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Extractive Spectrophotometric Determination of Tolterodine Tartrate in Pure and Pharmaceutical Forms

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Abstract. Simple, rapid, sensitive and extractive methods were developed for the estimation of Tolterodine tartrate (TOL) both in pure and in pharmaceutical formulations. These methods are based on the formation of 1:1 ion-pair complexes of the drug with three acid dyes namely Bromophenol blue (BPB), Bromocresol green (BCG) and Bromocresol purple (BCP) dyes. The ion paired complexes were extracted at optimized pH values with chloroform and the absorbance values were determined at wavelength (λ_{max}) of 416, 419 and 404 nm for (BPB), (BCG) and (BCP) respectively. The proposed method was applied to the determination of the drug in pharmaceutical formulations and the results demonstrated that the method is equally accurate, precise and reproducible as the official methods. The validity of method was established by recovery studies with satisfactory results.

Keywords: Tolterodine tartrate, Spectrophotometry, ion-pair complexation.

1. Introduction

Tolterodine tartarate (TOL), (R)-2-[3-[bis(1-methylethyl)-amino]1-phenylpropyl]-4-methylphenol [R-(R*,R*)]- 2,3dihydroxybutanedioate (1:1) (salt), Fig. (1) is a white, crystalline powder. The pKa value is 9.87 and the solubility in water is 12 mg/mL.

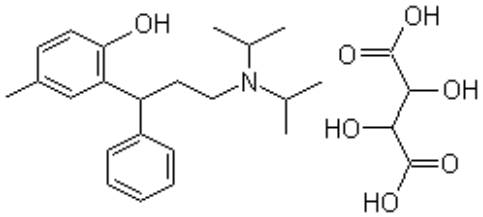

Fig. 1: Chemical structure of Tolterodine tartarate.

TOL is a muscarinic receptor antagonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency [1].

Several methods have been reported for the analysis of TOL, these include gas chromatography – mass spectrometry (GC-MS) [2], capillary liquid chromatography-tandem mass spectrometry [3], [4] and liquid chromatography – mass spectrometry (LC-MS) [5]. These methods rely on powerful MS detectors to reach limits of quantitation in the pg/mL levels which is needed in the analysis of biological samples in pharmacokinetic studies.

Enatiomeric separation has also been achieved by liquid chromatography with quantitation limits reaching 0.05 μg/mL[6], [7].

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With the objective of catering to the needs of such routine analysis, a group of direct and derivative UV spectrophotometric methods have been reported for the analysis of TOL in bulk raw material form as well as in pharmaceutical dosage forms [8]-[11] and HPLC [12]. This level may be adequate for the assay of bulk API but it is not suitable when attempting to evaluate the drug release where the dose of the drug (2-4 mg) is dissolved in 900 mLs of dissolution medium and where the characterization of the early points of the release profile (~ 10% of the complete release corresponding to ~2 μg/mL) is needed.

A recent work was done for spectrophotometric determination of (TOL) based on charge transfer complexation reaction [9].

We propose the development of simple spectrophotometric method for the determination of Tolterodine tartrate in pure and pharmaceutical preparations as an alternative procedure for the more costly and demanding HPLC.

In the present investigation, we report that the development of accurate, reproducible, and adequately sensitive four extractive spectrophotometric methods based on the formation of chloroform soluble ion-pair complexes between Tolterodine tartrate with anionic dye namely bromophenol blue (BPB), bromocresol green (BCG) and bromocresol purple (BCP). The proposed methods are simple and suitable for routine determination of Tolterodine tartrate. Also these methods provide economic procedures, less time consuming, and more sensitivity compared with other reported spectrophotometric methods.

2. Materials and Method

2.1. Apparatus

A double-beam optical system **SpectroScan 80D UV-VIS spectrophotometer** with spectral bandwidth of **2 nm**, wavelength accuracy **± 0.3 nm** (with automatic wavelength correction), wavelength range (**190 nm-1100 nm**), wavelength reproducibility **± 0.2 nm** and a pair of **1-cm** matched quartz cells was used to measure absorbance of the resulting solution.

2.2. Reagents and chemicals

All chemicals used were of analytical reagent grade and the solvents were spectroscopic grade. Double distilled water was used wherever required.

(BPB) ,(BCG) and (BCP) were used without further purification (BDH Chemicals Ltd., Poole, England). Reagent grade Chloroform was used as extracting solvent.

Tolterodine tartarate in (2 mg) drug formulations was used as DETROL and DETRUCITOL products.

2.3. Preparation of solutions

(TOL) standard solution was prepared by dissolving 0.025 g of the drug in 100 mL water. BPB, BCG and BCP solutions were prepared by dissolving 25 mg of these dyes in a very small volume of water and then made up to 100 ml in a calibrated flask.

The Buffer solutions were prepared from standard 0.2 M HCl and 0.2 M KCl to prepare appropriate different pH solutions.

2.4. Proposed methods

Aliquots of (0.2–2.0 mL) of the standard drug solutions (250 mgL^{-1}) were transferred to 10mL measuring flasks and 3.0 mL of KCl buffer of pH 3.0, 3.4 and 3.2 were added, then 3.0 mL of each of the dye solution were added and shacked . The mixture was then extracted twice with 5.0mL chloroform by shaking for 2.0 min, then allowed to stand for clear separation of the two phases and the chloroform layer was passed through anhydrous sodium sulphate. The absorbance of the yellow colored complexes were measured at 416, 419 and 402 nm for BPB, BCG and BCP respectively, against corresponding reagent blank similarly prepared. All measurements were made at room temperature (25±2 ◦C).

