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Spectrophotometric Determination of Citalopram Hydrobromide in Pharmaceuticals

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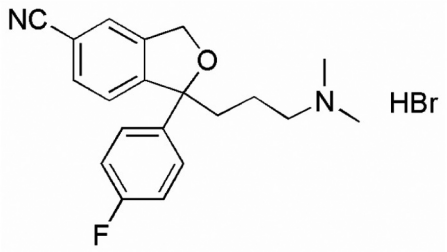
Abstract. Simple, rapid and sensitive methods are described for the spectrophotometric determination of citalopram hydrobromide (CIT) in pharmaceuticals. The method A is based on the oxidation of citalopram by a known excess of bromate-bromide mixture in hydrochloric acid medium, reduction of the residual 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 system obeys Beer's law in the concentration range of 1.0-7.0 μg mL^{-1} of CIT for method A and 0.6-6.2 μg mL^{-1} of CIT for method B. No interference observed from common pharmaceutical adjuvants. 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 2.10×10^4 L mol^{-1} cm^{-1}, 0.019 μg cm^{-2} , 7.30×10^4 L mol^{-1} cm^{-1} and 5.5×10^{-3} μg cm^{-2}, respectively. The methods have been successfully applied to the determination of citalopram hydrobromide in pure and dosage forms.
Keywords: Citalopram hydrobromide, spectrophotometry, bromate-bromide mixture, thiocyanate, 1,10-phenanthroline.

Resumen. Se describen dos métodos, simples y rápidos para la determinación espectrofotométrica del bomhidrato de citalopram (CIT) en fármacos. El método A está basado en la oxidación de citalopram mediante un exceso de mezcla bromato-bromuro en un medio de ácido clorhídrico, así como de la reducción del oxidante residual por una cantidad de hierro(II), y la formación del complejo de hierro(III)-tiocianato, el cual se determina a 480 nm. En el método B, se emplea la 1.10-fenantrolina como agente complejante, y la formación de hierro(II)-1,10-fenantrolina se determina a 510 nm. El sistema obedece la ley de Beer en un intervalo de concentración de 1.0-7.0 μg mL^{-1} de CIT para el método A, y de 0.6-6.2 μg mL^{-1} de CIT para el método B. No se observa interferencia de la parte de aditivos farmacéuticos. Ambos métodos son igualmente precisos como lo muestran los valores menores de 2% de desviación estándar relativa. Se encuentran valores de 2.10×10^4 L mol^{-1} cm^{-1}, 0.019 μg cm^{-2} , 7.30×10^4 L mol^{-1} cm^{-1} y 5.5×10^{-3} μg cm^{-2} para las absortividades molares y la sensibilidad de Sandell para los métodos A y B, respectivamente. Los métodos fueron utilizados exitosamente para la determinación de bromhidrato de citalopram en forma pura o en dosificación.
Palabras Claves: Bromhidrato de citalopram, espectrofotometría, mezcla bromato-bromuro, tiocianato, 1,10-fenantrolina.

Introduction

Citalopram is a selective and potent serotonin reuptake inhibitor with a very broad spectrum of therapeutic activity against depression, anxiety, obsessive and impulse control disorders [1,2]. Citalopram is a Pgp substrate and is actively transported by that protein from the brain. The efficiency of citalopram in people possessing a certain version of Pgp (genetic TT-allele) is likely to be diminished. This suggests that in non-responders to citalopram a switch to antidepressant which is not a Pgp substrate, such as fluoxetine (Prozac, Fontex) or mirtazapine (Remeron)—but not to venlafaxine (Effexor), amitriptyline (Elavil) or paroxetine (Paxil), which are Pgp substrates—may be beneficial [3]. Distinct from some other agents in its class, citalopram exhibits linear pharmacokinetics and minimal drug interaction potential, making it a better choice for the elderly or comorbid patients [4].

Citalopram should be taken with caution when using St John's wort, as resulting drug interactions could be adverse [5]. This may be caused by compounds in the plant extract reducing the efficacy of the hepatic cytochrome P450 enzymes that process citalopram. It has also been suggested that such compounds, including hypericin, hyperforin and flavonoids, could have SSRI-mimetic effects on the nervous system,



citalopram hydrobromide

although this is still subject to debate [6]. One study found that hypericum extracts had similar effects in treating moderate depression as citalopram, with fewer side effects [7]. Several analytical methods have been reported for the determination of citalopram [8-21].

