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Spectrophotometric determination of flavoxate hydrochloride in bulk and pharmaceutical formulation

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ABSTRACT

Two simple, rapid and sensitive extractive spectrophotometric methods have been developed for the determination of flavoxate hydrochloride (FLH) in pure and pharmaceutical formulations. These methods are based on the formation of chloroform soluble ion-association complexes of FLH with bromothymol blue (BTB) and with bromophenol blue (BPB) in potassium phthalate-HCl buffer of pH 3.6 (Method A) and glycine-HCl buffer of pH 3.0 (Method B) with absorption maximum at 417 nm and 411 nm respectively. Reaction conditions were optimized to obtain the maximum color intensity. The absorbance was found to increase linearly with increase in concentration of FLH, which was corroborated by the calculated correlation coefficient values (0.9996 and 0.9995). The systems obeyed Beer's law in the range of 2–20 μg/ml and 1–25 μg/ml for Method A and B respectively. Various analytical parameters have been evaluated and the results are validated by statistical data. No interference was observed from common excipients present in pharmaceutical formulations. These proposed methods were simple, accurate and suitable for routine quality control applications.

KEYWORDS

Spectrophotometric determination;
Flavoxate hydrochloride;
Bromothymol blue;
Bromophenol blue.

INTRODUCTION

Flavoxate hydrochloride (FLH) is designated chemically as 3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxylic acid-2-(1-piperidinyl) ethyl ester, belongs to a series of flavone derivatives, which exhibit strong smooth muscle relaxant activity, especially on the urogenital tract[1,2]. It is used for the symptomatic relief of pain, urinary frequency, and incontinence associated with inflammatory disorders of the urinary tract and also used for the relief of vesico-urethral spasms resulting form instrumentation or surgery[3]. The literature survey reveals that FLH was analyzed in its pharmaceutical formulations by UV-Spectrophotometry[4,5], capillary electrophoresis[6] voltammetric[7] and high performance liquid chromatography[8-10]. The official method for determination of FLH is non-aqueous titration using perchloric acid as titrant in pure form and spectrophotometry in tablets[5].

No reports have been appeared dealing with the extractive spectrophotometric method for the determination of FLH in drug forms so far. This prompted us to develop simple, accurate and more sensitive extractive spectrophotometric method for the determination FLH in bulk and pharmaceutical formulation. The methods are based on the formation of ion-pair with BTB and BPB as an ion-pair complexing reagents. The extractive spectrophotometric procedures are popular for their

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sensitivity for the assay of drugs and therefore ion-pair extraction spectrophotometry has received considerable attention for the quantitative determination of many pharmaceutical compounds[11-13].

EXPERIMENTAL

Apparatus

A Elico double beam UV-Vis spectrophotometer model SL-164 with 1 cm path length quartz cells were used for the absorbance measurements.

Materials and Reagents

All chemicals and solvents used were of analytical grade or chemically pure grade and used without further purification, double distilled water was used throughout the experiment. Pharmaceutical grade FLH was kindly supplied by Sairam Organics Pvt. Ltd., India. Tablets containing FLH was purchased from local drug store, each tablet was labeled to contain 200 mg of FLH. Bromothymol blue and Bromophenol blue were purchased from s.d.fine-chem. Ltd., Mumbai.

Preparation of Standard and Reagent Solutions

Standard solution of FLH was prepared as 1 mg/ml in methanol and this stock solution was further diluted to get a working standard solution containing the concentration of 100 μg/ml of the drug. Aqueous solution of 0.1% w/v of BTB and BPB were prepared in water and a series of buffer solutions of KCl-HCl (pH 1.0–2.2), sodium acetate-acetic acid (pH 3.8-5.6), Glycine-HCl (pH 2.2-3.6) and potassium hydrogen phthalate-HCl (pH 2.2-3.8) were prepared by the standard methods.

