Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 7, Issue 6, 2015

Original Article

SPECTROPHOTOMETRIC DETERMINATION OF OXYBUTININE HYDROCHLORIDE BY ION-PAIR EXTRACTIONIN IN PHARMACEUTICAL PREPARATIONS

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Received: 14 Feb 2015 Revised and Accepted: 28 Apr 2015

ABSTRACT

Objective: Simple, sensitive, precise, reproducible and validated visible spectrophotometric methods have been developed for the determination of an antimuscarinic drug, namely oxybutynin hydrochloride (OXB) in pure form and in pharmaceutical preparations.

Methods: Two spectrophotometric methods are based on the formation of yellow colored ion-pair complexes between the studied drug, and two sulphonphthalein acid dyes, bromocresol purple (BCP) and bromophenol blue (BPB) with absorption maxima at 410 and 416 nm, respectively.

Results: The stoichiometric ratio of the formed ion-pair complexes was found to be 1:1 (drug: reagent) for both methods as deduced by Job's method of continuous variation. Several parameters such as pH, buffer type, and reagent volume, sequence of addition and effect of extracting solvent were optimized to achieve high sensitivity, stability, low blank reading and reproducible results. Under the optimum reaction conditions, linear relationships with good correlation coefficients (0.9996-0.9999) were found between the absorbance's and the concentrations of oxybutynin over the concentration ranges of 1.0–8.0 µg ml^{-1} and 1.0–12 µg ml^{-1} with LOD of 0.21 and 0.19 µg ml^{-1}, using BCP and BPB methods, respectively. Various analytical parameters have been evaluated and the results have been validated by statistical data.

Conclusion: The proposed methods were validated in accordance with ICH guidelines and successfully applied to the analysis of pharmaceutical formulation. Statistical comparison of the results obtained by applying the proposed methods with those of the reference method revealed good agreement and proved that there was no significant difference in the accuracy and precision between the results.

Keywords: Oxybutynin hydrochloride, Ion-pair complex, Bromocresol purple, Bromophenol blue, Spectrophotometry, Pharmaceutical formulations.

INTRODUCTION

Oxybutynin hydrochloride is chemically designated as 4-(diethylamino) -2-butynyl (RS)-2-cyclohexyl-2-hydroxy-2-phenyl acetate hydrochloride (fig. 1) [1]. It is an antimuscarinic drug with a great selection for the muscarinic receptors of the bladder. It is used in the management of urinary frequency, urgency, and incontinence in detrusor instability and in the treatment of nocturnal enuresis [2].

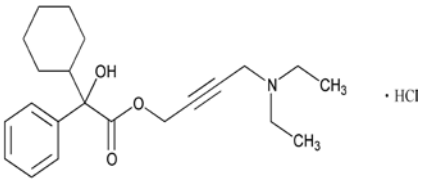


Fig. 1: The chemical structure of oxybutynin hydrochloride (OXB)

The literature survey revealed that few methods have been performed for the determination of OXB such as spectrophotometry [3-9], spectrofluorimetry [5], electrochemical methods [10, 11], HPTLC [9, 12] and HPLC [8, 13-16]. Most of the reported methods (except spectrophotometric methods) are either not appropriately sensitive or tedious and utilized expensive instruments that are not available in most quality control laboratories and the procedures are not simple to perform.

Visible spectrophotometric methods represent the most convenient analytical technique in most quality control laboratories because of their selectivity. In addition, they are easier, less expensive and less time consuming compared with many other methods. The reported methods for OXB in spite of being spectrophotometric method, but they lack the simplicity which is found usually in this technique (table 1). The analytically important functional groups of OXB were not properly exploited for designing suitable spectrophotometric methods for the determination of OXB. Hence a new sensitive and flexible visible spectrophotometric method was developed based on the reactivity of OXB with two acid dye reagents such as BCP and BPB because of the presence of the aliphatic tertiary amino group (the basic group) in OXB.

Therefore the aim of this work is to develop a simple, sensitive, accurate, precise, low-cost and validated two spectrophotometric methods for the determination of oxybutynin hydrochloride (OXB) in pure form and in pharmaceutical formulations with no need for any expensive or sophisticated instruments. The proposed methods are based on the ability of OXB to form stable ion-pair complexes with BCP and BPB.

