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# Application of chrome azurol S for the extractive spectrophotometric determination of fluoxetine and fluvoxamine

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**Abstract**

Chrome azurol S has been tested as a spectrophotometric reagent for the determination of fluoxetine (FXT) and fluvoxamine (FXM). It reacts in aqueous media with FXT and FXM forming coloured, sparingly soluble in water compounds. These compounds can be quantitatively extracted with some organic solvents. This property has been exploited for the development of the extractive spectrophotometric methods for the determination of fluoxetine and fluvoxamine. © 2000 Elsevier Science B.V. All rights reserved.

*Keywords:* Fluoxetine; Fluvoxamine; Analysis spectrophotometry

## 1. Introduction

Fluoxetine and fluvoxamine are new antidepressants, which potently inhibits neuronal reuptake of serotonin [1]. Several studies [2] showed that fluoxetine and fluvoxamine have an overall therapeutic efficacy comparable with some tricyclic antidepressants.

Reported methods for the determination of fluoxetine and fluvoxamine are based mainly on high-performance liquid chromatography [3–8] and gas chromatography [9–11]. Fluoxetine was also determined by the fluorimetric method [12] and with the use NMR technique [13]. Alhaider et al. [14] and Atmaca [15] proposed chloranil and 2,4,6-trinitrobenzene sulphonic acid for the spectrophotometric determination of fluvoxamine.

As a continuation of our previous studies a determination of phenothiazines [16,17] using triphenylmethane dyes, this paper deals with the application of chrome azurol S to the extractive spectrophotometric determination of fluoxetine and fluvoxamine. We have found that fluoxetine and fluvoxamine react with chrome azurol S forming ion-association compounds. The composition of these compounds was established. The spectroscopic studies in UV–VIS and IR region were performed.

The proposed method was successfully employed for the determination of fluoxetine hydrochloride and fluvoxamine maleate. The

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method is a rapid, simple, sensitive and can be recommended for routine analysis of these components in pharmaceutical preparations (Prozac and Fevarin).

## 2. Experimental

### 2.1. Reagents

Fluoxetine hydrochloride, (I) (Eli Lilly, USA) and fluvoxamine maleate, (II) (Duphar Scient. Off in Riyadh) were used as aqueous 200 ppm solutions. Chrome azurol S, (III) (Sigma, USA).

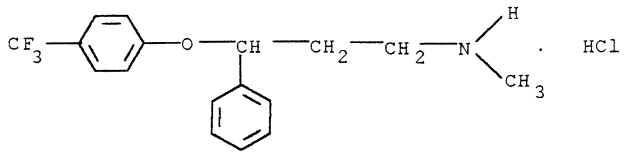
Other reagents and solvents used were of analytical grade.

### 2.2. Apparatus

A Hewlett Packard model 845217 diode-array spectrophotometer.

A Spekol-11 spectrophotometer (Carl Zeiss, Jena, Germany).

I.



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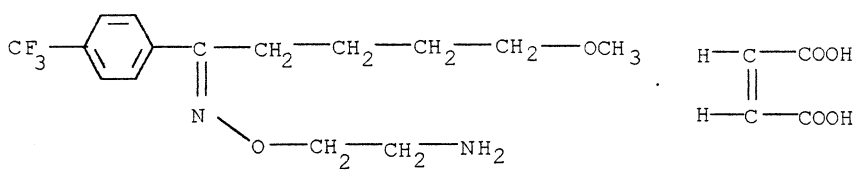

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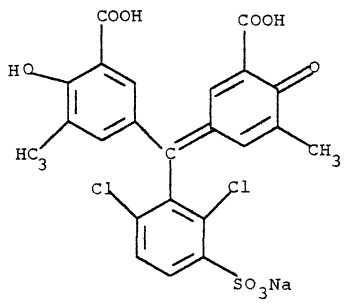


Table 1
Optimal conditions for the extraction of compounds of fluoxetine and fluvoxamine with chrome azurol S

| Parameters | FXT–CAS system | FXM–CAS system |
|---|---|---|
| Reagents concentrations | [FXT] $= 2.32 \times 10^{-4}$ M<br>[CAS] $= 1.16 \times 10^{-4}$ M | [FXM] $= 2.76 \times 10^{-4}$ M<br>[CAS] $= 0.92 \times 10^{-4}$ M |
| Medium | $[H_2SO_4]$ $= 1.5 \times 10^{-4}$ M | $\approx$ pH 6.5 |
| Organic solvent | $CHCl_3$ | $CHCl_3 + C_4H_9OH$ (3+1) |
| The colour of extracts | Orange–red | Pink |
| Stability of extracts | 2.5 h | 1.5 h |

