

## SPECTROPHOTOMETRIC DETERMINATION OF FLUVOXAMINE AS MALEATE BY SELECTIVE METHODS

Medikondur Kishore<sup>a\*</sup>, K.Surendrababu<sup>a</sup>, Y.Hanumantharao<sup>b</sup>, G. Naga hima bindu<sup>c</sup>, M.Janardhan<sup>c</sup>

<sup>a\*</sup>Department of chemistry, SVRM College, Nagaram, Guntur (District) Andhra Pradesh, India- 522268 (\*Author for correspondence) E.mail:medikissi@gmail.com

<sup>b</sup>Department of chemistry, Andhra Loyola College (Autonomous), Vijayawada, Krishna (District) Andhra Pradesh, India- 520008

<sup>c</sup>Department of chemistry, Nalanda Degree College, Vijayawada, Krishna (District) Andhra Pradesh, India- 520003

**ABSTRACT:** Simple, accurate and reproducible visible spectrophotometric methods for the assay of drug fluvoxamine as maleate were established based on the formation of oxidative coupling reaction between the corresponding drug, Brucine-NaIO<sub>4</sub> and DCQC. The procedures described were applied successfully to the determination of the compound in their dosage forms. The results showed that the proposed procedures compared favorably with the reference methods and satisfactory sensitivity, accuracy and precision. The optical characteristics such as Beer's law limits, molar absorptivity and sandell's sensitivity are reported. Regression analysis using the method of least squares was made to evaluate the slope (b), intercept (a) and correlation coefficient (r) and standard error of estimation (Se) for the drug.

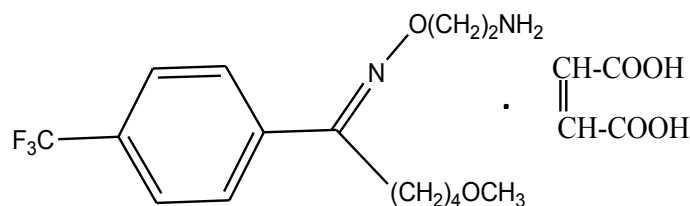
**Key Words:** Fluvoxamine maleate, spectrophotometric methods, oxidative coupling reaction, statistical analysis, recovery studies.

## INTRODUCTION

Fluvoxamine (The Merck Index, 2001) maleate (FXA) is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to the chemical series, the 2-aminoethyl oxime ethers of aralkyl ketones in the treatment of a variety of depressed states (P.Benfield, 1986, Karen McClellan et.al, 2000). It is chemically designated as 5-methoxy-4'-(trifluoromethyl) valerophenone-(E)-O-(2-aminoethyl) oxime maleate (1:1), (Figure-I) and has the empirical formula C<sub>15</sub>H<sub>21</sub>O<sub>2</sub>N<sub>2</sub>F<sub>3</sub>.C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>, molecular weight is 434.41.

Fluvoxamine maleate is a white to slightly off-white, odourless, crystalline powder, sparingly soluble in water, freely soluble in ethanol and chloroform, practically insoluble in diethylether. For the determination of fluvoxamine maleate in dosage forms, various analytical techniques including HPLC (G.J. Jong de, et. al, 1980, C. E. Werkhoven - Goewie et. al, 1980, S. Atmaca, et. al, 1995, H.C. Innemee, 1987, N.H.Foda, 1995) fluorimetry (C. Schweitzer, et. al, 1986) UV- Visible spectrophotometry (S. Atmaca, et. al, 1995, V. Annapurna et.al, 2010, Barbara Starczewska, 2001) and DC (K. Albert, 1990), polarographic (Fikriye ELMALI, et. al, 2000) are used.

Fluvoxamine with its oxime ether group has a structural feature that could be used for electrochemical reduction (K. Albert, 1984). The analytically useful functional groups in FXA have not been fully exploited for designing suitable visible spectrophotometric methods and so still offer a scope to develop more visible spectrophotometric methods with better sensitivity, selectivity, precision and accuracy.



**Figure 1: Fluvoxamine maleate**

Existing analytical methods reveal that relatively little attention was paid in developing visible spectrophotometric methods by exploiting the analytically useful functional groups. Hence there is a need to develop sensitive and flexible visible spectrophotometric methods which prompted the author to carry out in this accord.

### Instruments used

An Elico, UV – Visible digital spectrophotometer with 1cm matched quartz cells were used for the spectral and absorbance measurements. An Elico LI-120 digital pH meter was used for pH measurements.

### Preparation of reagent solutions

Brucine Solution (Loba; 0.2 %,  $5.067 \times 10^{-3}$  M): Prepared by dissolving 200 mg of brucine in 100 ml of distilled water.

