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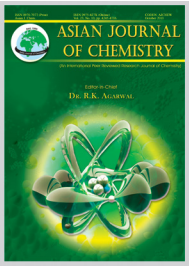

Use of Ion-Association Reactions for the Spectrophotometric Determination of Quetiapine

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Two simple and sensitive spectrophotometric methods (A and B) for the assay of quetiapine as fumarate in pure and dosage forms based on the formation of chloroform soluble ion-associates under specified experimental conditions are described. Two acidic dyes namely tropaeoline ooo (method A) and naphthol blue black (method B) are utilized. The formed complexes showed absorbance maxima at 480 nm and 590 nm for method A and method B respectively. Beer,s law is obeyed in the concentration range 4.0-20 and 2.2-10 µg/mL with molar absorptivity of 1.24×10^4 and 3.13×10^4 L mol^{-1} cm^{-1} respectively. These methods are found to be suitable for the assay of quetiapine in pharmaceutical formulations. The results of analysis have been validated statistically and by recovery studies.

Key Words: Quetiapine, Ion-association, Spectrophotometry.

INTRODUCTION

Quetiapine as fumarate (QTP) is an antipsychotic drug belonging to a new chemical class, the dibenzothiazepine derivatives. Quetipaine is intended for the treatment of schizophrenia and other psychotic syndromes in human. The drug with mixed serotonin ($5HT_2$) and dopamine(D_2) receptors has selective mono aminergic antagonistic properties. Quetiapine induces a lower incidence of extrapyramidal side effects. Chemically known as 2-[2-(4-dibenzo[b,f]-[1,4]thiazepin-11-yl-piperazinyl)ethoxy] ethanol. Literature survey reveals that spectrophotometry[1-4], high performance liquid chromatography[5-11], gas chromatography[12], gas chromatography-mass spectroscopy[13,14] and liquid chromatography-tandem mass spectroscopy[15,16] methods are reported for the determination of quetiapine in biological fluids and pharmaceutical formulations. We developed a simple, accurate and reliable UV spectrophotometric methods for the determination of quetiapine.

EXPERIMENTAL

Spectral and absorbance measurements were made with digital Elico UV-VIS spectrophotometer SL 159 and pH measurements were made with Digisun Electronics digital pH meter model DI-707.

All the chemicals and reagents were of analytical grade and the freshly prepared solutions were always used in the investigations. Aqueous solutions of 5.70×10^{-3} M tropaeolin ooo (TP ooo) and, 0.1 M HCl were prepared for method A. Aqueous solutions of 3.17×10^{-3} M naphthol blue black (NBB), buffer solution of pH 1.5 were prepared by mixing 289 mL of 0.1 M glycine solution with 711 mL of 0.1 M HCl and pH of the solution was adjusted to 1.5 for method B. Chloroform was used in both methods A and B.

Quetiapine fumarate (-100 mg) was accurately weighed 100 mgand dissolved in minimum amount of 0.1 N HCl followed by dilution to 100 mL with distilled water in standard flask. A portion of stock solution was diluted stepwise with the distilled water to obtain the working standard quetiapine fumarate solution of concentrations of 100 µg/mL (methods A and B).

Procedure for the assay

Methods A and B: Into a series of 125 mL separating funnels containing aliquots of standard quetiapine solution 0.5-2.5 mL, 100 µg/mL, 6.0 mL of 0.1 M HCl (method A) or buffer solution pH-1.5 (method B) and 2.0 mL of dye solutions (TP ooo **method-A**) and naphthol blue black (NBB, **method-B**) were added. The total volume of aqueous phase in each separating funnel was adjusted to 15 mL with distilled water and organic layer to 10 mL with $CHCl_3$. The contents were shaken for 2 min. The two phases were allowed to separate and the absorbances of the separated chloroform layer were measured at λ_{max} 480 nm (method A) and 590 nm (method B) against a similar reagent blank. The amount of quetiapine present was deduced from the appropriate calibration curve.