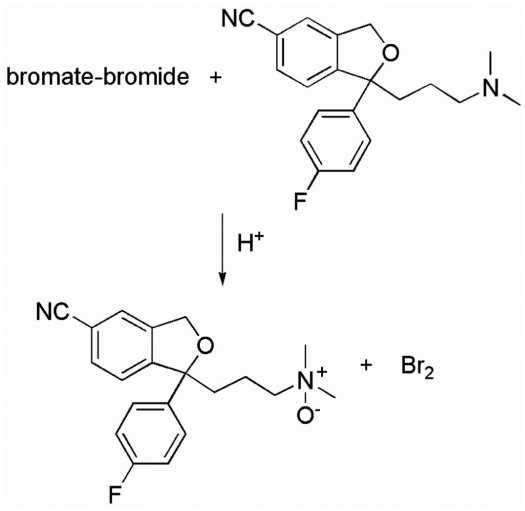
The development of new methods capable of determining drug concentration in pharmaceutical formulations and biological samples is important. The low cost and ease of operation make the spectrophotometric method highly desirable alternative for the assay of citalopram hydrobromide. Hence simple, sensitive and selective methods for the determination of citalopram hydrobromide have been developed and validat-

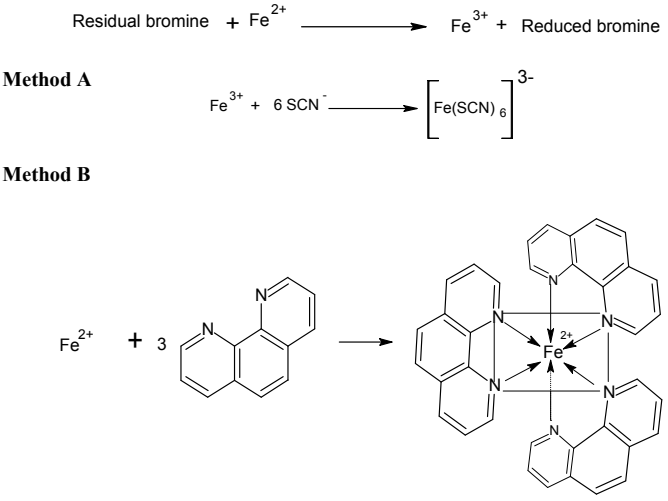
ed according to ICH guidelines. The method is more sensitive than the existing methods and are free from such experimental variables such as heating or extraction step. The method rely on the use of simple, cheap chemicals and techniques but provide sensitivity comparable to that achieved by sophisticated 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 citalopram in pharmaceutical samples.

Results and Discussion

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 scheme. The reduction of residual oxidant by iron(II) resulting in the formation of iron(III). In method A, resulting iron(III) is complexed with thiocyanate and measured at 480 nm (Figure 1). 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 (Figure 2). 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, citalopram 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 citalopram at the respective $\lambda_{max.}$ In method B, citalopram 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.





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 $\mu g ml^{-1}$) obtained by the method of least squares.

Accuracy and Precision

The accuracy and precision of the method was established by analyzing the pure drug solution at 5 different levels (within working limits). The results are summarized in table 3 and 4.

Interference Study

In pharmaceutical analysis, it is important to test the selectivity towards the excipients added to the pharmaceutical preparations. Commonly encountered excipients such as glucose,

Table 1. Analytical Parameters:

	Method A	Method B
λmax (nm)	480	510
Beer's law limit (μgmL^{-1})	1.0-7.0	0.6-6.2
Molar absorptivity ($L\ mol^{-1}cm^{-1}$)	2.10×10^4	7.30×10^4
Sandell's sensitivity (μgcm^{-2})	0.019	5.5×10^{-3}
Limit of detection** (μgmL^{-1})	0.550	0.086
Limit of quantification** (μgmL^{-1})	1.670	0.263
Regression equation*	$Y = a + bX$	
Slope(b)	-0.006	0.038
Intercept(a)	0.057	0.130
Correlation coefficient(r)	-0.9972	0.9751

*Y is the absorbance and X is the concentration in (μgmL^{-1})
** calculated using ICH-Guidelines

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

Amount taken ($\mu g\ mL^{-1}$)	Amount found[a] ($\mu g\ mL^{-1}$)	Recovery (%)	SD (%)	RSD
2.00	1.95	97.50	0.03	1.53
3.00	2.95	98.33	0.04	1.36
4.00	3.98	99.50	0.05	1.26
5.00	4.99	99.80	0.03	0.60
6.00	5.97	99.50	0.03	0.50

[a] Average of five determinations, SD- standard deviation

starch, talc, lactose, sucrose did not interfere in the determination of CIT.