MATERIALS AND METHODS

Apparatus

All absorption spectra were made using Kontron Unikon 930 (UV-Visible) spectrophotometer (German) with a scanning speed of 200 nm min^{-1} and a band width of 2.0 nm, equipped with 10 mm matched quartz cells. The pH values of different buffer solutions were checked using a Hanna pH-meter instrument (pH 211) (Romania) equipped with a combined glass-calomel electrode.

Materials and reagents

All reagents and chemicals used were of analytical or pharmaceutical grade and all solutions were prepared fresh daily.

Materials-Pure sample of oxybutynin hydrochloride (OXB) was kindly supplied by the Egyptian Company for Chemicals and Pharmaceuticals (ADWIA) (10^{th} of Ramadan City, Egypt), with a purity of 99.84±0.40% by applying the official method [1].

Pharmaceutical formulations

The following tablets containing the drug were purchased from local pharmacies.

-Ditronin® tablets, batch # 4034003, labeled to contain 5.0 mg OXB per tablet, product of Pharaonia Pharmaceuticals Company (Alexandria, Egypt).

-Uripan® tablets, batch # 140576, labeled to contain 5.0 mg OXB per tablet, product of ADWIA Co. S. A. E, 10th of Ramadan City, Egypt.

Table 1: Comparison between the reported methods for spectrophotometric determination of OXB

Method	Wavelength (nm)	Beer's law (µg ml^{-1})	Molar absorptivity (l mol^{-1} cm^{-1})	Detection limit (µg ml^{-1})	Reference
Tropaoline OOO (TPOOO)	480	1.0-7.5	1.954 x 10^4	0.062	[3]
Alizarin red S (ARS)	430	2.0-15	1.545 x 10^4	0.11	
2,3-dichloro-5,6-dicayno-p-benzoquinone (DDQ)	457	20-80	-	0.205	[4]
2,5-dichloro-3,6-dihydroxy-p-benzoquinone (p-CLA)	520	30-160	-	0.524	
Malonic acid anhydride in acetic acid anhydride	375	4.0–40	-	1.12	[5]
Bromothymol blue (BTB)	414	2.5-12.5	0.0579	-	[6]
Fe(III)/phenanthroline mixture	510	0.8-4.8	-	-	[7]
Picric acid	344	-	-	-	[8]
Bromocresol purple (BCP)	410	1.0-8.0	2.34 x 10^4	0.21	Proposed work
Bromophenol blue (BPB)	416	1.0-12	1.22 x 10^4	0.19	

Preparation of stock standard solution

A stock standard solution (100 µg ml^{-1}) and (1.0 × 10^{-3} mol l^{-1}) of OXB were prepared by dissolving 10 and 39 mg of pure drug in 10 ml of ethanol in a 100 ml volumetric flask and completed to 100 ml with bidistilled water. This solution was stable for at least 7.0 days when kept in the refrigerator. Serial dilution with the same solvent was performed to obtain the appropriate concentration range

Reagents

All reagents and solvents used were of analytical-reagent grade.

Bromocresol purple (BCP) and bromophenol blue (BPB) (BDH Chemicals LTD, Poole, England) and used without further purification. Stock solutions (1.0×10^{-3} mol l^{-1}) of reagents were prepared by dissolving the appropriate weight of each dye in 5.0 ml of ethanol (96%) and diluted to 100 ml in a calibrated flask with bidistilled water. These solutions were kept in the refrigerator.

Series of buffer solutions of KCl–HCl (pH=1.0-2.2), NaOAc–HCl (pH=1.99-4.92), NaOAc–AcOH (pH=3.4-5.6) and potassium hydrogen phthalate–HCl (pH=2.0-7.0) were prepared by following the standard methods [17]. The pH of each solution was adjusted to an appropriate value by the addition of 0.2 mol l^{-1} hydrochloric acid or sodium hydroxide with the help of the pH meter. Freshly prepared solutions were always employed. Chloroform and methylene chloride (BDH), anhydrous sodium sulfate (Prolabo), ethanol (BDH).