The method has also been applied to pharmaceutical formulations. The tablet powder equivalent to 100 mg of quetiapine was taken and treated with (3 × 25 mL) portions of chloroform. The combined chloroform extract was made upto 100 mL with the same solvent to get 1 mg/mL stock solution. From one portion of chloroform extract (20 mL), $CHCl_3$ was gently evaporated.

The residue was dissolved in minimum volume of 0.1 N HCl and subsequently the volume was brought to 50 mL with distilled water to get 400 µg/mL. It was further diluted stepwise with the distilled water as described under standard solution preparation to obtain 100 µg/mL for methods A and B.

The UV spectrophotometric method, which was suggested for the identification of quetiapine in water has been moulded for its assay and chosen as a reference method for ascertaining the accuracy of the proposed methods. The results are compared with those obtained using UV spectrophotometric method in water at 254.7 nm.

RESULTS AND DISCUSSION

Due to the presence of tertiary amine group in quetiapine, it forms an ion-association complex with an acid dye TP ooo or naphthol blue black to produce coloured chromogens exhibiting λ_{max} at 480 nm (method A) and 590 nm (method B) which are extractable into chloroform from the aqueous phase.

The optical characteristics such as Beer's law limits, absorption maxima, molar absorptivity, Sandell's sensitivity are presented in Table-1. The regression analysis using the method of least squares was made for the slope (b), intercept (a) and correlation coefficient (r) obtained from different concentrations and the results are summarized in Table-1. The per cent relative standard deviation and per cent range of errors (0.05 level and 0.01 confidence limits) were calculated for the two methods and the results are given in Table-1. The optimum conditions for the colour development were established by varying the parameters one at a time in each method, keeping the others fixed and observing the effect produced on the absorbance of the coloured species. The values obtained for the determination of quetiapine in tablets 1 and 2 by the proposed and UV methods are compared in Table-2. To evaluate the validity and reproducibility of the method, known amounts of pure drug were added to previously analyzed pharmaceutical preparations and the mixtures were analyzed by the proposed methods. The per cent recoveries are given in Table-2.

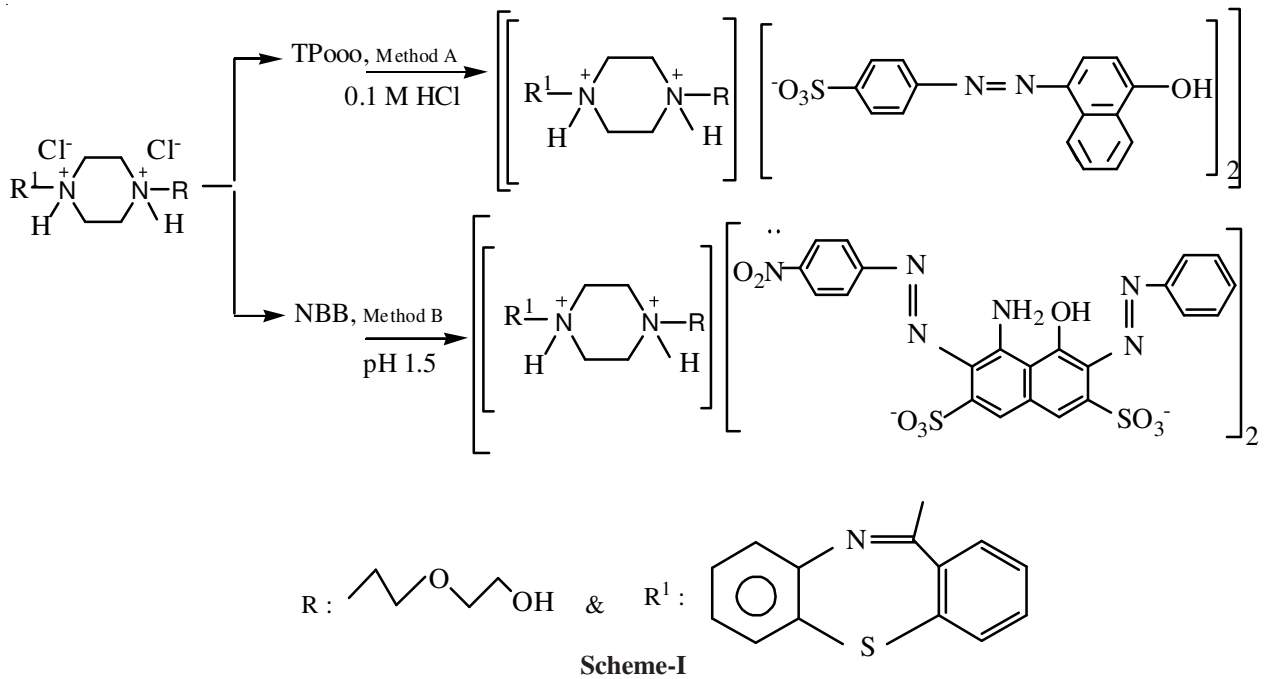
TABLE-1
OPTICAL CHARACTERISTICS, PRECISION, ACCURACY OF THE METHODS PROPOSED IN THE DETERMINATION OF QUETIAPINE

