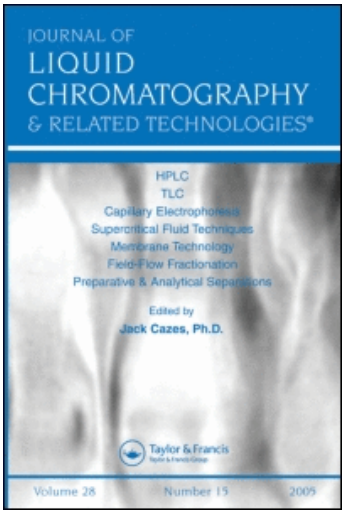

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QUANTITATIVE ANALYSIS OF FLUVOXAMINE MALEATE IN TABLET FORMULATIONS BY HPLC

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ABSTRACT

A rapid, specific and reliable high performance liquid chromatographic assay of flavoxamine maleate in tablets has been developed. Reversed-phase chromatography was conducted using a mobile phase of 0.05M ammonium acetate and acetonitrile, (40% v/v) and detection at 240nm. The recovery and coefficient of variation from six placebo tablets containing 100 mg of fluvoxamine maleate were 100.56% and 0.439% respectively. Relicate regression analyses of three standard plots in the concentration range of 0.5 - 12 mcg/ml obtained on three different days gave a correlation coefficient > 0.9997 and the coefficient of variation of the slopes < 0.1%. The assay was precise within day and between days as indicated by ANOVA test. The recoveries from 10 replicate tablets of two commercial tablets (50,

100mg) was 99.2, 101.8 and 100.3% of the label amount and their coefficients of variation were 1.854 and 1.119%.

INTRODUCTION

Fluvoxamine is a specific 5-hydroxy tryptamine inhibitor (1,2), which belongs to antidepressants. Very few methods have been developed for the determination of Fluvoxamine Maleate in tablets, spectrophotometric (3) and Hplc method (4). The Hplc method (4) developed by Hagga et al, the minimum detectable amount of drug was 15 mcg/ml which is considered a relatively very high concentration. The purpose of this study was to develop a simple and direct HPLC assay for the quantitation of Fluvoxamine Maleate in tablet formulations.

EXPERIMENTAL

Chemicals and Reagents : Fluvoxamine maleate(5) and propyl paraben(6) were used without further purification. Acetonitrile(7), methanol(7) and water were HPLC grade. All other chemicals and reagents were USP or ACS quality and were used as received.

Instrumentation : A water HPLC systems(8) was used consisting of the following components : Model 45 pump, the WISP model 710 B autosampler, the model 481 UV detector set at 273 nm at 0.02 AUFS, the model 730 data system. Chromatographic separation was

accomplished using C18 column, 8 mm i.d. x 10cm u Bonda Pack C18 column with 10 um packing.

Chromatographic Conditions : The eluting medium consisting of 40% v/v of 0.05M ammonium acetate and acetonitrile at pH 5.2 with glacial acetic acid, was prepared and degassed by bubbling helium gas for 5 min prior to use. Column equilibrium with the eluting solvent was established by pumping the mobile phase at a rate of 0.2ml/min overnight. The flow rate was set at 0.8 ml/min during analysis. The chromatogram was recorded and integrated at a speed of 0.2 cm/min.

Internal Standard : Stock solution of propyl paraben containing 10 mg in 100ml methanol was prepared weekly and stored at 4°C.

Standard Solution of Fluvoxamine Maleate : A stock solution of fluvoxamine maleate was prepared by dissolving 10 mg of fluvoxamine maleate in 10 ml of methanol. Nine aliquots equivalent to 0.5, 1, 2, 4, 6, 8, 10 and 12 mcg of fluvoxamine were added to 1 ml volumetric flasks. After an aliquot of the internal standard equivalent to 5 mcg was added, the flasks were brought to volume by acetonitrile and thoroughly mixed. Twenty uL of the standard solutions was injected onto the column for analysis.

The peak area ratio of the drug : internal standard were plotted against the standard fluvoxamine concentrations. Least square linear regression analysis was performed to determine the slope, y intercept, and the correlation coefficients of the standard plots.

Sample Preparation : Individual tablets were pulverized using a morter and pestle, and completely transferred to 100 ml volumetric flask. The volume was adjusted with methanol and the flask was mechanically

shaken for five min. Five ml of the solution was removed into a centrifuge tube and centrifuged at 3000 r.p.m for 5 min. Fifty uL was transferred to a one ml volumetric flask containing 50 uL of propyl paraben stock solution, and diluted to the volume with acetonitrile. Twenty uL was loaded into the sample loop for chromatography. Ten replicate commercial tablets of fluvoxamine were analyzed for statistical evaluation of the assay.

Quantitation : The amount of fluvoxamine per tablet was determined from the following equation :

$$Q = [\ R/A + B\ ]\ X \text{ Dilution factor}$$

were Q is the mg fluvoxamine per tablet, R is the peak area ratio (drug / internal standard), A is the slope of the calibration curve and B is the y-intercept.

