

SPECTROPHOTOMETRIC DETERMINATION OF ESCITALOPRAM IN PHARMACEUTICALS

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ABSTRACT:

A new, simple, fast and sensitive two spectrophotometric methods has been developed for determination of Escitalopram in bulk and tablet dosage forms. The method A is based on the oxidation of Escitalopram by a known excess of bromate-bromide mixture in hydrochloric acid medium, reduction of the residual oxidant by a fixed amount of iron(II) and the formation of iron(III)-thiocyanate-complex which is measured at 480 nm. In the method B, 1,10-phenanthroline is used as a complexing agent and the formation of iron(II)-1,10-phenanthroline, which is measured at 510 nm. The methods obeys Beer's law in the concentration range of 0.5 - 8.0 $\mu\text{g mL}^{-1}$ and 0.5-6.5 $\mu\text{g mL}^{-1}$ of Escitalopram for method A and B respectively. No interference observed from common pharmaceutical adjutants. Both methods are equally precise as shown by the relative standard deviation values less than 2%. The apparent molar absorptivities and Sandell's sensitivity for method A and B are found to be $1.4 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$, $0.013 \mu\text{g cm}^{-2}$, $6.8 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$ and $4.2 \times 10^{-3} \mu\text{g cm}^{-2}$, respectively. The methods have been successfully applied to the determination of Escitalopram in pure and dosage forms.

Keyword: determination, escitalopram, spectrophotometry, thiocyanate, 1, 10-phenanthroline.

1. Introduction

Escitalopram (Figure 1) is a pure S- enantiomer of the racemic, bicyclic phthalane derivative of citalopram. It is freely soluble in methanol and Dimethylsulfoxide (DMSO). Escitalopram is a (S)-1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1, 3-dihydroisobenzofuran-5-carbonitrile^{1, 2}. The antidepressant and antiobsessive-compulsive actions of Escitalopram are presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Escitalopram blocks the reuptake of serotonin at the serotonin reuptake pump of the neuronal membrane, enhancing the actions of serotonin on 5HT1A auto receptors³.

Literature survey reveals several spectroscopic^{4,5,6}, HPLC⁷ and HPTLC^{8, 9, 10, 11, 12, 13, 14, 15, 16} methods for estimation of Escitalopram oxalate individually as well as combination with other drugs. All the reported HPLC methods used buffer in the mobile phase and long retention time. The present study was aimed to develop a simple, rapid, precise, and accurate spectroscopy method for estimation of Escitalopram in bulk and dosage forms.

The development of new method for determining drug concentration in pharmaceutical formulations is important. The low cost and ease of operation make the spectrophotometric method highly desirable alternative for the assay of Escitalopram. The methods rely on the use of

simple, cheap chemicals and techniques but provide sensitivity comparable to that achieved by sophisticated and expensive technique like HPLC. Statistical analysis of the results indicates that the method yields exact values. Hence the proposed method has been successfully applied to the determination of Escitalopram in pharmaceutical samples.

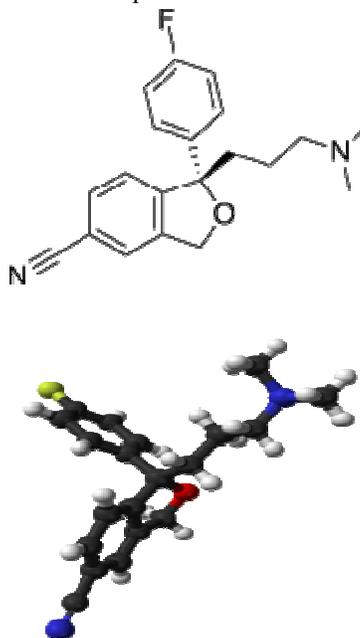


Figure 1: Structure of Escitalopram

2. Experimental

2.1 Apparatus: A Shimadzu UV-1650 UV-VIS Spectrophotometer with 1 cm matched quartz cells were used for the absorbance measurements.

2.2 Reagents and Solutions: All reagents used were of analytical reagent grade and distilled water was used for the preparation of all solutions. Escitalopram hydrobromide was prepared as method which reported by Robert Dancer et al.¹⁷. A 1000 $\mu\text{g mL}^{-1}$ standard drug solution of Escitalopram hydrobromide was prepared in 50% ethanol and made up to the mark with distilled water and the stock solution was diluted appropriately to get the working concentration. Bromate-bromide mixture (30 and 50 $\mu\text{g mL}^{-1}$ in KBrO_3), ferrous ammonium sulphate (400 and 350 mg mL^{-1}), 1,10 phenanthroline (0.3%), ammonia (1:1), thiocyanate (1M) were used.