General recommended procedure

Accurately measured aliquots (0.1–1.2 ml) the of OXB (100 µg ml^{-1}) were transferred into 10 ml measuring flasks. A volume of 2.0 ml of 1.0×10^{-3} mol l^{-1} BCP or BPB was added. Then, 2.0 ml acetate buffers at the optimum pH 3.0 and 3.5 using BCP and BPB, respectively and the volume was completed to 10 ml with distilled water. The ion-pairs were extracted with 10 ml of dichloromethane by shaking for 2.0 min, and then the combined dichloromethane extracts were dried over anhydrous sodium sulfate. The absorbance of the yellow colored ion-pair complexes were measured at 410 and 416 nm, using BCP and BPB, respectively, within 20 min of extraction against the reagent blank similarly prepared in the same manner except an addition of drugs. All measurements were made at room temperature (25±2 °C). In both the methods, a standard curve was prepared by plotting the increasing absorbance values versus concentrations of drug. A linear equation for the standard curve was calculated by linear regression.

Procedure for commercial tablets

Twenty tablets were finely pulverized and weighed. A weighed quantity of the powdered tablets equivalent to 10 mg of OXB was transferred into a 100 ml volumetric flask, about 20 ml of ethanol was added and the flask was sonicated for 30 min. The volume was completed to the mark with bidistilled water, mixed well and filtered. Aliquots containing the drug in the final concentration ranges 1.0-8.0 and 1.0–12 µg ml^{-1} for BCP and BPB methods, respectively were analyzed as described under "Construction of the Calibration Graph". The concentration of the drug was determined either from the calibration curve or using the corresponding regression equation.

Stoichiometric relationship

The stoichiometric ratios of the ion-pairs formed between OXB and the reagents were determined by applying the continuous variation [18] and the molar ratio [19] methods at the optimum wavelengths. In continuous variation method, equimolar solutions were employed: a 1.0 x 10^{-3} mol l^{-1} standard solution of drug and 1.0 x 10^{-3} mol l^{-1} solution of dye was used. A series of solutions was prepared in which the total volume of the studied drugs and the dye was kept at 2.0 ml. The drug and reagent were mixed in various complementary proportions (0.2:1.8, 0.4:1.6, 0.6:1.4, 0.8:1.2, 1.0:1.0, 1.2:0.8, 1.4:0.6, 1.6:0.4, 1.8:0.2) and completed to volume in a 10 ml calibrated flask with the appropriate solvent for extraction following the above mentioned procedure. In the molar ratio method, the concentration of OXB was kept constant 1.0 ml of (1.0 x10^{-3} mol l^{-1}) while that of dyes (1.0 x10^{-3} mol l^{-1}) is regularly varied (0.2–2.4 ml). The absorbance of the prepared solutions measured at optimum condition and at the optimum wavelength for each complex.

RESULTS AND DISCUSSION

Absorption spectra

The proposed methods are based on the reactivity of tertiary amine group of OXB with two acid dyes (BCP and BPB). The nitrogenous drugs are present in positively charged protonated forms and anionic dyes of sulphonpthalein group present mainly in anionic form at a pH ≥ 3.0. So when treated with an acid dye at pH range (2.8-5.0) of acidic buffer solutions, a yellow ion-pair complex which is extracted with organic solvent is formed. The absorption spectra of the yellow ion-pair complexes of OXB-BCP and BPB), which were formed between OXB and BCP or BPB reagents and show maximum absorbance's at 41o and 416 nm, respectively against the blank solution.

Optimization of the reaction conditions

A number of preliminary experiments established optimum conditions necessary for rapid and quantitative formation of colored ion-paired complexes achieve the maximum stability and sensitivity. Optimum condition was fixed by varying one parameter at a time while keeping other parameter constant and observing its effect on the absorbance.

Effects of buffer type and pH

It was observed that the effective extraction of the complex depends on the type of the buffer used and its pH. The effect of pH was

studied by extracting the colored complexes in the presence of various buffers such as KCl–HCl (pH 1.0-2.2), NaOAc–HCl (pH 1.99-4.92) and NaOAc–AcOH (pH 3.6-5.6). It is evident that the maximum color intensity and maximum absorbance were found in NaOAc_HCl buffer. It is evident that the absorbance of the ion pair complex was maximal at pH 3.5 and 3.0 for BCP and BPB methods, respectively (fig. 2). Buffer volume was determined by applying the same experiment and variation the volume regularly (0.5-4.0 ml). The higher absorbance value and reproducible results were obtained by using 2.0 ml of buffer solutions.