Procedure for the Assay of Bulk Drug Sample

Suitable aliquot of the working standard solution of FLH (2-20 μg/ml) for Method A and (1-20 μg/ml) Method B were transferred into a series of 125 ml separating funnels. These drug solutions were mixed with 5 ml of potassium hydrogen phthalate-HCl buffer of pH 3.6 and 1.5 ml of BTB for method A and Glycine-HCl buffer of pH 3.0 and 2.5 ml of BPB for Method B. Finaly 10 ml of chloroform was added to each of the separating funnel and then the contents were shaken well and left at room temperature for a minute. The two phases were allowed to separate and the chloroform layer was passed through anhydrous sodium sulphate. The absorbances of the yellow colored complexes were measured at 417 nm and at 411 nm for Method A and B, respectively against the corresponding reagent blank. The calibration graph was plotted.

Assay Procedure for Tablets

Ten tablets containing FLH were weighed and finely powdered. An amount of the powder equivalent to 100 mg of FLH was weighed and dissolved in 250 ml beaker containing 50 ml methanol the solution was shaken thoroughly for about 10-15 min., filtered through a Whatman filter paper no. 41 to remove the insoluble matter and diluted to the mark in a 100 ml volumetric flask. The general procedure was then followed in the concentration ranges as mentioned above.

RESULTS AND DISCUSSION

Flavoxate hydrochloride forms ion-pair complexes in acidic buffer with dye stuffs such as BTB and BPB, and these complexes are quantitatively extracted into chloroform. The absorption spectra of the ion-pair complexes with BTB and BPB absorbed maximally at 417 and 411 nm respectively (Figure 1). The colorless reagent blanks under similar conditions showed no absorption.

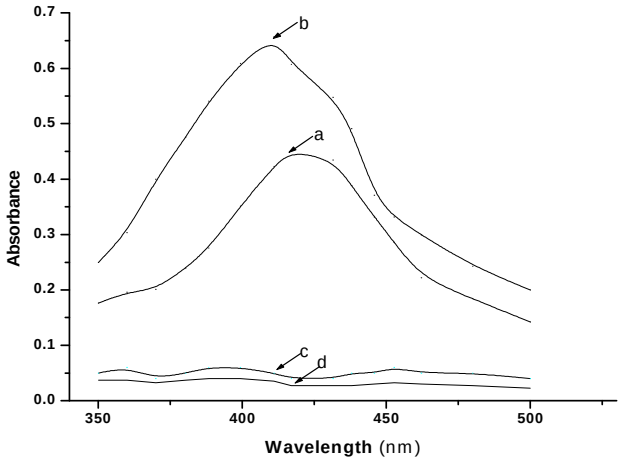
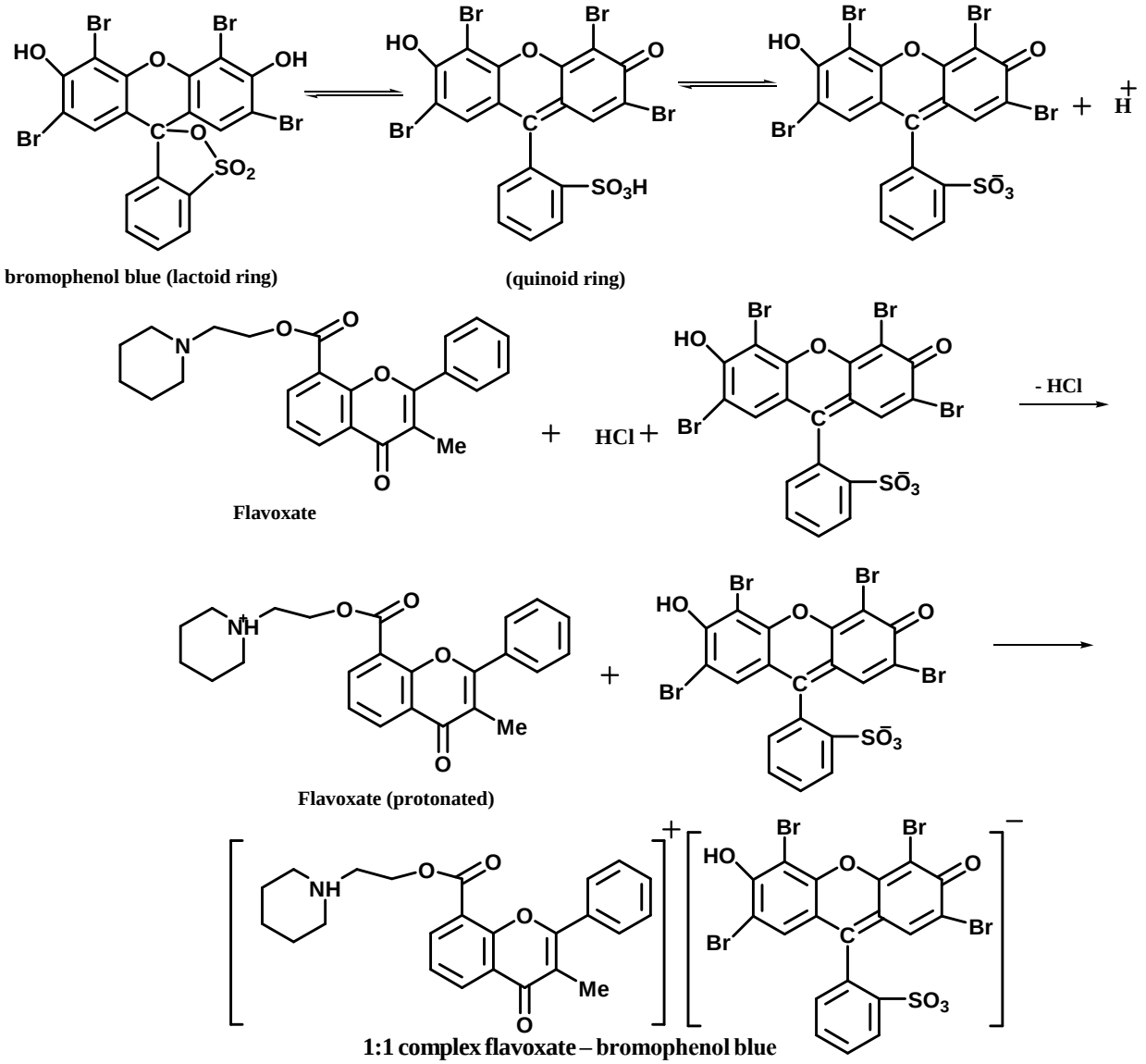