2.3 Spectrophotometric Methods: Method A: aliquots containing 0.5-8.0 $\mu\text{g mL}^{-1}$ of Escitalopram hydrobromide were transferred into a series of 10 mL standard flasks using a micro burette. To this, 1 mL of 5 mol L^{-1} HCl and bromate-bromide mixture (30 $\mu\text{g mL}^{-1}$ in KBrO_3) were added. The contents were shaken well and were set aside for 5 min with occasional shaking. Then, 1 mL of 400 $\mu\text{g mL}^{-1}$ ferrous ammonium sulphate was added and again the flask let stand for 15 min with occasional shaking followed by 3.5 mL of ammonium thiocyanate was added and diluted to the mark with distilled water, the absorbance of each solution was measured at 480 nm against the reagent blank.

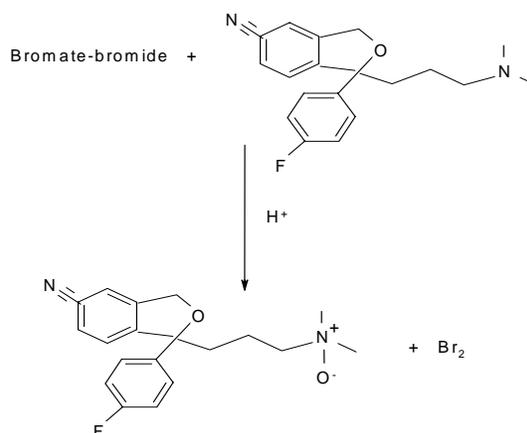
Method B: aliquots containing 0.5-6.5 $\mu\text{g mL}^{-1}$ of Escitalopram hydrobromide were transferred into a series of 10 mL standard flasks using a micro burette. To this, 1 mL of 5 mol L^{-1} HCl and bromate-bromide mixture (50 $\mu\text{g mL}^{-1}$ in KBrO_3) were added. The contents were shaken well and were set aside for 5 min with occasional shaking. Then, 1 mL of 350 $\mu\text{g mL}^{-1}$ ferrous ammonium sulphate was added and again the flask let stand for 15 min with occasional shaking followed by 1 mL each of 0.3% 1,10 phenanthroline and 1:1 NH_3 solution were added and diluted to the mark with distilled water, and the absorbance of each solution was measured at 510 nm against the reagent blank.

2.4 Sample preparation: To determine the content of Escitalopram in conventional tablets (Escitalopram (Ethics) 20 mg film-coated tablets), the sample stock solution was prepared by taking five tablets of Escitalopram equivalent to 100 mg were powdered using a mortar and pestle and transferring to a 100 mL volumetric

flask by washing with ethanol. The solution was shaken for 30 min and filtered through Whatman no.1 filter paper and the clear solution was made up to 100 mL. Pipetted out (2 mL for method A and 0.6 mL for method B) in to a 10 mL calibrated flasks, subjected to analysis by the proposed methods. The results are listed in table 2.

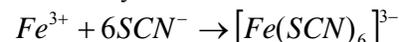
3 Results and Discussion

3.1 Spectroscopy methods: In this method bromate in acid medium acts as an oxidizing agent and there is the formation of nascent oxygen. The formed nascent oxygen oxidizes bromide to bromine and the in situ generated bromine oxidizes the drug. The unreacted bromine is determined by two different schemes. The reduction of residual oxidant by iron (II) resulting in the formation of iron(III).

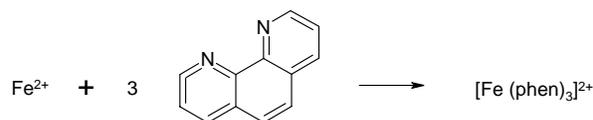


Scheme 1. Formation of nascent oxygen and bromine.

In method A, resulting iron(III) is complexed with thiocyanate and measured at 480 nm.



In method B, unreacted bromine is treated with a measured excess of iron(II) and remaining iron(II) is complexed with 1,10 phenanthroline and measured at 510 nm.



Preliminary experiments were performed to fix the reagent concentration. In the present method all parameters influencing the color development were investigated and are incorporated in the recommended procedure. In method A, Escitalopram when added in increasing concentration to a fixed concentration of bromate-bromide mixture, there was a decrease in the concentration of bromate-bromide mixture.