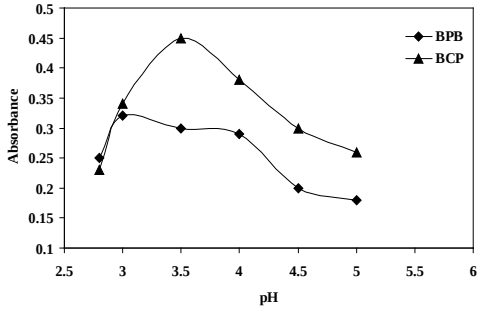


Fig. 2: Effect of pH of buffer solution on ion pair complex formation between (8.0 µg ml^{-1}) OXB and (1.0 x 10^{-3} mol l^{-1}) BCP and BPB reagents

Effect of reagent concentration

The OXB concentration was kept constant, while the concentrations of BCP or BPB was varied from 0.5–4.0 ml of 1.0×10^{-3} mol l^{-1}. The results showed that the absorbance of the extracted ion-pairs increased by increasing the BCP or BPB concentrations till 2.0 ml. After this volume, the absorbance remains constant by increasing the volume of the reagents (fig. 3). So an excess of reagents has no effect on the determination of the drug.

Choice of extracting solvent

Different organic solvents as dichloromethane, carbon tetrachloride, chloroform and ether were tested as extractive solvents for the proposed method. Dichloromethane was preferred to other solvents for its selective and obtained the highest absorbance with dichloromethane. It was also observed that only one extraction with total volume 10 ml solvent was adequate to achieve a quantitative recovery of the complexes, maximum absorbance intensity and considerably lower extraction ability for the reagent blank and the shortest time to reach the equilibrium between both phases.

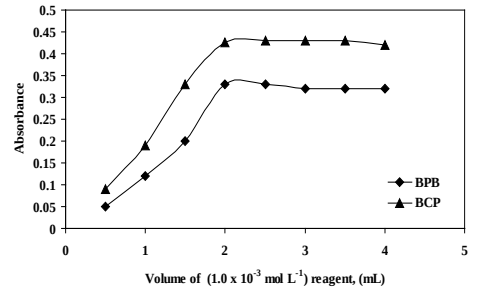


Fig. 3: Effect of volume of (1.0 ×10^{-3} mol l^{-1}) BCP and BPB reagent on the ion pair complex formation with (8.0 µg ml^{-1}) OXB

Effect of shaking time and temperature

The optimum shaking time was investigated by shaking from 0.5-5.0 min. Maximum and constant absorbance value were obtained when extracted after 1.5 min shaking. Therefore, shaking time of 2.0 min was maintained throughout the experiment. The effect of temperature on colored complexes was studied by measuring the absorbance values over the temperature range 20-35 °C. It was found that the absorbance of the colored ion pair complex was constantly up to 30 °C. At higher temperatures, the drug concentration was found to increase due to the volatile nature of the dichloromethane. Therefore, the temperature chosen was room temperature (25±2 °C) as the best temperature for micro-determination of OXB in pure and pharmaceutical formulations. The absorbance of both complexes remains stable for at least 12 h at room temperature.

Composition of the ion-pair complexes

The molar ratio between OXB and BCP or BPB in the ion-pair complexes was determined by Job's method of continuous variation. Job's method of continuous variation of equimolar solutions was employed: a 1.0 × 10^{-3} mol l^{-1} standard solution of drug base and 1.0 × 10^{-3} mol l^{-1} solution of BCP or BPB were used. A series solution was prepared in which the total volume of drug and reagent was kept at 2.0 ml in the total volume of 10 ml of the aqueous layer. The absorbance of extracting an ion-pair in each instance was measured at the optimum wavelength and plotted against the mole fraction of the drug. The results indicate that the molar ratio of (drug: dye) is (1:1) complex was formed through the electrostatic attraction between the positive charged OXB^{+}ions and negatively charged dye, D^{-} ions (fig. 4). The extraction equilibrium can be represented as follows:

$$OXB^{+}_{(aq)} + D^{-}_{(aq)} \longleftrightarrow OXB^{+}D^{-}_{(aq)} \longleftrightarrow OXB^{+}D^{-}_{(org)}$$

Where OXB^{+}andD^{-} represent the protonated drug and the anion of the dye (BCP^{-} or BPB^{-}), respectively, and the subscript (aq) and (org) refer to the aqueous and organic phases, respectively.