2.5. Assay procedure for drug formulations

An amount of finely ground tablet or capsules equivalent to 2.0 mg of TOL was accurately weighed into a 100-ml volumetric flask, the flask was sonicated for about 20 minutes using 70 mL KCl buffer solution as

mentioned above, then the volume was made up to the mark by the same solution. The content was kept aside for 5 min, and filtered using 0.45 µm GHP filter paper. Then a suitable aliquot was used for the assay as described under General analytical procedure for the proposed method or using HPLC method [13].

3. Results and Discussion

3.1. Optimization conditions

Tolterodine tartrate shows no absorption band in the visible region. The nitrogenous drugs are present in positively charged protonated forms and anionic dyes of sulphonpthalein group present mainly in anionic form at pH≥3. So when treated with an acid dye at pH 3.0, 3.4 and 3.2 of potassiumchloride buffer using BPB, BCG and BCP respectively, a yellow ion-pair complex which is extracted with chloroform is formed. The absorption spectra of the ion-pair complexes, which were formed between (TOL) and each of BPB, BCG and BCP were measured in the range 350–550 nm against the blank solution. The ion-pair complexes show maximum absorbance at 415, 412, 417 and 414 nm for BPB, BCG and BCP respectively.

The optimum reaction conditions for determination of the ion-pair complexes were established. Then linearity, accuracy, precision, sensitivity, and stability of proposed methods were described and these developed methods applied to pharmaceutical preparations as tablets and obtained results evaluated statistically.

3.2. Stoichiometry

Job's method of continuous variation of equimolar solutions was employed: a 1.0×10^{-3}M standard solution of drug base and 1.0×10^{-3}M solution of BPB, BCG and BCP respectively, were used.. A series of solutions was prepared in which the total volume of drug and reagent was kept at 10mL for BPB, BCG and BCP, respectively. The absorbance was measured at 416, 419, and 402 nm for BPB, BCG and BCP, respectively. The molar ratio of the reagents (drug:dye) in the ion-pair complexes was determined by the method continuous variations (Job's method). The results shown in (Fig. 2) indicate that 1:1 (drug:dye) ion-pair complexes are formed.

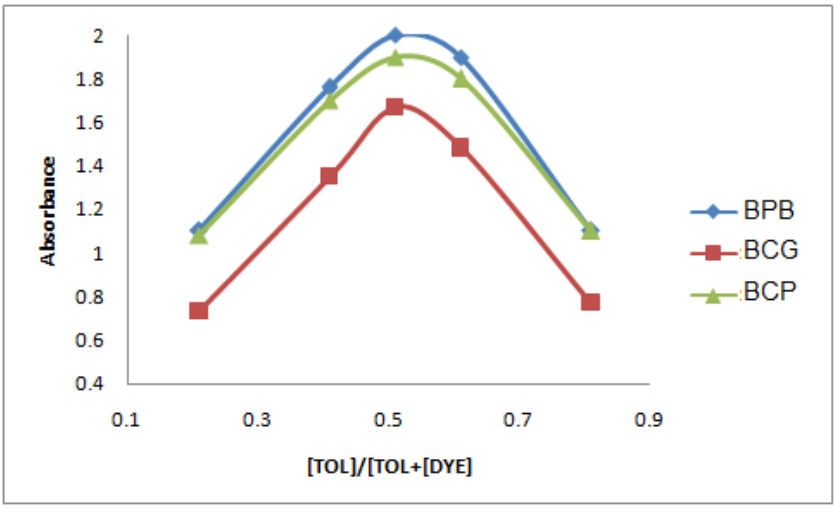

Fig. 2: Method of continuous variation for ion pair complexation

3.3. Method validation

The linear regression equations, standard deviation, slopes and intercepts, correlation coefficients, relative standard deviation of response factors, and linearity ranges were given in (Table 1) for each proposed spectrophotometric method. The molar absorptivities of each methods was calculated and these values showed that the molar absorptivity of BPB > BCP > BCG ion-pair complexes.

Specificity of ion-pair reaction and selective determination of TOL which was the basic nitrogenous compounds with sulphonphthalein dyes could be possible. Percentage relative standard deviation (R.S.D.%)

Statistical comparison of the accuracy and precision of the proposed methods with an HPLC method [13] was performed using Student's t-tests at a 95% confidence level. The t-values did not exceed the theoretical

values; there is no significant difference in accuracy or precision between the proposed and the official method as shown in Table 2.

Table 1: Statistical analysis of calibration graphs and analytical data in the determination of Tolterodine tartrate by BPB, BCG, and BCP methods (*n*=5)

Parameter	**Proposed method**		
	BPB	**BCG**	**BCP**
Wavelength (nm)	416	419	404
Slope	0.064	0.054	0.062
Intercept	0.175	0.114	0.163
R^2	0.994	0.995	0.994
Beer's law limits	2-22	1-19	1-18
LOD	0.288	0.231	0.242
R.S.D	1.24	0.867	0.972

Table 2: Comparison between the proposed method and the standard method

Drug	Proposed method		Standard method		t-value[a]
	Amount taken µg/ml	Recovery ± RSD%	Amount taken µg/ml	Recovery ± RSD%	
TOL + BPB	50	97% ± 8	50	98% ±2	0.85
TOL + BCG	50	98% ± 8	50	97% ±2	0.56
TOL + BCP	50	98% ± 8	50	97% ±2	0.56

[a] Tabulated student t-value at 95% confidence level and 6 degrees of freedom. (2.44)

4. Conclusion

The development of accurate, reproducible and sensitive three extractive spectrophotometric methods based on the formation of chloroform soluble ion-pair complexes between Tolterodine tartrate with anionic dye namely bromophenol blue (BPB), bromocresol green (BCG) and bromocresol purple (BCP). The proposed methods are simple and suitable for routine determination of Tolterodine tartrate in pure and pharmaceutical form.

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