### 2.3. Procedure

The course of the formation and extraction of the coloured compounds of fluoxetine and fluvoxamine with chrome azurol S depends on the acidity of the solutions and the reagents concentrations and on the nature of organic solvent used. These factors were investigated as follows. Suitable amounts of fluoxetine or fluvoxamine, 1.5 ml of $1 \times 10^{-3}$ M $H_2SO_4$ (only for FXT) and 4-fold excess of chrome azurol S with respect of FXT or FXM were mixed in 25 ml separating funnels, and diluted to 10 ml with water. The mixture was shaken and extracted with two successive 4–5 ml portions of chloroform in FXT–CAS system or chloroform–buthanol (3 + 1) in FXM–CAS system. The extracts were combined in a 10-ml volumetric flasks and diluted to the mark with organic solvent. The absorbance was measured at once at 500 and 502 nm against the blank for FXT and FXM, respectively. The optimal conditions for the formation and extraction of the compounds studied are summarized in Table 1.

The quantitative extraction of the compounds into chloroform–buthanol (3 + 1) can be used for the spectrophotometric determination of fluoxetine and fluvoxamine.

### 2.4. Extractive spectrophotometric determination of fluoxetine and fluvoxamine

In a 25-ml separators funnel place up from 0.25 to 2.5 ml of 200 ppm fluoxetine, 1.5 ml $1 \times 10^{-3}$ M $H_2SO_4$ and 4-fold excess of chrome azurol S with respect to FXT and dilute to 10 ml with water. After the shaking the mixture, extract the compound into chloroform. Transfer the extracts to 10-ml volumetric flasks and dilute to the mark with chloroform. Measure the absorbance at 500 nm. The same procedure was elaborated for the determination of fluvoxamine. In a 25-ml separator funnel place up from 0.35 to 5.0 ml of 200 ppm fluvoxamine and 4-fold excess of chrome azurol S with respect to FXM and dilute to 10 ml with water. The product of FXM, which forms in neutral medium, can be quantitatively extracted with the mixture of chloroform–buthanol (3 + 1). The absorbance is measured at 502 nm.

Under the described experimental conditions, the standard calibration graphs for fluoxetine and fluvoxamine were constructed. The results obtained are presented in Table 2.

#### 2.4.1. Determination of fluoxetine and fluvoxamine in pharmaceutical preparations

Transfer an accurately weighed amount of the powered tablets equivalent to 100 mg fluoxetine

Table 2
Characteristics the methods for the determination of fluoxetine (FXT) and fluvoxamine (FXM)

| Sample | Linearity range (ppm) | $\varepsilon$, ($l \cdot mol^{-1} \cdot cm^{-1}$) | Intercept | Slope | Correlation coefficient | R.S.D. (%) | $t_{0.95}s$ |
|---|---|---|---|---|---|---|---|
| FXT | 5–50 | $1.02 \times 10^4$ | −0.0006 | 0.03 | 0.9974 | 1.64 | 0.0394 |
| FXM | 7–100 | $9.05 \times 10^3$ | +0.0126 | 0.02 | 0.9986 | 1.76 | 0.0273 |

Table 3
Determination of fluoxetine (FXT) and fluvoxamine (FXM) in pharmaceutical preparations

| Product | Sample | Nominal content mg tablet$^{-1}$ | Found (mg) | Found average (mg) | Error | $S$ | $t_{0.95}S_r$ | R.S.D. (%) |
|---|---|---|---|---|---|---|---|---|
| Prozac | Fluoxetine hydrochloride | 20 | 20.10 | 20.0 | +1.0050 | 0.132 | 0.328 | 0.66 |
| | | | 20.05 | | +1.0025 | | | |
| | | | 19.85 | | −0.9925 | | | |
| Fevarin | Fluvoxamine maleate | 100 | 100.1 | 100.1 | +1.001 | 0.1 | 0.248 | 0.099 |
| | | | 100.0 | | +1.000 | | | |
| | | | 100.2 | | +1.002 | | | |

hydrochloride or fluvoxamine maleate into a 100 ml standard flask. Dilute to the mark with water and methanol (3 + 1), shake well and filter. Accurately dilute a suitable volume of the filtrate tenfold with water to obtain a sample concentration of 100 ppm.

In a 25-ml separator funnel place up to 2 ml of 100 ppm fluoxetine or fluvoxamine 1.5 ml of $1 \times 10^{-3}$ M $H_2SO_4$ (only for FXT) and 4-fold excess of chrome azurol S with respect to drugs and dilute to 10 ml with water. After the shaking the mixture extract the compound into chloroform (or chloroform–buthanol (3 + 1) in FXM–CAS system) and measure the absorbance at 500 nm. Results obtained are presented in Table 3.