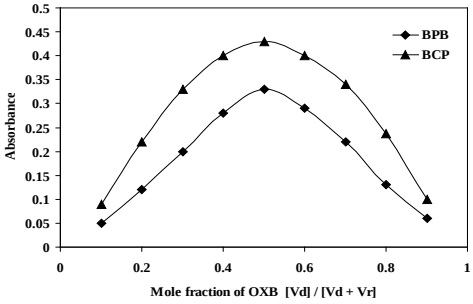


Fig. 4: Job's method of continuous variation graph for the reaction of OXB with the studied dyes, [drug] = [dye] = (1.0×10^{-3} mol l^{-1})

Method of validation

Linearity

At described experimental conditions for OXB determination, standard calibration curves with reagents were constructed by plotting absorbance vs. concentration of OXB. The statistical parameters were given in the regression equations calculated from the calibration graphs A = aC+b, where A is the absorbance and C is concentration in µg ml^{-1}. The linearity of calibration graphs was proved by the high values of the correlation coefficient (*r*) and the small values of the *y*-intercepts of the regression equations. The apparent molar absorptivity of the resulting colored ion-pair complexes and relative standard deviation of response factors for each proposed spectrophotometric method were also calculated and recorded in table 2. The molar absorptivity of BCP>BPB ion-pair complexes.

Sensitivity

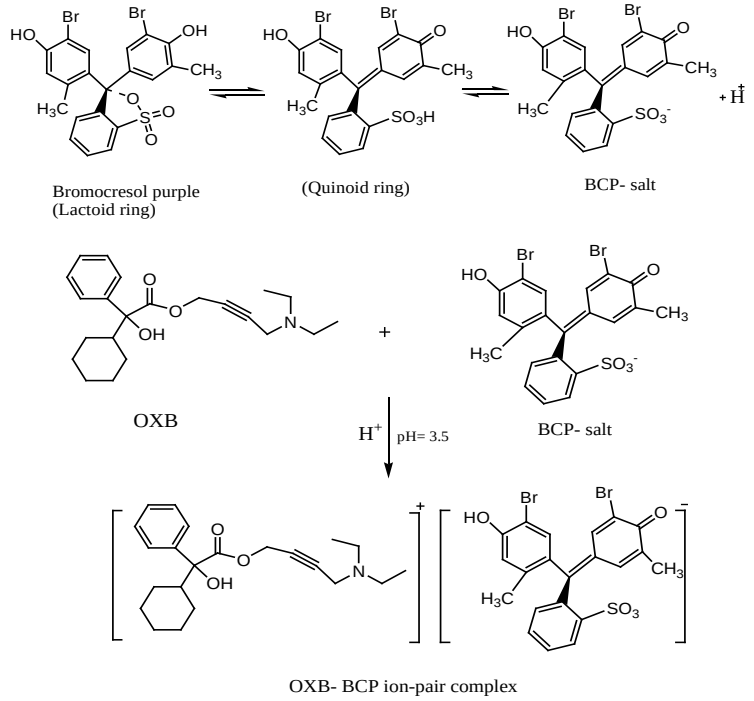
The limits of detection (LOD) and quantitation (LOQ) for the proposed methods were calculated using the following equation [20, 21]:

$$LOD = 3s/k \text{ and } LOQ = 10\,s/k$$

Where *s* the standard deviation of the response of the blank or the standard deviation of intercepts of regression lines and *k* is the sensitivity, namely the slope of the calibration graph. In accordance

with the formula, the limit of detection was found to be 0.21 and 0.19 µg mL^{-1} for BCP and BPB methods, respectively.

According to this equation, the limit of quantitation was found to be 0.70 and 0.63 µg ml^{-1} for BCP and BPB methods, respectively.



