Development and Application of Spectrophotometric Methods for the Determination of Citalopram Hydrobromide in Dosage Forms

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Study was carried out to develop two simple, fast, accurate and sensitive spectrophotometric methods (A and B) for the determination of citalopram hydrobromide in commercial tablet formulations. In method A, UV spectrophotometer determined the contents of citalopram hydrobromide in tablets at 240 nm in methanol solvent. The linear range was 5—40 $\mu g\,ml^{-1}$ with molar absorptivity $1.4\times10^{4}\,l\,mol^{-1}\,cm^{-1}$. While the method B based on the reaction of citalopram base as *n*-electron donor with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone as π-acceptors to give highly colored complex species that absorb maximally at 590 nm. Beer's law was obeyed in the concentration limit of 10—250 $\mu g\,ml^{-1}$ with molar absorptivity $3.3\times10^{3}\,l\,mol^{-1}\,cm^{-1}$ for citalopram hydrobromide. The limits of detection and limit of quantification was calculated and found to be 5.2 $\mu g\,ml^{-1}$ and 17.4 $\mu g\,ml^{-1}$ respectively. The proposed methods were found to be rapid, accurate, precise and sensitive for the determination of citalopram hydrobromide in commercial tablet formulations with out interferences from common additives encountered.

Key words spectrophotometric method; citalopram hydrobromide; dosage form; pharmaceutical analysis

Citalopram is a highly selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitor (SSRI) with minimal effects on the neuronal reuptake of norepinephrine and dopamine. It is a bicyclic phthalane derivative (racemic), which is not related to the tricyclic or tetracyclic antidepressants. It is used in the treatment of major depressive disorder. The hydrobromide salt of it is administered orally. Chemically, it is (±)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, hydrobromide.[1)]

A very few analytical methods appeared in the literature for the determination of citalopram hydrobromide in tablets are generally based HPLC with UV detection[2)] HPLC with fluorescence detection,[3)] capillary zone electrophoretic method[4)] densitometric HPTLC, and videodensitometric HPTLC methods.[5)] HPLC-electrospray ionization mass spectrometry (HPLC-MS/ESI)[6)] and HPLC-positive ion electrospray mass spectrometry method has been reported for the quantification of citalopram in human plasma.[7)] Officially assay of citalopram hydrobromide is not described in pharmacopoeias. In the present work, an attempt was made to provide a simple, accurate and low cost spectrophotometric method for the quantitative determination of citalopram hydrobromide in pharmaceutical preparations without the interferences of other constituent in the formulations.

Experimental

Apparatus A Hitachi U 1100, UV/Vis spectrophotometer (Japan) with silica glass cell of 1 cm thickness was used. Officially calibrated Pyrex glassware was used throughout this study.

Reagents and Standards Citalopram hydrobromide was supplied by Bio Fine pharmaceuticals (Pvt.) Ltd. Multan, Pakistan. Commercial dosage forms of citalopram hydrobromide were purchased from a local market. All reagents and solvents used were of Analytical Reagent Grade. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Fluka, Switzerland) 2.0 $mg\,ml^{-1}$ solution was prepared in 1,4-dioxan.

The standard solutions (1 $mg\,ml^{-1}$) of citalopram hydrobromide were prepared in methanol for method A and citalopram hydrobromide base in chloroform for method B. An aqueous solution of sodium carbonate (0.5 M, Merck, Germany) was prepared in doubly distilled water.

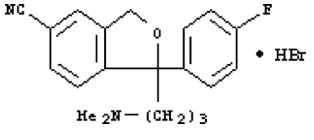
Recommended Procedures. Method A Different aliquots of standard solution of citalopram hydrobromide (5—40 $\mu g\,ml^{-1}$) were prepared in methanol. Absorbance of these solutions was noted at 240 nm against a reagent blank.

Procedure for the Assay of Citalopram Hydrobromide in Pharmaceutical Formulations Twenty tablets were accurately weighed and powdered. A portion equivalent to 100 mg of citalopram hydrobromide was stirred with 30 ml methanol and the volume was made up to 50 ml in volumetric flask. The solution was filtered with Whatman filter paper No. 1. Then take aliquot of the filtrate made up to 100 ml volume with methanol in volumetric flask. The absorbance was measured at 240 nm against reagent blank.