Recovery of fluvoxamine from the fabricated placebo tablets : The reference tablets containing 100 mg of fluvoxamine and 50 mg each of starch and lactose were prepared and subjected to the described HPLC assay to measure the accuracy and precision.

RESULTS AND DISCUSSION

Figure 1 shows a typical chromatogram obtained following analysis of fluvoxamine in tablets. Using the chromatographic conditions described, fluvoxamine and propyl paraben were well separated and their retention times were 9 and 7 min, respectively. For both compounds sharp and symmetrical peaks were obtained with good

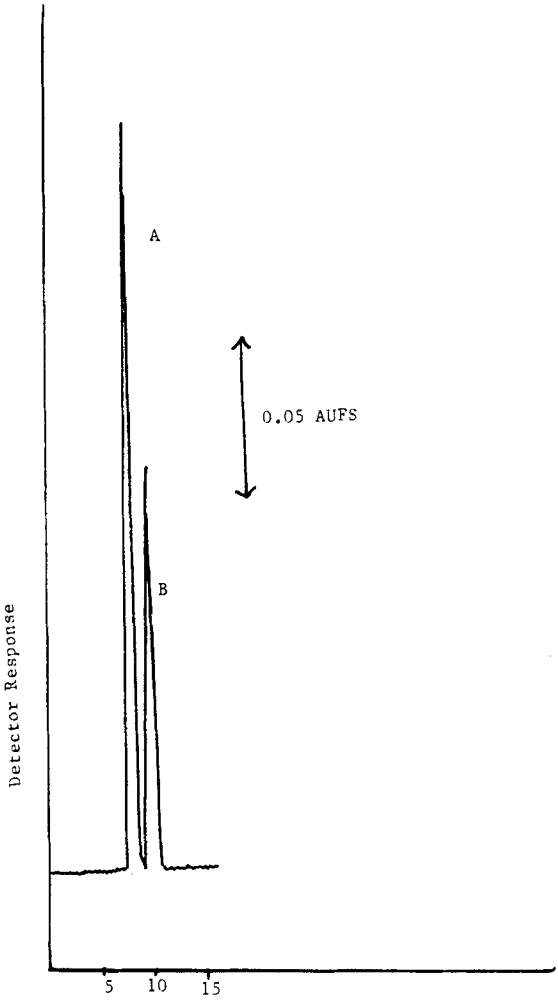

Figure 1. Chromatogram of Fluvoxamine Maleate Tablet
Key A-Propylparaben, B-Fluvoxamine Maleate

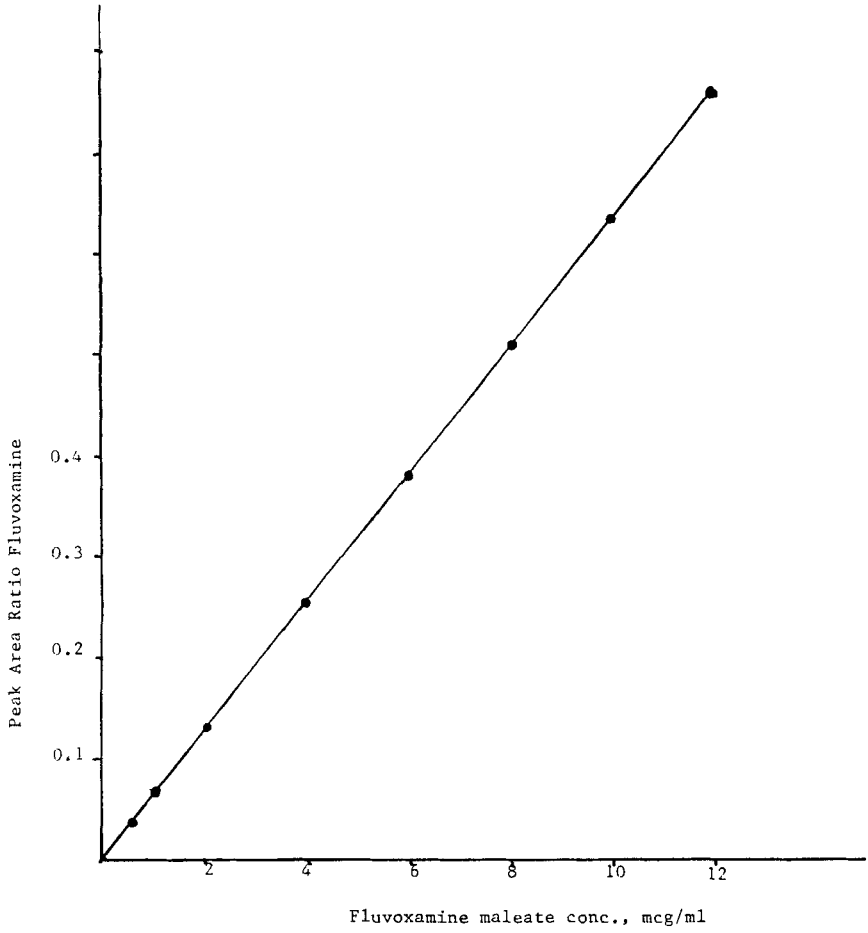

Figure 2. Standard Calibration Plot of Fluvoxamine Maleate.