Scheme 1: Proposed reaction mechanism for the ion pair complex formation between OXB and BCP

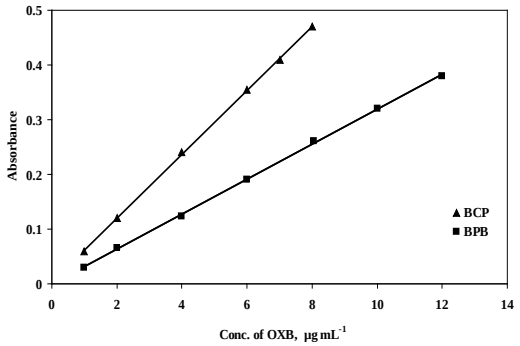


Fig. 4: Calibration curves for determination of OXB (1.0–8.0 µg ml^{-1}) using BCP and (1.0–12 µg ml^{-1}) using BPB

Table 2: Statistical analysis of calibration graphs and analytical data in the determination of OXB using the proposed methods

Parameters	BCP	BPB
Wavelengths λ_{max} (nm)	410	416
Beer's law limits (µg ml^{-1})	1.0-8.0	1.0-12
Molar absorptivity ε, (l mol^{-1} cm^{-1}) x 10^4	2.34	1.22
Sandell·s sensitivity (ng cm^{-2})	16.84	32.41
Regression equation [a]		
Intercept (*a*)	0.0033	-0.0009
Standard deviation of intercept (*Sa*)	0.0064	0.0027
Slope (b)	0.0584	0.032
Standard deviation of slope (*Sb)*	0.001	0.002
Correlation coefficient (*r*)	0.9999	0.9994
LOD (µg ml^{-1})[b]	0.18	0.24
LOQ (µg ml^{-1})[b]	0.60	0.80
mean±SD	99.63±0.57	99.76±0.88
RSD%	0.57	0.88
RE%	0.60	0.92
t-test [c]	0.67	0.19
F-test[c]	2.03	4.84

[a]A = a+bC, where C is the concentration in µg mL^{-1}, A is the absorbance units, [b]LOD, limit of detection; LOQ, limit of quantification; ε,molar absorptivity, [c]The theoretical values of t and F at P= 0.05 are 2.571 and 5.05, respectively.

Accuracy and precision

Specificity of ion-pair reaction and selective determination of OXB which was the basic nitrogenous compound with acid dyes could be possible. Percentage relative standard deviation (RSD %) as precision and percentage relative error (RE %) as accuracy of the suggested methods was calculated. Precision was carried out by six determinations at three different concentrations in these spectrophotometric methods. The percentage relative error calculated using the following equation:

RE % = [(founded–added)/added] x 100

The inter-day and intra-day precision and accuracy results are shown in (table 3). These results of accuracy and precision show that the proposed methods have good repeatability and reproducibility.

Table 3: Intra-day and Inter-day precision and accuracy data for OXB obtained by the proposed methods

Method	Added (µg ml^{-1})	Intra-day				Inter-day			
		Recovery %	Precision RSD % [a]	Accuracy RE %	Confidence limit [b]	Recovery %	Precision RSD % [a]	Accuracy RE %	Confidence limit [b]
BCP	2.0	99.10	0.43	-0.90	1.982± 0.009	100.50	0.50	-0.50	2.01± 0.011
	6.0	99.60	0.72	-0.40	5.976± 0.045	99.50	0.80	-0.50	5.97± 0.05
	8.0	100.50	1.30	0.50	8.04± 0.11	100.70	1.60	0.70	8.056±0.135
BPB	2.0	99.70	0.65	-0.30	1.994± 0.014	99.00	0.48	-1.0	1.98± 0.01
	6.0	101.00	0.90	1.0	6.06± 0.057	99.20	0.75	-0.80	5.952± 0.047
	10	99.00	1.50	-1.0	9.90± 0.156	101.00	1.25	1.0	10.10± 0.133

[a]Mean of six determination, RSD%, percentage relative standard deviation; RE%, percentage relative error, [b]Confidence limit at 95% confidence level and five degrees of freedom (t = 2.571).

Table 4: Method robustness and ruggedness expressed as intermediate precision (RSD %) for OXB-BCP ion pair complex

OXB taken (µg mL^{-1})	Robustness			Ruggedness	
	Parameters altered			Inter-analysts	Inter-instruments
	Volume of BCP [a]	Volume of buffer [b]	Reaction time [c]	(RSD/%) (N=3)	(RSD/%) (N=3)
2.0	1.48	1.10	1.0	1.35	1.20
4.0	1.70	1.20	1.40	1.10	1.90
8.0	1.90	1.80	1.60	2.0	1.65

[a]The volumes of BCP dye used were 2.0±0.2 ml, [b]The volumes of buffer used were 2.0±0.2 ml, [c]The reaction times were 2.0±0.5 min.