When known volume of Fe(II) was added to the same mixture, unreacted oxidant was reduced by a fixed amount of iron(II) and it showed a proportional decrease in the concentration of iron(III). The result could be observed by decrease in the absorbance with the increase in the concentration of Escitalopram at the respective λ_{max} . In method B, Escitalopram when added in increasing concentration to a fixed concentration of bromate-bromide mixture, there was a decrease in the concentration of bromate-bromide mixture. When the decreasing amount of oxidant are reacted with a fixed amount of iron(II), it showed a proportional increase in the concentration of iron(II). As a result there is a proportional increase in the absorbance with the increasing concentration of the drug.

Hydrochloric acid medium was found to be ideal for both the steps in method A and B, addition of excess of acid are not preferable since they would require large quantities of ammonia to raise the pH to 4, required for iron(II)-phenanthroline complex formation.

3.2 Analytical Data: Adherence to Beer's law was studied by measuring the absorbance values of solutions varying in drug concentration. The analytical parameters such as molar absorptivity, Sandell's sensitivity, detection limit, quantitation limit, slope, intercept, correlation coefficients for method A and method B are incorporated in table 1. The calibration graphs are described by the equation: $Y = a + b X$ (where Y = absorbance, a = intercept, b = slope and X = concentration in $mg\ ml^{-1}$) obtained by the method of least squares.

Table 1: Analytical parameters

Analytical Parameters	Method A	Method B
λ_{max} (nm)	480	510
Beer's law limit ($\mu g/mL$)	0.5 – 8.0	0.5 – 6.5
Molar absorptivity (L mol)	1.4×10^4	6.8×10^4
Sandell's sensitivity ($\mu g/cm$)	0.0130	0.0042
Limit of detection** ($\mu g/mL$)	0.351	0.066
Limit of quantification** ($\mu g/mL$)	0.982	0.170
Regression equation* $Y = a + bX$		
Slope(b)	0.002	0.026
Intercept(a) 0.057 0.130	0.033	0.062
Correlation coefficient(r)	0.9981	0.9952

*Y is the absorbance and X is the concentration in ($\mu g\ mL^{-1}$)

** calculated using ICH-Guidelines.

3.3 Applications: The proposed methods have been applied to the determination of Escitalopram in tablets. The results for the tablets were compared statistically with those of the tabulated value at 95% confidence level. The calculated student's t-test did not exceed the tabulated value. Table 2 gives the results of the determination from which it is clear that there is close

agreement between the results obtained by the proposed methods and label Esc. The parameters showing the sensitivity of the method such as molar absorptivity, Sandell's sensitivity were found high. The low values of the relative standard deviation in percentages and the error indicated the high accuracy of the two methods.

Table 2. Results of Assay of Formulations by the Proposed methods

Sample	Labeled amount mg.	Amount (Method A) found mg.	Amount (Method B) found mg.
Esc.	20.00	19.985	19.973
		% Label Esc. \pm SD ^a	% Label Esc. \pm SD ^a
		99.925 \pm 0.05	99.865 \pm 0.07
		t-test ^b = 1.46	t-test ^b = 1.12

a- Average of five determinations, b-Tabulated t-value at 95% confidence level is 2.31.

3.4 Accuracy and Precision: The accuracy and precision of the method was established by analyzing the pure drug solution at 4 different levels (within working limits). The results are summarized in tables 3 and 4.

towards the excipients added to the pharmaceutical preparations. Commonly encountered excipients such as glucose, starch, talc, lactose, sucrose did not interfere in the determination of Escitalopram.

3.5 Interference Study: In pharmaceutical analysis, it is important to test the selectivity

Table 3. Evaluation of Accuracy and Precision - Esc. (Method A).

Amount taken ($\mu\text{g mL}^{-1}$)	Amount found ^a ($\mu\text{g mL}^{-1}$)	Recovery (%)	SD (%)	RSD
1	0.97	97.00	0.06	1.19
3	2.98	99.33	0.04	0.83
5	5.01	100.20	0.02	0.97
7	6.96	99.43	0.03	1.25

a- Average of five determinations, SD- standard deviation

Table 4. Evaluation of Accuracy and Precision - Esc. (Method B).

Amount taken ($\mu\text{g mL}^{-1}$)	Amount found ^a ($\mu\text{g mL}^{-1}$)	Recovery (%)	SD (%)	RSD
1	1.01	101.00	0.01	1.42
2	1.99	99.50	0.03	1.11
3	2.98	99.33	0.02	1.09
4	3.99	99.75	0.02	1.63

a- Average of five determinations, SD- standard deviation

Conclusions

Simple, sensitive and selective spectrophotometric methods for the determination of Escitalopram have been developed and validated according to ICH guidelines. The methods are easy to perform and do not contain any stringent experimental variables which effect the reliability of the results. There is no interference from common additives and excipients. The methods thus can be used in the determination of Escitalopram in pure and dosage forms

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