$\text{NaIO}_4$  solution (BDH; 0.2 %,  $9.35 \times 10^{-3}$  M) : Prepared by dissolving 200mg of sodium meta periodate in 100 ml of distilled water and standardised iodometrically.  $\text{H}_2\text{SO}_4$  solution (Qualigens, 2.3 M): Prepared by diluting 6.38 ml of 18 M  $\text{H}_2\text{SO}_4$  to 100 ml with distilled water.

DCQC Solution (BDH: 0.04 %,  $1.9 \times 10^{-3}$  M): Prepared by dissolving 40 mg of 2, 6-dichloroquinone chlorimide (DCQC) in 100 ml of isopropanol.

Buffer solution (pH 9.4): Prepared by mixing 250 ml of 0.2 M Boric acid with 160 ml of 0.2 M sodium hydroxide and diluting to 1L with distilled water. The pH of the solution was adjusted to 9.4 with the pH meter

### Preparation of standard drug solution

A 1 mg/ml solution was prepared by dissolving 100 mg of pure FXA in 100 ml of 0.1N HCl and this stock solution was diluted step wise with distilled water to get the working standard solutions of concentration of 500  $\mu\text{g/ml}$ .

### Recommended procedure

**Method I ( $M_1$ ):** Aliquots of FXA solution (0.5-3.0 ml, 500  $\mu\text{g/ml}$ ) were transferred into different 10 ml graduated tubes. 3 ml of brucine solution, 1.5 ml of sodium metaperiodate solution and 2 ml (2.3 M) of sulphuric acid were added to each tube and the total volume was made up to 9 ml with distilled water. The tubes were thoroughly shaken and placed in a boiling water bath for 15 min. The reaction mixture was then cooled to room temperature and total volume was adjusted to 10 ml with distilled water. The absorbance of each solution was measured at 520 nm against a reagent blank.

**Method II (M<sub>2</sub>):** In this method, aliquots of standard FXA solution (0.5-3.0ml, 500 µg/ml) were transferred into a series of 25 ml calibrated tubes. Then 5.0 ml of buffer (pH 9.4) and 2.0 ml of DCQC were added successively. Mixed well and kept aside for 10 min and diluted to mark with distilled water. The absorbance of the colored solution was measured at 460 nm against a reagent blank prepared simultaneously. The amount of FXA in the sample solution was computed from the appropriate calibration graph.

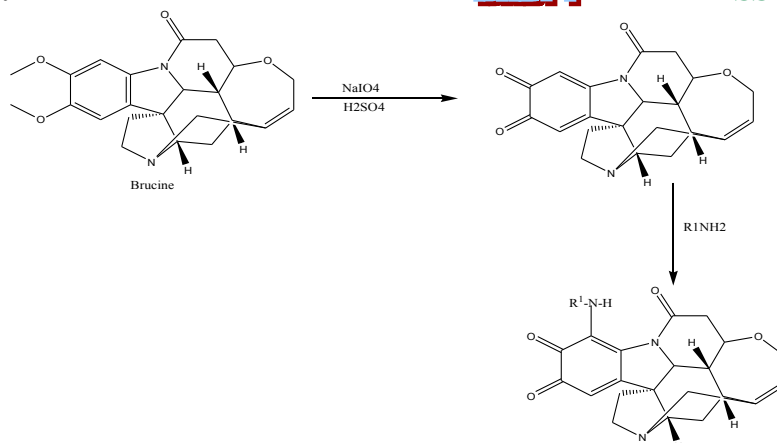
## Reference Method

An accurately weighed amount of tablet powder equivalent to 100 mg of drug was transferred into a 100 ml volumetric flask. Added about 75 ml of ethyl alcohol and shaken well for about 15 min. The contents were diluted with ethanol upto the mark and mixed thoroughly. The solution was filtered. Then 2 ml of filtrate was pipette out into a 100ml volumetric flask and made up the solution upto the mark with ethanol for obtaining a concentration of 20 µg/ml. Into a series of 5ml graduated tubes, aliquots of drug solution ranging from 0.5-3.0 µg/ml were taken and diluted to mark with ethanol. Read the absorbance at 240 nm against a solvent blank. The drug was read from its calibration graph.