baseline resolution and minimal tailing, thus facilitating accurate measurement of the peak area ratio. No interfering peaks were found in the chromatogram due to tablet excipients. Figure 2 shows a calibration plot for the peak area ratio of varying amounts of fluvoxamine (0.5 - 12 mcg/ml) to a constant amount of propyl paraben

Table 1

Regression Analyses of the Three Standard plots of Fluvoxamine

Standard[a]	Slope[b]	Intercept[b]	Correlation[b] Coefficient
1.	0.06229	0.00333	0.99985
2.	0.6234	0.00353	0.99972
3.	0.6224	0.00346	0.99980

a) obtained in 3 different days.

b) the mean of 3 determinations at each drug concentration.

(20 mcg/ml). The plots wer linear (r = 0.99985) and the regression analysis of the data gave the slope and intercept as :

$$Y = 0.06229\ x + 0.003335$$

were Y and x are the peak area ratio and fluvoxamine concentration, respectively. Three replicate analyses of fluvoxamine at concentration of 0.5-12 mcg/ml were performed at three different days over one week period. The results of this evaluation are summarized in table 1. The average correlation coefficient was higher than 0.9997 and the coefficient of variation of the slopes of the three lines was < 0.1%. Analysis of variance of the data showed no detectable difference in the slopes of the three standard plots ($F=3.5$, $P > 0.01$). The similarities in the slopes and the high correlation coefficients indicate that the assay possesses excellent reporducibility and linearity.

Table II

Analysis of Variance for Intra- and Inter day Precision

Day/Assay	1	2	3	4	5	6
1	100.2	10.6	100.3	100.4	101.1	100.2
2	100.8	99.6	98.4	100	100.2	101.1
3	100.4	99.2	99.2	99.6	99.9	99.8
4	99.8	98.6	101.4	98.8	99.8	99.6

Mean 99.95 mg

ANOVA TEST

Source of variation	DF	Sum of squares	Mean of squares	F ratio	P
Within day	5	2.2021	0.44042	0.7322	0.05
Between day	3	2.4346	0.81153	1.349	0.05
Error	15	9.0229	0.6015	0.6168	
Total	23	13.6596			

Thus, the method should be accurate and precise within the assay day as well as between assay days.

Precision and accuracy : Six placebo tablets containing 50 mg each of lactose and starch and 100 mg of fluvoxamine were assayed for four consecutive days for intra and interday precision studies. The average recovery shown in Table II was 99.95 mg (100.08%) with the

Table III

Recoveries From Spiked Placebo Tablets

Fluvoxamine Maleate mg added	mg Recovered	% Recovery
100	100.1	100.1
100	100.9	100.9
100	100.5	100.5
100	99.9	99.9
100	101.1	101.1
100	100.9	100.9
Mean	100.56	100.56
SD	0.442	0.442
CV	0.439	0.439

coefficient of variation of 0.886%. Estimates of day to day and within day precision were calculated by ANOVA test. The calculated F values, $F_{0.05}$ (5, 15) = 0.73 and $F_{0.05}$ (3, 15) = 1.349 were smaller than the table values $F_{0.05}$ (5, 15) = 2.44 and $F_{0.05}$ (3, 15) = 2.24 respectively. Thus it was concluded that there was no significant difference for the assay which was tested within day and between days.

Recovery : Table III shows the average recovery for the placebo tablets containing 100 mg fluvoxamine and 50 mg each of lactose and starch. The average recovery was 100.56 and its relative standard deviation was 0.442.

Table IV

Analysis of Dosage Form of Fluvoxamine

Sample	n[a]	Mean % Recovery	SD	% CV
A	10	99.2	1.84	1.854
B	10	101.8	1.14	1.119

a) Number of replicates

Analysis of Fluvoxamine tablets : Table IV present the results obtained from analysis of fluvoxamine (50, 100 mg) commercially available. The mean percent recoveries were 99.2, 101.8.

The stability indicating nature of the assay has not been demonstrated in this study, since no sign of degradation was observed by TLC after subjecting the drug solution(pH3 and 9) at 70°C for 2 hrs which was also evident from the absence of any additional peaks in the chromatograms.

Conclusion : The HPLC method developed in this study has the advantages of simplicity, precision and convenience. It also allows for the direct determination of fluvoxamine. Therefore, the method should be useful for routine analytical and quality control assay of fluvoxamine in dosage forms.

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