Method B. Preparation of Citalopram Base Solution A citalopram base solution was prepared by transferring 100 ml of 0.5% citalopram hydrobromide solution (aqueous) into 250 ml separating funnel, followed by 25 ml of 0.5 M sodium carbonate solution. The contents of separating funnel were mixed well, shaken for two minutes ad then extracted with 100 ml chloroform. The two phases were allowed to separate and the chloroform layer was dried over anhydrous sodium sulphate.

Proposed Procedure Aliquots of 10—250 $\mu g\,ml^{-1}$ of the citalopram base solution were pipetted into a series of 10 ml standard volumetric flasks. Then, 1 ml DDQ solution was added to each flask. The color develops immediately. Make up the volume up to the mark with chloroform. The absorbance was measured within the stability period of 2 h after dilution at 590 nm against reagent blank.

Procedure for Determination of Dosage Forms An accurately weighed portion of powdered tablet equivalent to 250 mg of citalopram hydrobromide was stirred well with 20 ml distilled water and left standing for 5 min. The residue was filtered on Whatman filter paper No. 42 and washed with distilled water. The filtrate and washings were diluted to the volume in 50 ml measuring flask with same solvent. The citalopram hydrobromide solution was converted into citalopram base following the procedure given under the head "preparation of citalopram base solution", and the subjected to the recommended procedure for the determination.



Structural formula of citalopram hydrobromide

Results and Discussion

The method A is based on the simple scanning of citalopram hydrobromide in methanol solvent and its determination in the presence of various excipients. While the method B is based on the charge-transfer (CT) reaction. The CT reaction has been widely studied recently. Many drugs are easy

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to be determined by spectrophotometry based on color CT complexes formed with electron acceptors.[8,9] The CT complexes are formed between electron donors, having sufficiently low ionization potential, and acceptors, having sufficiently high electron affinity. The transfer of an electron from a donor to an acceptor is readily possible in the CT process.[10] DDQ is a π-electron acceptor as a result of the strong electron withdrawing halo and cyano groups conjugated with the π-system.[11,12] DDQ reacts instantaneously with basic nitrogenous compounds to form CT complexes of n–π type. This complex is formed by the lone pair of electron donated by the citalopram base as n-donor and the CT reagent as an electron acceptor, which a partial ionic bond ($D^+ A^-$) is assumed to be formed.

$$\underset{\text{donor acceptor}}{D+A} \longrightarrow \underset{\text{donor-acceptor complex}}{[D \longrightarrow A]} \longrightarrow \underset{\text{radical anion}}{D^+ + A^-}$$

Effect of Color Producing Reagent and Time For Method B, the effect of volume of 2 mg ml^{-1} DDQ solution was studied over the range of 0.2—2.0 ml, in a solution containing 100 μg ml^{-1} citalopram. The results revealed the fact that 1 ml of DDQ solution was required to achieve the maximum intensity of the color. Therefore 1 ml was the optimum value and maintained throughout the experiment. The reaction gets stabilized within the 2 min of mixing at room temperature and absorbance remained constant at least for 2 h.

Interference Study To study the potential interference problems from the commonly used excipients and other additives such as microcrystalline cellulose, lactose, povidone, starch, primojel and magnesium stearate, recovery studies were carried out. Under the experimental conditions employed, to a known amount of drug (citalopram hydrobromide 100 μg ml^{-1}), excipients in different concentrations were added and analyzed. Results of the recovery analysis are presented in Table 1. Excipients up to the concentrations shown in the Table 1 do not interfere with the assay. In addition recoveries in most cases were around 100% and the lower values of the RSD indicate the good precision of the method.

Sensitivity The results for the determination of citalopram are shown in Table 3, which show the sensitivity, validity and reproducibility of the proposed methods. These are also reasonably precise and accurate, as the amount taken from identical samples is known and the amount found does not exceed a relative standard deviation of 0.72 and 0.69 (N=5). The calibration graph is linear in the range of 5—40 μg ml^{-1} for method A and 10—250 μg ml^{-1} for method B. The apparent molar absorptivity calculated for method A and B is 1.4×10^4 l mol^{-1} cm^{-1} and 3.3×10^3 l mol^{-1} cm^{-1} respectively. The correlation between absorbance and concentration for method A and B is 0.999 and 0.999 respectively.