## 3. Results and discussion

The composition of the compounds was established by Job's continuous variation method and by spectrophotometric titration. It was found that molar ratio of FXT:CAS = 2:1 and FXM:CAS = 3:1.

The absorption spectra in UV–vis regions of the compounds were recorded. Table 4 summarizes the results of these experiments.

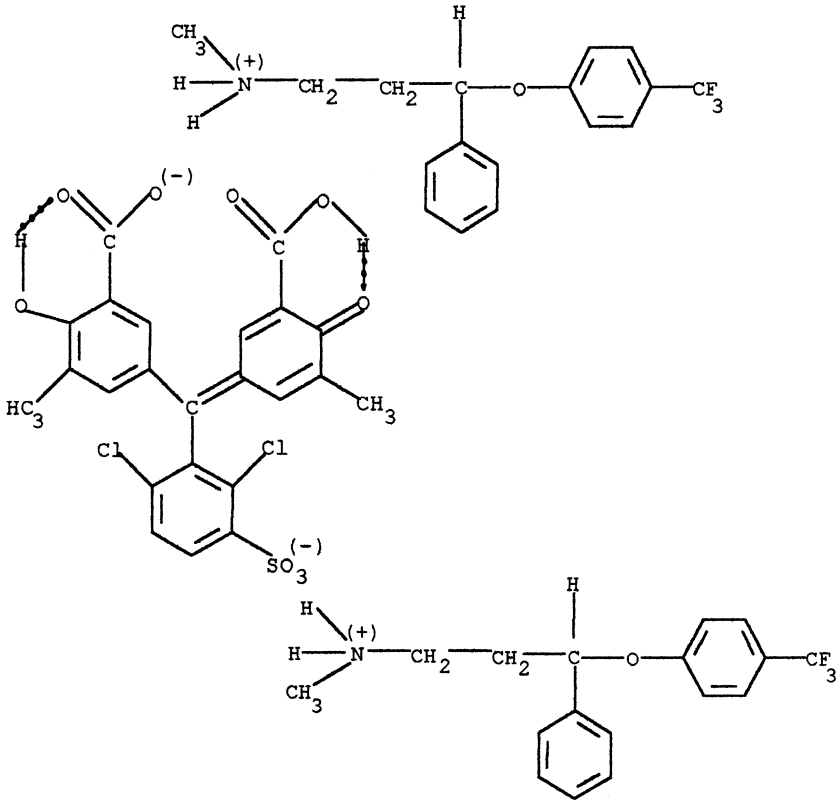
Infrared spectra of the compounds studied were measured (KBr discs) in the region 400–4000 cm$^{-1}$ with spectrophotometer IR, Perkin–Elmer 577.

The spectra of the compounds in the region 600–1800 cm$^{-1}$ are the sum of the spectra of reagents. Significant changes in the spectra are observed in the region 2300–3700 cm$^{-1}$. The bands of the N–H bond 2400–2700 cm$^{-1}$ of fluoxetine and fluvoxamine are shifted towards higher frequencies in the spectra of the compounds, with the intensity decreasing.

On the basis of the results it can be concluded that the compounds studied are ion-association complexes. The amino nitrogen of aliphatic chain of FXT and FXM are responsible for formation of the complexes.

Table 4
Values of $\lambda_{max}$ of the compounds forming in FXT–CAS and FXM–CAS systems

| Compound | Region | |
|---|---|---|
| | $UV_{\lambda\ max}$, nm | $Vis_{\lambda\ max}$, nm |
| FXT | 202, 226, 264 | – |
| FXM | 208, 246 | – |
| CAS | 270, 302 | 492 |
| FXT–CAS | 280, 306 | 500 |
| FXM–CAS | 285 | 502 |



The compounds of fluoxetine and fluvoxamine precipitated from acidic and neutral media solution respectively, in the form an orange–red sediments, can be quantitatively extracted with chloroform or chloroform–buthanol (3 + 1). Taking advantage of these properties the extractive spectrophotometric methods of the determination of fluoxetine and fluvoxamine have been elaborated. Beer's law was obeyed in the range 5–50 ppm of fluoxetine and 7–100 ppm of fluvoxamine in organic solvent. The reproducibility of the measurements, expressed as relative standard deviations, is 0.8–2.6% depending on the FXT or FXM concentrations. The absorbance of the extracts is stable for 1.5–2.5 h. The proposed methods have been successfully applied to the determination of fluoxetine and fluvoxamine in some commercial and laboratory prepared tablets.

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