2\text{SO}_4$ . Three millilitres of 1 M NaOAc, 2 drops of TBPE indicator solution and 5 ml of DCE were added and mixed well. The mixture was titrated against  $4 \times 10^{-3}$  M STPB solution with vigorous stirring to a yellow end point.

#### Method B (using SLS as titrant)

An aliquot of the standard drug solution equivalent to 5.0-25.0 mg of QTF was transferred into a clean 500 ml beaker and the volume was adjusted to 10 ml by adding 0.1 M  $\text{H}_2\text{SO}_4$ . Ten milliliters of water, 0.5 ml of 0.01% DMY and 5 ml of dichloromethane were added and the mixture was titrated with 0.01 M SLS with vigorous stirring until a color change from yellow to pink occurs in the organic phase at the end-point. A reagent blank prepared in the same way was titrated and necessary corrections were applied to the sample titer volume.

The amount of drug in the measured aliquot was calculated separately in both the methods.

### Procedure for tablets

Twenty tablets were weighed accurately and ground into a fine powder. Required amount of tablet powder [equivalent to 200 mg (method A) and 250 mg (method B)] was weighed and transferred into a clean 100 ml calibrated flask containing about 60 ml of 0.1 M  $\text{H}_2\text{SO}_4$ . The extraction was done by shaking thoroughly for about 20 min; then the volume was made up to the mark with the same acid and mixed well. After 5 min, the solution was filtered using a Whatman No. 42 filter paper. The first 10 ml portion of the filtrate was discarded. The resulting (2.0 or 2.5 mg/ml) QTF solution was subjected to analysis following the respective general procedures.

### Results and Discussion

The two-phase ion-association titration was applied to the determination of some basic pharmaceutical compounds using indicators for visible end-point detection. Earlier, end-point detection in two-phase titrations was based on the movement of the indicator from one phase to other and it was difficult to detect the end point because the color of the indicator in the aqueous phase or organic phase will be reflected in the other phase [48].

An alternative approach is to use hydrophobic indicators, which remain in the organic phase throughout the titration and give a very sharp color change [49].

Eppert and Liebscher [50] used dimethyl yellow (cationic) indicator in their titration whereas Tsubouchi et al. [51] used the potassium salt of the ethyl ester of tetrabromophenolphthalein (anionic) indicator for the two-phase titration. The above indicators are useful in the detection of the end point as the color change depends on the pH.

## Chemistry

### Method A

When QTF, NaOAc, DCE and TBPE indicator were mixed well, the aqueous phase became colorless, and a red-violet color developed in the DCE phase; because the indicator forms an organophilic ion-pair complex with the drug. Near the equivalence point, the organic phase starts to turn green and when one drop excess of the titrant was added, the color of the organic phase changed from red-violet to yellow.

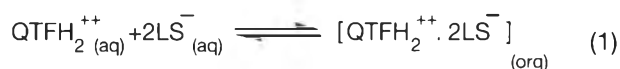
This titration procedure yielded a reaction stoichiometry of 1:1 (drug:titrant) and using  $4 \times 10^{-3}$  M STPB, 4.0-18 mg of QTF was successfully determined. The relationship between the drug amount and the titration end point was examined. The linearity between two parameters is apparent from the correlation coefficient of 0.9876 obtained by the method of least squares. From this it is implied that the reaction between QTF and STPB proceeds stoichiometrically in the ratio 1:1 in the range studied.

### Method B

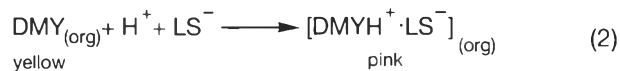
In this method, SLS was used as titrant with DMY as indicator in the presence of DCM. After treating tertiary amine (QTF) with  $H_2SO_4$ , the resulting protonated amine ( $QTFH_2^{++}$ ) was titrated with SLS using DMY. Dimethyl yellow does not possess any hydrophilic group. Therefore, color change occurs only in the organic phase. The azoid (DMY) form of DMY is yellow in colour and the acid form of DMY [quinoid ( $DMYH^+$ )] is pink in colour [52]. The salts of both the forms of DMY with SLS are soluble in DCM and the end-point is indicated by a pink color in the organic phase only. The aqueous phase remains colourless throughout the titration.

The possible reaction pathway at the equivalence point between the protonated drug ( $QTFH_2^{++}$ ) and

lauryl sulphate ( $LS^-$ ) is believed to be as follows [53].



Beyond the equivalence point, the excess  $LS^-$  forms complex with indicator in the following manner.



The above titration reaction produced a stoichiometry of 1:2 (drug:titrant) which served as the basis for calculation. Using 0.01 M SLS, 5.0-25 mg of QTF was conveniently determined. The relationship between the drug amount and the titration end point was examined. The linearity between two parameters is apparent from the correlation coefficient of 0.9976 obtained by the method of least squares. From this it is implied that the reaction between QTF and SLS proceeds stoichiometrically in the ratio 1:2 in the range studied.