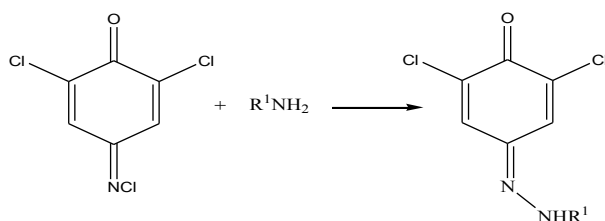
## RESULTS AND DISCUSSION

The functional groups such as aliphatic primary amine present in FXA were exploited for developing the proposed methods. The nature of colour species formed in each one has been explained basing on the analogy and probability. The dimethoxy benzene nucleus of brucine is attacked by  $\text{IO}_4^-$  with the formation of o-quinone (bruciquinone) which in turn undergoes nucleophilic attack on the most electron rich portion of the coupler (aliphatic primary amine) to give 1-monosubstituted bruciquinone derivative (Scheme 1) and the colour formation by DCQC with FXA may be explained as (Scheme 2.)

The optical characteristics such as Beer's law limits, absorption maxima, molar absorptivity, and sandell's sensitivity are presented in Table I. The regression analysis using the method of least squares was made for the slope (b), intercept (a) and correlation (R) obtained from different concentrations and the results are summarized in Table I. The percent relative standard deviation and percent range of errors (0.05 level and 0.01 confidence limits) were calculated for the two methods and the results are given in Table I. 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 FXA in tablets by the proposed methods are compared in Table II. To evaluate the validity and reproducibility of the method, known amounts of pure drug were added to previously analyze pharmaceutical preparations and the mixtures were analyzed by the proposed methods. The percent recoveries are also given in Table II.



Scheme 1



Scheme 2

Table I Optical and regression characteristics, precision and accuracy of the proposed methods for FXA

Parameter	M <sub>1</sub>	M <sub>2</sub>
$\lambda_{\text{max}}$ (nm)	520	460
Beer's law limits ( $\mu\text{g/ml}$ )	25-150	10-60
Detection limit ( $\mu\text{g/ml}$ )	7.081	2.565
Molar absorptivity ( $1 \text{ mol}^{-1} \cdot \text{cm}^{-1}$ )	$8.862 \times 10^2$	$2.628 \times 10^3$
Sandell's sensitivity ( $\mu\text{g} \cdot \text{cm}^{-2}/0.001$ absorbance unit)	0.6155	0.3012
Optimum photometric range ( $\mu\text{g/ml}$ )	40-125	126-250
Regression equation ( $Y = a + bc$ )		
slope (b)	0.0101	0.012077
Standard deviation on slope ( $S_b$ )	$5.452 \times 10^{-3}$	$1.5021 \times 10^{-4}$
Intercept (a)	$8.249 \times 10^{-3}$	$6.25 \times 10^{-3}$
Standard deviation on intercept ( $S_a$ )	$4.520 \times 10^{-3}$	$4.983 \times 10^{-3}$
Standard error on estimation ( $S_e$ )	$4.310 \times 10^{-3}$	$4.751 \times 10^{-3}$
Correlation coefficient (r)	0.9989	0.9997
Relative standard deviation (%) <sup>*</sup>	0.2041	1.359
% Range of error (confidence limits)		
0.05 level	1.06	1.563
0.01 level	1.36	2.450

<sup>\*</sup> Average of six determinations considered

**Table II Assay of FXA in pharmaceutical formulations**

Formulations*	Amount taken (mg)	Amount found by Proposed Methods**		Percentage recovery by proposed methods***		
		M <sub>1</sub>	M <sub>2</sub>	Reference method	M <sub>1</sub>	M <sub>2</sub>
Tablet I	50	49.63 ± 0.52 F = 2.547 t = 0.71	49.56 ± 0.61 F = 1.851 t = 0.84	49.91 ± 0.83	99.85 ± 0.33	99.95 ± 0.39
Tablet II	50	49.76 ± 0.41 F = 2.2867 t = 0.74	49.67 ± 0.48 F = 1.668 t = 0.97	49.98 ± 0.62	99.95 ± 0.45	99.91 ± 0.63
Tablet III	50	49.68 ± 0.32 F = 1.890 t = 1.85	49.85 ± 0.35 F = 1.580 t = 1.0658	50.09 ± 0.44	99.76 ± 0.16	99.86 ± 0.47
Tablet IV	50	49.73 ± 0.29 F = 1.627 t = 1.154	49.74 ± 0.23 F = 2.587 t = 1.21	49.95 ± 0.37	99.82 ± 0.63	99.91 ± 0.45

\*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 = 2.57

\*\*\*Recovery of 10 mg added to the preanalysed pharmaceutical formulations (average of three determinations).

## CONCLUSIONS

The developed spectrophotometric methods for the estimation of FXA were found to be simple and useful with high accuracy, precision, and reproducible. Sample recoveries in all formulations using the above methods were in good agreement with their respective label claim or theoretical drug content, this suggesting the validity of the method and non interference of formulation excipients in the estimation.

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