Figure 1 : Absorption spectra of FLH-dye complexes extracted into 10 ml chloroform: a) for Method A, b) for Method B, c) Blank for Method A and d) Blank for Method B

Flavoxate hydrochloride contains tertiary amino group which is protonated in acid medium while sulphonic acid group is present in BTB, which is the

only group undergoing dissociation in the pH range 1–5, BPB is an example of sulphonaphthalein type of dye. The color of such dyes is due to the opening of lactoid ring and subsequent formation of quinoid group which forms ion-pair complex with protonated flavoxate hydrochloride with dye stuffs, which are quantitatively extracted into chloroform. The possible reaction mechanism was shown in scheme.



Optimization Studies

Optimum ion-pair complex formation conditions with respect to λ_{max}, pH range, solvent extraction time, amount of the reagent and stability of the complex formation were established by a number of preliminary experiments. It was observed that the effective extraction of the complex depends on the type of buffer used and its pH. The effect of pH was studied by extracting the colored complex in presence of various buffers such as KCl-HCl (pH=1.0-2.2), NaOAc-HCl (pH=1.99-4.92), NaOAc-AcOH (pH=3.6- 5.6), potassium hydrogen phthalate-HCl (pH = 2.2-3.8) and Glycine-HCl (pH = 2.2-3.6). It was noticed that the maximum color intensity and constant absorbance was observed in potassium hydrogen phthalate-HCl buffer of pH range 2.2-3.8 (for Method A) and Glycine-HCl buffer of pH range 2.2-3.6 (for Method B). Hence, potassium hydrogen phthalate-HCl buffer of pH 3.6 for Method A and Glycine-HCl buffer of pH 3.0 for Method B were selected for all subsequent measurements. Further, the

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volume of buffer solution was optimized, 5.0 ml of potassium hydrogen phthalate-HCl buffer for Method A and 2.5 ml of Glycine-HCl buffer for Method B gave maximum absorbance and reproducible results.