## Method development and optimization

### Method A

The methods were optimized by titrating fixed amount of the drug and varying other parameters and the stoichiometric amount of the drug found was calculated in each case.

The results obtained in sulphuric acid medium were better than in other acids. Therefore, sulphuric acid was selected as choice of solvent to dissolve QTF. The end point of the titration was not very sharp and there was no consistent stoichiometry was obtained in the presence of additional 0.1 M or higher concentration of  $H_2SO_4$ . The titration was performed in the presence of 1M NaOAc by varying its volume with a fixed amount of drug. The results of study indicated the reaction stoichiometry remained virtually constant with 2-5 ml of 1 M NaOAc solution. Volume of NaOAc less than 2.0 ml produced incorrect stoichiometry. Therefore, 3 ml of 1 M NaOAc was fixed to yield sharp end point and consistent stoichiometry. Studies on the effect of volume of DCE and indicator on the effective formation of ion-pairs revealed that a 5 ml of DCE and 2 drops of TBPE were found to be adequate and the same amount was fixed throughout the investigation.

### Method B

The method was investigated for optimum pH, volume of water, indicator and DCM. A series of studies were performed to fix the pH of the aqueous phase by adding 0.1 M H<sub>2</sub>SO<sub>4</sub> and the results revealed that at pH 1.6 ± 0.01 better results were obtained. Below and above this pH value, there was a drastic change in the stoichiometry of the reaction. The results obtained by the variation of amount of water (5-20 ml) produced same results but with 10 ml of water, end point colour change was very clear and cloudiness of the aqueous phase was less. Therefore, to a total volume of 20 ml (which includes 10 ml each of 0.1 M H<sub>2</sub>SO<sub>4</sub> and QTF solution) of aqueous phase no additional acid/base was added and 10 ml of water was fixed as optimum. The colour change at the end point was clear when the amount of indicator varied from 0.2 ml to 1.5 ml. There was clear and better separation of the organic and aqueous layers and clear indication of the end point when the volume of DCM was maintained at more than 5 ml in a total volume of 25 ml. Therefore, 0.5 ml indicator and 5 ml of DCM were used in the assay.

### Method validation

#### Intra-day and inter-day accuracy and precision

Accuracy was evaluated as percentage relative error between the measured and taken amounts of QTF (Bias %). The results, compiled in Table 1, show that the accuracy is good for both methods. Precision of the methods was calculated in terms of intermediate

precision (intra-day and inter-day) [54]. Three different concentration of QTF (within the working limits) were analyzed in seven replicates during the same day (intra-day precision) and five consecutive days (inter-day precision). RSD (%) values of the intra-day and inter-day studies showed that the precision was good for the both methods.

#### Selectivity

To determine the selectivity of the methods, the analytical placebo blank was prepared and subjected to analysis by the proposed methods. It was confirmed that the change in the titrant value with respect to the water blank was caused only by the analyte. To identify the interference by common tablet excipients, a synthetic mixture with the composition: QTF (200 mg in method A and 250 mg in method B), talc (80 mg), starch (160 mg), calcium gluconate (80 mg), lactose (80 mg), sodium alginate (40 mg) and magnesium stearate (40 mg), was prepared and subjected to analysis by the proposed methods after solution preparation using the procedure described for tablets. The percent recoveries of QTF were 98.60 ± 0.52 (n=5) and 103.20 ± 1.26 (n=5) by methods A and B, respectively, suggesting no interference by the excipients in the assay of QTF under the described optimum conditions.

#### Robustness and ruggedness of the methods

The robustness of the methods was evaluated by making small incremental changes in volumes of NaOAc (3 ± 0.2 ml/DCE (10 ± 1 ml) in method A and volumes of indicator/DCM in method B) and the effect

Table 1 Evaluation of intra-day and inter-day precision and accuracy

Method	QTF taken mg	Intra-day (n=7)			Inter-day (n=5)		
		QTF found <sup>a</sup>	Precision <sup>b</sup>	Accuracy <sup>c</sup>	QTF found <sup>a</sup>	Precision <sup>b</sup>	Accuracy <sup>c</sup>
A	5.0	5.06	1.26	1.20	5.11	1.56	2.20
	10.0	10.16	0.89	1.60	10.19	1.55	1.90
	15.0	14.95	0.98	0.33	15.08	1.21	0.53
B	5.0	4.99	1.14	0.03	4.95	1.25	1.00
	12.5	12.51	0.61	0.08	12.45	1.02	0.40
	20.0	19.99	0.21	0.05	19.86	0.95	0.70

<sup>a</sup>Mean value of n determinations

<sup>b</sup>Relative standard deviation (%)

<sup>c</sup>Relative error (%): [(found-taken)/taken] x 100

**Table 2** Method robustness ruggedness expressed as intermediate precision (%RSD)

Method	QTF taken*, mg	Robustness		Ruggedness
		Parameters altered		Inter-analysts (%RSD), (n=4)
		Volume of NaOAc/DCE*	Volume of indicator/DCM**	
A	5.0	1.61	-	1.69
	10.0	1.14	-	1.89
	15.0	1.12	-	2.01
B	5.0	-	1.51	1.22
	12.5	-	1.63	1.47
	20.0	-	1.79	1.58