For limit of detection first we calculate the absorbance "p" by following equation

$$p=b+3\mathrm{SD}$$

Where b is the average of five replicate readings of blank and SD is standard deviation of five replicates. The value of limit of detection is calculated by comparing the absorbance "p" with the absorbance of known concentration of sample. The limit of quantification (LOQ) is determined by taking the ratio of the standard deviation (σ) of the blank with respect to water and the slope of the calibration curve multiplied by the factor 10. This means that LOQ is approximately 3.3 times greater than LOD. LOD is well below the lower limit of the Beer's law range.

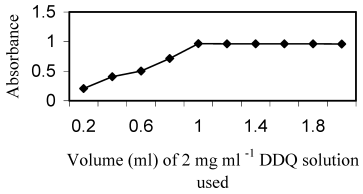

Fig. 1. Effect of Reagent Concentration on Color Development

Table 1. Determination of Citalopram Hydrobromide in the Presence of Excipients

Excipients	Amount taken (μg ml^{-1})	% Recovery ±RSD (N=5) method A	% Recovery ±RSD (N=5) method B
Microcrystalline cellulose (PH 102)	300	101.5±0.40	100.5±0.30
Lactose monohydrate	300	100.2±0.35	99.2±0.25
Povidone	100	99.26±0.40	99.8±0.45
Starch	200	102.7±0.20	100.7±0.25
Magnesium stearate	300	99.52±0.48	99.9±0.40
Primojel	50	98.95±0.30	99.5±0.30

For interferences studies, 10 μg ml^{-1} of citalopram was taken for method A and 100 μg ml^{-1} for method B.

Table 2. Analytical Parameters

Parameter	Values for method A	Values for method B
λ_{max} (nm)	240	590
Beer's law verification range (μg ml^{-1})	5—40	10—250
Molar absorptivity (l mol^{-1} cm^{-1})	1.4×10^4	3.3×10^3
Sandell's sensitivity (μg cm^{-2})	2.7×10^{-2}	1.2×10^{-1}
Regression equation ($Y^{a)}$)		
Slope (b)	0.0357	0.0083
Intercept (a)	0.00931	−0.001
Correlation coefficient (r)	0.999	0.999
RSD$^{b)}$ (%)	0.72	0.69
Limit of detection (μg ml^{-1})	4.6	5.2
Limit of quantification (μg ml^{-1})	15.2	17.4

a) $Y=a+bC$ (where C is the concentration of analyte (μg ml^{-1}) and Y is absorbance). *b*) Calculated from five determinations.

Application The applicability of the proposed methods for the determination of citalopram hydrobromide in commercial dosage forms was examined by analyzing marketed products. The results of the proposed methods were statistically compared with reference method [2] and summarized in Table 3. It is evident from the table that the calculated t-test value and F-test values[13] are less than the theoretical ones at 95% confidence level, indicating no significant difference between the methods compared. The proposed methods are sensitive, simple, and accurate and are successfully applied for the quality control of pure citalopram hydrobromide in pharmaceutical dosage forms.

Conclusion

It is concluded that the newly developed spectrophotometric methods for the determination of citalopram hydrobro-

Table 3. Determination of Citalopram Hydrobromide in Pharmaceutical Formulations by the Proposed and Reference[2] Method

Formulation	Method A				Method B				Reference method	
	Recovery* (%)	RSD (%)	*t*-value	*F*-value	Recovery* (%)	RSD (%)	*t*-value	*F*-value	Recovery* (%)	RSD (%)
Cipramil	100.07	0.66	0.41	3.02	99.34	0.78	0.33	2.65	99.88	0.45
S-Pram	99.60	0.48	0.32	3.12	101.56	0.39	0.23	2.26	99.23	0.56
Pramcit	99.86	0.52	0.21	1.25	100.85	0.43	0.35	2.49	100.65	0.47
Cheer	98.53	0.44	0.42	4.01	99.12	0.39	0.46	3.98	99.78	0.59
Citopram	98.72	0.43	0.28	4.28	99.33	0.39	0.24	4.62	99.58	0.42

N=5.

mide are reliable, simple, sensitive, accurate, rapid, and economical. The results are in good agreement with reference method. The literature indicated that this color reaction have not been reported previously.[14]

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