The effects of the reagents were studied by measuring the absorbance of solutions containing a fixed concentration of FLH and varied amounts of the respective reagent. Maximum absorption shows with 1.5 ml of 0.1% BTB for Method A and 2.5 ml of 0.1% BPB for Method B. Several organic solvents viz, chloroform, carbon tetrachloride, ethyl acetate, xylene, diethyl ether, toluene, dichloromethane and chlorobenzene were tried for effective extraction of colored species from aqueous phase. Only partial extraction of the complex was achieved with solvents other than chloroform. Shaking times of 1-2 min. produced constant absorbances and hence a shaking time of 1 min. was maintained throughout the experiment.

Effect of Temperature on the Colored Complexes

To study the effect of temperature on formed colored complexes, the absorbance was measured by varying temperature it was found that up to 35 ^{0}C the complexes were stable. At higher temperatures concentration of drug increases due to volatile nature of chloroform. However, at room temperature the complexes were stable for more than 6 h. for Method A and Method B respectively.

Stoichiometry

The stoichiometry of ion-pair complexes was determined by Job's method of continuous variation[14] and was found to be 1:1 with BTB as well as with BPB.

Analytical Parameters

With these experimental conditions, calibration graphs for both methods were constructed. TABLE 1. summarizes the values of Beer's law limit, molar absorptivity, regression equation, correlation co-efficient, Sandell's sensitivity, Limit of detection (LOD) and Limit of quantification (LOQ) for each method. A linear relationship was found between the absorbance at λ_{max} and the concentration of the drug in the ranges of 2-20 and 1-25 μg ml^{-1} for BTB and BPB method respectively, the correlation co-efficient were 0.9996 and 0.9995 for both methods indicating good linearity. The graph shows negligible intercept and are described by the regression equation Y = bX + c (where Y is the absorbance of 1cm layer, b is the slope, c is the intercept and X is the concentration of each drug solution in μg ml^{-1}) and are obtained by the least-squares method[15].

TABLE 1 : Optical Characteristics, Precision and Accuracy Data

Parameters	Method A	Method B
λ_{max} (nm)	417	411
Beer's Law limits (μg ml^{-1})	20-Feb	25-Jan
Molar absorptivity (L mol^{-1}cm^{-1})	2.228 x 10^4	3.194 x 10^4
Sandell's sensitivity (μg ml^{-1})	19.25	13.39
Regression equation** (Y = bx + c)		
Slope(b)	0.4702	0.0941
Intercept(c)	0.0362	0.0206
Correlation coefficient (r)	0.9996	0.9995
% Relative Standard Deviation (R.S.D)*	0.1935	1.269
% Range of error (Confidence)*		
0.05 level	0.0077	0.0073
0.01 level	0.0113	0.0106
Limit of Detection (μg ml^{-1})	0.086	0.08
Limit of Quantification (μg ml^{-1})	0.2863	0.2664
Stability (h.)	6	6

****Y = bX+c, where Y is the absorbance and X is the concentration of drug in μg /ml**

***Average of six determinations.**

The LOD and LOQ values were calculated according to the analytical method committee[16], the LOD values were found to be 0.086 and 0.080 μg ml^{-1} for BTB and BPB method respectively. The LOQ values were observed to be 0.2863 and 0.2664 for FLH with BTB (Method A) and with BPB (Method B), which shows the sensitivity of the method.

Accuracy and Precision

In order to determine the accuracy and precision of the recommended procedures, six replicate determinations of drug were carried out. The range, percentage error and relative standard deviation obtained are given in TABLE 1. This indicates that the proposed methods were highly accurate and reproducible.