Applications

The proposed methods have been applied to the determination of citalopram 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 claim. The parameters showing the sensitivity of the method such as molar absorptivity, Sandell's sensitivity were found to be higher compared with the existing method in the literature [22]. 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	Amount (method A) found(mg)	Amount (method B) found(mg)
Citalopram	20.00	19.97	19.96
		% Label claim± SD	%Label claim± SD
		99.85 ± 0.03	99.80 ± 0.06
		[b]t - test = 2.24	[b]t-test = 1.49

[a]Average of five determinations, [b]Tabulated t-value at 95% confidence level is 2.31.
Citalopram tablet- Sun Pharmaceutical Industries

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

Amount taken	Amount found[a]	Recovery	SD	RSD
1.20	1.23	102.50	0.02	1.63
1.40	1.39	99.28	0.01	0.72
1.60	1.64	102.50	0.03	1.83
1.80	1.77	98.33	0.02	1.13
2.00	1.98	99.00	0.03	1.52

a- Average of five determinations, SD- standard deviation

Conclusions

Simple, sensitive and selective spectrophotometric methods for the determination of citalopram hydrobromide have been developed and validated according to ICH guidelines. The developed methods have the advantage of sensitivity compared with the existing method in the literature [22]. 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 CIT in pure and dosage forms

Experimental

Apparatus

A Shimadzu UV-2550 UV-VIS Spectrophotometer with 1 cm matched quartz cells were used for the absorbance measurements.

Reagents and Solutions

All reagents used were of analytical reagent grade and distilled water was used for the preparation of all solutions. A 1000

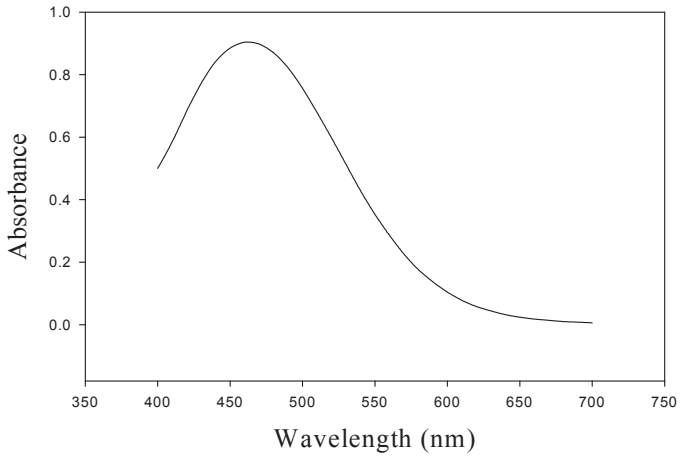


Fig. 1 Absorption Spectrum of Ferricyanide Complex (Method A)

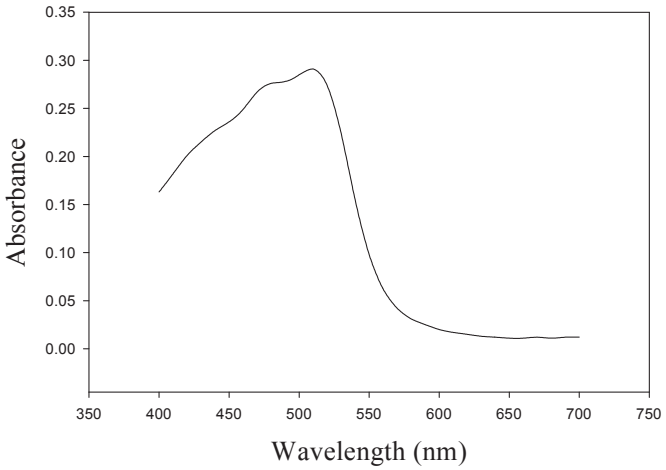


Fig. 2 Absorption Spectrum of Iron(II)- 1, 10-Phenanthroline Complex (Method B)

µg mL^{-1} standard drug solution of CIT 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. Purity of the citalopram hydrobromide is found to be 99.51% (a gift sample from CAD Pharma Inc, India). Bromate-bromide mixture (30 and 50 µg mL^{-1} in $KBrO_3$), ferrous ammonium sulphate (400 and 350 ìg mL^{-1}), 1,10 phenanthroline (0.3%), ammonia (1:1), thiocyanate (1M) were used.

Spectrophotometric Method A

Aliquots containing 1.0-7.0 µg mL^{-1} of CIT 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 µg 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 µg 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.

Spectrophotometric Method B

Aliquots containing 0.6-6.2 µg mL^{-1} of CIT 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 µg 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 µg 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.

Analysis of Dosage Forms

To determine the content of citalopram in conventional tablets (label claim: 20 mg/ tablet), the sample stock solution was prepared by taking five tablets of citalopram 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.

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