S. no.	Optical characteristics	Method A	Method B
1.	λ_{max} (nm)	480	590
2.	Beer's law limits (µg/mL)	4.0-20	2.2-10
3.	Molar absorptivity (1 $mol^{-1}cm^{-1}$)	1.24×10^4	3.13×10^4
4.	Correlation coefficient (r)	0.9999	0.9998
5.	Sandell's sensitivity (µg/cm^2/0.001 absorbance unit)	0.172	0.093
6.	Regression equation (y = a + bC)		
	(i) Slope (b)	0.014	0.035
	(ii) Intercept (a)	-0.001	-0.0003
7.	Relative standard deviation*	1.117	0.888
8.	% Of range error (confidence limit)		
	(i) 0.05 level	1.173	0.933
	(ii) 0.01 level	1.839	1.462

*Average of six determinations considered

Each method uses a specific reagent and the λ_{max} and ε_{max} values of each method (A and B) are different. Stastistical analysis of the results show that the proposed procedures are in good precision and accuracy. Results of the analysis of pharmaceutical formulations revealed that the proposed methods are suitable for their analysis with virtually no interference of the usual additives present in pharmaceutical formulations.

Scheme of the reaction: As quetiapine possesses a tertiary amine group, it forms an ion-association complex with an acid dye (TP ooo or naphthol blue black), which is extractable into chloroform from the aqueous phase. The protonated nitrogen (positive charge) of quetiapine is expected to attract the oppositely charged part (negative charge) of the dye and behave as a single unit being held together by electrostatic attraction. Based on analogy the structures of ion-association complexes are shown in **Scheme-I**.



Scheme-I

TABLE –2
DETERMINATION OF QUETIAPINE IN PHARMACEUTICAL FORMULATIONS

Sample*	Labelled amount (mg)	Amount found by proposed methods**		Ref. Method (UV method)	% Recovery by proposed methods***	
		Method A	Method B		Method A	Method B
Tab I	25	24.96 ± 0.06, F = 4.00 t = 1.34	24.98 ± 0.09, F = 1.77, t = 0.82	25.03 ± 0.12	99.84 ± 0.24	99.92 ± 0.35
Tab II	25	24.87 ± 0.16, F = 1.41, t = 0.32	24.84 ± 0.17, F = 1.26, t = 0.57	24.90 ± 0.19	99.47 ± 0.64	99.36 ± 0.68
Tab III	100	99.91 ± 0.423, F = 2.03, t = 0.57	99.85 ± 0.342, F = 3.12, t = 0.40	99.74 ± 0.604	99.91 ± 0.42	99.85 ± 0.34
Tab IV	100	99.78 ± 0.196, F = 1.53, t = 0.98	99.91 ± 0.139, F = 1.29, t = 0.34	99.88 ± 0.158	99.78 ± 0.20	99.91 ± 0.14

*Tablets from four different pharmaceutical companies; **Average ± standard deviation of six determinations, the t-and F-test values refer to comparison of the proposed method with the reference method. Theoretical values at 95% confidence limit, F = 5.05, t = 2.228; *** Recovery of 10 mg added to the preanalyzed pharmaceutical formulations (average of three determinations).

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