Recovery Studies

Recovery studies were carried out by standard addition method, for this known quantity of pure FLH was mixed with definite amounts of pre-analyzed formulations and mixtures were analyzed as before. The

total amount of the drug was then determined and the amount of the added drug was calculated by difference. The results of analysis of pharmaceutical formulations are presented in TABLE 2. The average percentage recoveries obtained were quantitative (98.9 % - 99.1%) indicating good accuracy of the methods.

TABLE 2 : Determination of FLH in Pharmaceutical Formulations and Statistical Comparison with the Reported Method.

Method	Tablet brand name	Labelled amount mg/tablet	% Recovery[a] ± SD (%)	
			Proposed	Reference[4]
A	Flavoxate Hydrochloride	200	98.97 ± 0.54	99.98 ± 0.15
B	Flavoxate Hydrochloride	200	99.10 ± 0.25	99.98 ± 0.15

[a]**Average of six determinations ± S. D.**

Interference Studies

The effects of common excipients and additives were tested for their possible interferences in the assay of FLH; it was observed that the glucose, sucrose, lactose, dextrose, talk and starch did not interfere in the determination at the levels normally found in dosage from (TABLE 3).

TABLE 3 : Determination of FLH[a] in the Presence of Excipients

Excipients	Amounttaken/mg	% Recovery ± %RSD[b]
Glucose	20	98.05 ± 0.36
Sucrose	20	98.27 ± 0.58
Lactose	25	99.14 ± 0.46
Dextrose	20	98.22 ± 0.82
Talc	25	99.55 ± 0.22
Starch	20	100.36 ± 0.81

[a]**10 µg / ml FLH were used.**

[b]**mean value of six determinations.**

CONCLUSIONS

The proposed methods are thus simple, rapid, precise and inexpensive, which an ordinary analytical laboratory can afford. Moreover, the methods are free from interference by common additives and excipients. The proposed methods thus can be used in routine quality control analysis of FLH in pure form and in pharmaceutical formulations.

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REFERENCES

[1] E.Pedersen; Urol.Int., **32**, 202 **(1977)**.
[2] D.V.Bradley, R.J.Cazort; J.Clin.Pharm.and new drugs., **10**, 65 **(1970)**.
[3] S.C.Sweetman; Martindale, The Complete Drug Reference, 33rd ed., Pharmaceutical Press, **(2002)**.
[4] A.Gova, I.Setnikar; Drug Research, **25**, 1707 **(1975)**.
[5] British Pharmacopoeia Stationary Office, London, **(2005)**.
[6] C.X.Zhang, Z.P.Sun, D.K.Ling; J.Chromatogr., **612**, 287 **(1993)**.
[7] M.M.Ghoneim, M.A.El-Attar, S.A.Razeq; Centr.European J.Chem., **5(2)**, 496 **(2007)**.
[8] Y.Wang, T.J.Wang, T.L.Zhang; J.Yaowu-Fenxi-Zazhi. **22**, 202 **(2002)**.
[9] S.S.Zarapkar, U.B.Salunkhe, B.B.Salunkhe, V.J.Doshi, S.V.Sawant, R.V.Rele; Indian drugs., **26**, 354 **(1989)**.
[10] Alaa El-Gindy, Shehab Sallam, A.Randa, Abdel-Salam; J.Pharm.and Biomed.Anal., **44**, 274 **(2007)**.
[11] K.Siddappa, M.Mallikarjun, Tukaram Reddy, Mahesh Tambe, Shobha Manujunath, Appal Raju; Inter.J.Chem.Sci., **5(5)**, 2302 **(2007)**.
[12] K.Basavaiah, V.S.Charan; Indian J.Chem.Tech., **11**, 309 **(2004)**.
[13] C.S.P.Sastry, K.Rama Rao, D.Siva Prasad; Talanta., **42**, 105 **(1995)**.
[14] W.C.Vocburgh, G.R.Cooper; J.Amer.Chem.Soc., **63**, 437 **(1941)**.
[15] J.C.Miller, J.N.Miller; Statistics in Analytical Chemistry, 3rd ed., Ellis Horwood, Chichester, **(1993)**.
[16] Analytical Methods committee; Analyst., **112**, 199 **(1987)**.