Table 5: Application of the standard addition technique for the determination of OXB in dosage forms using the proposed methods

Sample	Taken (µg ml^{-1})	BCP		BPB		Official method [1]
		Added (µg ml^{-1})	Recovery[a] (%)	Added (µg ml^{-1})	Recovery[a] (%)	
Ditronin® tablets	1.0	-	99.40	-	99.10	
		1.0	99.10	2.0	100.50	
		3.0	100.70	5.0	99.00	
		5.0	99.80	7.0	99.20	
		7.0	98.90	9.0	99.10	
mean±SD			99.58± 0.712		99.38± 0.63	99.83±0.75
R. S. D%			0.715		0.63	0.75
V			0.507		0.397	0.56
S. E			0.32		0.282	0.31
t-value[b]			0.54		1.03	
F-value[b]			1.10		1.41	
Uripan® tablets	1.0	-	99.10	-	99.30	
		1.0	100.20	2.0	99.80	
		3.0	99.80	5.0	98.60	
		5.0	98.90	7.0	100.40	
		7.0	100.60	9.0	99.00	
mean±SD			99.72± 0.719		99.36± 0.796	99.26±0.67
R. S. D%			0.72		0.791	0.665
V			0.517		0.633	0.445
S. E			0.32		0.356	0.274
t-value[b]			1.05		0.215	
F-value[b]			1.16		1.42	

[a]Average of six determinations, [b]The theoretical values of t and F are 2.571 and 5.05, respectively at confidence limit at 95% confidence level and five degrees of freedom (p= 0.05).

Robustness and ruggedness

For the evaluation of the method robustness, some parameters were interchanged; pH, dye concentration, wavelength range, and shaking time. The capacity remains unaffected by small deliberate variations. Method ruggedness was expressed as RSD% of the same procedure applied by two analysts and in two different instruments on different days. The results showed no statistical differences between different analysts and instruments, suggesting that the developed methods were robust and rugged (table 4).

Effects of interference

To assess the usefulness of the method, the effect of diluents, excipients and additives which often accompany OXB in its formulations (nasal spray and drops) was studied. The results indicated that there is no interference from excipients and additives, indicating a high selectivity for determining OXB in its formulations.

Applications to pharmaceutical formulations

The proposed methods have been successfully applied to the determination of OXB in dosage forms (Ditronin® tablets and Uripan® tablets). The results in table 4 showed that the excipients in the dosage forms do not interfere. A statistical comparison of the results for determination of OXB from the same batch of material by the proposed and official method [1] is shown in table 4. The results agreed well with the label claim and also are in agreement with the results obtained by the reference method. Statistical analysis of the results using Student's t-test for accuracy and F-test for precision revealed no significant difference between the proposed and reference method at the 95 % confidence level with respect to accuracy and precision [21] (table 5). To ascertain the accuracy and validity of the proposed methods, recovery experiment was performed *via* standard addition technique. With a fixed and known amount of OXB in dosage form (pre-analyzed), pure drug was added at different concentrations and the total was found by the proposed methods. The results of this study presented in table 4 indicated that the commonly added excipients did not interfere with the assay.

CONCLUSION

This paper describes the application of extractive ion–pair complexation reaction with acid dyes for the quantification of OXB in pure form and pharmaceutical formulations. Compared with the existing visible spectrophotometric methods, the proposed methods have the advantages of relatively simple, rapid, cost-effective, free from auxiliary reagents and more sensitive for determining OXB in pure form and pharmaceutical formulations. Moreover, the proposed methods are free from tedious experimental steps such as heating unlike the previously reported spectrophotometric methods cited earlier. The most attractive feature of these methods is its relative freedom from interference by the usual diluents and excipients in amounts far in excess of their normal occurrence in pharmaceutical formulations. The statistical parameters and the recovery data reveal high precision and accuracy of the methods besides being robust and rugged. Therefore, the validated method could be useful for routine quality control assay of the studied drug in pure form and pharmaceutical formulations.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests with the company name used in the paper.

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