\*Volumes NaOAc varied were 2.8, 3.0 and 3.2 ml and volumes of DCE varied were 4.8, 5.0 and 5.2 ml

\*\*Volumes indicator varied were 0.48, 0.5 and 0.52 ml and volumes of DCM varied were 4.8, 5.0 and 5.2 ml

**Table 3** Results of analysis of tablets by the proposed methods and statistical comparison of the results with the reference method

Tablet brand name	Nominal amount, (mg/tablet)	Found* (Percent of label claim $\pm$ SD)		
		Reference method	Proposed methods	
			Method A	Method B
Qutipin-200	200	97.67 $\pm$ 0.62	98.32 $\pm$ 0.92	98.83 $\pm$ 0.87
			t = 1.33	t = 2.46
			F = 2.20	F = 1.97
Qutipin-100	100	99.32 $\pm$ 0.76	98.67 $\pm$ 0.38	100.40 $\pm$ 0.54
			t = 1.80	t = 2.55
			F = 4.00	F = 1.98

\*Mean value of 5 determinations

(Tabulated t-value at the 95% confidence level and for four degrees of freedom is 2.77).

(Tabulated F-value at the 95% confidence level and for four degrees of freedom is 6.39).

of the changes was studied by calculating the RSD values. The changes had negligible influence on the results as revealed by small intermediate precision values expressed as % RSD. The values were lying in the range 1.12-1.79%. Method ruggedness was expressed as the RSD of the same procedure applied by four different analysts and the RSD values were within 2.01%. This results suggesting that the developed methods were rugged. The results of these studies are compiled in Table 2.

### Application

The described titrimetric procedures were successfully applied for the determination of QTF in its pharmaceutical formulations. The results obtained (Table 3) were statistically compared with those obtained

by UV spectrophotometric method [32]. The method consisted that UV spectrophotometric measurement of QTF in water at 290 nm. Statistical analysis of the results did not detect any significant difference between the performance of the proposed methods and reference method with respect to accuracy and precision as revealed by the Student's t-value and variance ratio F-value [55]. The results of assay are given in Table 3.

### Recovery study

Accuracy and the reliability of the methods were further ascertained by performing recovery experiments. To a fixed amount of drug in formulation (pre-analyzed): pure drug at three different levels was added, and the total was found by the proposed methods. Each test was repeated three times. The recoveries were in the

**Table 4** Results of recovery study via standard-addition method

Tablets studied	Method A				Method B			
	QTF in tablet, mg	Pure QTF added, mg	Total found, mg	Pure QTF recovered (Percent $\pm$ SD*)	QTF in tablet, mg	Pure QTF added, mg	Total found, mg	Pure QTF recovered (Percent $\pm$ SD*)
Qutipin-200	5.90	3.0	8.94	101.30 $\pm$ 0.72	7.92	4.0	11.94	100.60 $\pm$ 0.77
	5.90	6.0	12.12	103.70 $\pm$ 1.12	7.92	8.0	15.82	98.73 $\pm$ 0.62
	5.90	9.0	15.13	102.60 $\pm$ 0.84	7.92	12.0	20.14	101.80 $\pm$ 0.56
Qutipin-100	5.92	3.0	8.91	99.76 $\pm$ 1.26	8.03	4.0	12.17	103.60 $\pm$ 0.92
	5.92	6.0	11.76	97.37 $\pm$ 0.78	8.03	8.0	16.36	104.10 $\pm$ 0.66
	5.92	9.0	14.97	100.50 $\pm$ 0.92	8.03	12.0	20.21	101.50 $\pm$ 0.47

\*Mean value of three determinations.

range from 97.37-104.1% with standard deviation in the range 0.47-1.26% indicating that commonly added excipients to tablets did not interfere in the determination and closeness of the results to 100% showed the fairly good accuracy of the methods. These results are shown in Table 4.

## Conclusion

For the first time two titrimetric methods based on ion-association extraction/reaction employing sodium tetraphenyl boron and sodium lauryl sulphate as titrants, tetrabromophenolphthalein ethyl ester and dimethyl yellow as indicators in the presence of 1,2-dichloroethane and dichloromethane as extraction solvents have been developed and validated for the determination of quetiapine fumarate. Both methods gave very sharp end points and allowed to determine quetiapine fumarate in very wide milligram range. The results revealed that method B is more accurate and precise than method A which can be seen by very less %RSD and %RE values. In addition to this the proposed methods are more advantageous because most of the reported methods except UV methods [25,32,33], require expensive instrumental set up and well trained personal to handle the instrument. In addition, these methods neither involve pre-extraction procedures nor consume longer time. The most striking features of the proposed methods are their simplicity and rapidity, low cost per analysis, without the need for time-consuming steps and highly skilful operative personnel as found in the reported methods.

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