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Sensitive Extraction-Free Spectrophotometric Methods for the Determination of Trandolapril Using Bromothymol Blue and Bromocresol Green

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ABSTRACT: *Two simple, rapid and sensitive spectrophotometric methods have been developed for the determination of trandolapril (TRP) in pure and capsules. The methods are based on the instant formation of highly yellow colored complex species between TRP and two chromogenic reagents; bromothymol blue (BTB) and bromocresol green (BCG) in acetone medium. The formed complexes were quantified spectrophotometrically at their absorption maxima at 401 and 408 for BTB and BCG, respectively. The reaction conditions were studied and optimized. Beer's law is obeyed over TRP concentration range of 2.0 – 26.0 µg/mL for BTB and 2.0 – 30.0 µg/mL for BCG. High molar absorptivity values of 18108 $M^{-1}cm^{-1}$ and 21314 $M^{-1}cm^{-1}$ were obtained with BTB and BCG, respectively. The developed methods showed high sensitivity with very low detection and quantification limits and were validated according to the ICH guidelines. The proposed methods were successfully applied to the analysis of trandolapril in pure form and capsules with good precision and accuracy and without interference from common additives. The results obtained by the proposed methods were compared with those of reference HPLC method. The mechanism of the reaction has also been discussed.*

Keywords: *trandolapril, bromothymol blue, bromocresol green, ion-pair complex, spectrophotometry.*

I. INTRODUCTION

Trandolapril is the ethyl ester prodrug of the angiotensin converting enzyme (ACE) inhibitor, trandolaprilat. Trandolapril is chemically described as (2S, 3aR, 7aS)-1-[(S)-N-[(S)-1-Carboxy-3phenylpropyl]alanyl] hexahydro-2-indolinecarboxylic acid, 1-ethyl ester. Its empirical formula is $C_{24}H_{34}N_2O_5$ and its structural formula is:

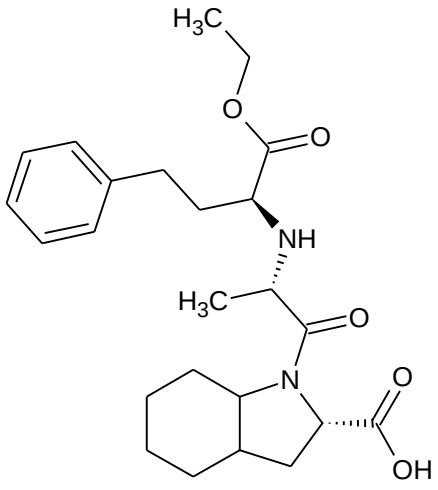


Fig. 1 Trandolapril structure

Trandolapril belongs to the category of Angiotensin converting enzyme inhibitors (ACE inhibitors) that prevent the conversion of angiotensin I to angiotensin II. ACE inhibitors are used in all grades of heart failure, and particularly indicated for hypertension in patients with type I diabetes with nephropathy [1].

Scientific literature reported only few chromatographic methods for the determination of trandolapril in its bulk, dosage forms and human plasma, such as high performance liquid chromatography [2-8], HPLC-MS [9], high performance thin layer chromatography [10,11] and spectrofluorimetry [12]. However, the chromatographic methods were found to have certain drawback, such as the requirement of expensive instrumentation and long analysis time. On the contrary, spectrophotometers are simple and affordable instruments that available almost in every laboratory. In addition, spectrophotometric methods are simple, sensitive and fast. There is only one spectrophotometric method [13] for the determination of trandolapril. Thus, it is still significant to develop new simple spectrophotometric methods for determination of trandolapril.

There seems to be no reports on spectrophotometric determination of trandolapril using ion pair reagents, which shows several advantages such as simplicity, high sensitivity, low detection limit, ease of use and less time consumption comparing with other analytical methods.

BTB and BDG have been used for the determination of many pharmaceutical compounds [14-27]. However, the reaction between TRP and these reagents has not been investigated so far. Therefore, the present study was devoted to explore BTB and BCG as complexation reagents in the development of simple, sensitive and extraction free spectrophotometric methods for the determination of TRP in capsules.

II. EXPERIMENTAL

2.1. Apparatus

Absorption spectra were recorded using UV-Visible spectrophotometer (Jasco V650, Japan) with scanning speed 1000 nm/min, and band width 1.0 nm equipped with 10 mm matched quartz cells.
Chromatographic analysis was performed on (Agilent, Germany) apparatus equipped with UV detector, autosampler, and column oven. Chromatographic separation was achieved on C18 column (5 µm, 100 mm × 4.6 mm).

2.2. Reagents and solutions

Trandolapril (Aurobindo pharma - India) stock standard solution of 1.0 mg/mL was prepared in acetone. This solution was stable for several weeks at refrigerator. BTB (Merck, Germany) standard solution of 1×10^{-3} M was prepared in chloroform. BCG (BDH Laboratories, England) standard solution of 1×10^{-3} M was prepared in chloroform. Reagent solutions were stable for one week at 4°C. Acetone and chloroform were purchased from Surechem Products LTD. (SCP), England. All other solvents were of analytical grade.Trandolapril capsules (Gopten®, Abbott) containing 2 mg were purchased from local medical store.

2.3. General procedure

Aliquots of trandolapril working standard solution (0.1 mg/mL) were transferred into series of 5 mL volumetric flasks that contain 1.0 mL of BTB solution (1×10^{-3} M) or BCG solution (1×10^{-3} M). Volume was completed to mark with acetone and mixed before the absorbance was measured at 401 nm and 408 nm, for BTB and BCG methods, respectively. Measurements were obtained against reagent blank prepared in the same manner.

2.4. Procedure for pharmaceutical samples

The contents of 10 capsules were pulverized carefully. An accurately weighed amount of the powder equivalent to 4 mg was transferred to a 10 mL volumetric flask and dissolved in acetone under ultrasound bath for 15min. The solution was then centrifuged at 5000 rpm for 10 min. 0.25 mL of the supernatant was taken and analyzed as described under BTB and BCG procedures.

2.5. Stoichiometric relationship

The composition ratios of the colored complexes were established using job's continuous variation method and molar ratio method. In job's method, equimolar solutions of trandolapril and BTB (2.5×10^{-4} M) and BCG (2.5×10^{-4} M) were used. Solutions were mixed in which the total moles of drug and reagents were kept at 5.0×10^{-7} moles with both BTB and BCG. Volumes were completed up to 5 mL with acetone and absorbance was measured at optimum wavelengths against a reagent blank prepared similarly. A plot of absorbance values against the mole fraction of reagent was then constructed. On the other hand, the molar ratio method was carried out. Increasing volumes of each reagent were added to a fixed volume of drug solution. The obtained absorbance values were then plotted against reagent molar ratio.

III. RESULTS AND DISCUSSION

3.1. Absorption spectra

The reaction of TRP with BTB and BCG yields intense yellow color species absorbing maximally at 401 and 408 nm, respectively. (Fig. 2). It is important to point out that the reagents blank has a pale yellow color and exhibits weak absorbance at the same maximum wavelengths of complexes. Even though, only a small contribution of the reagents was noted.

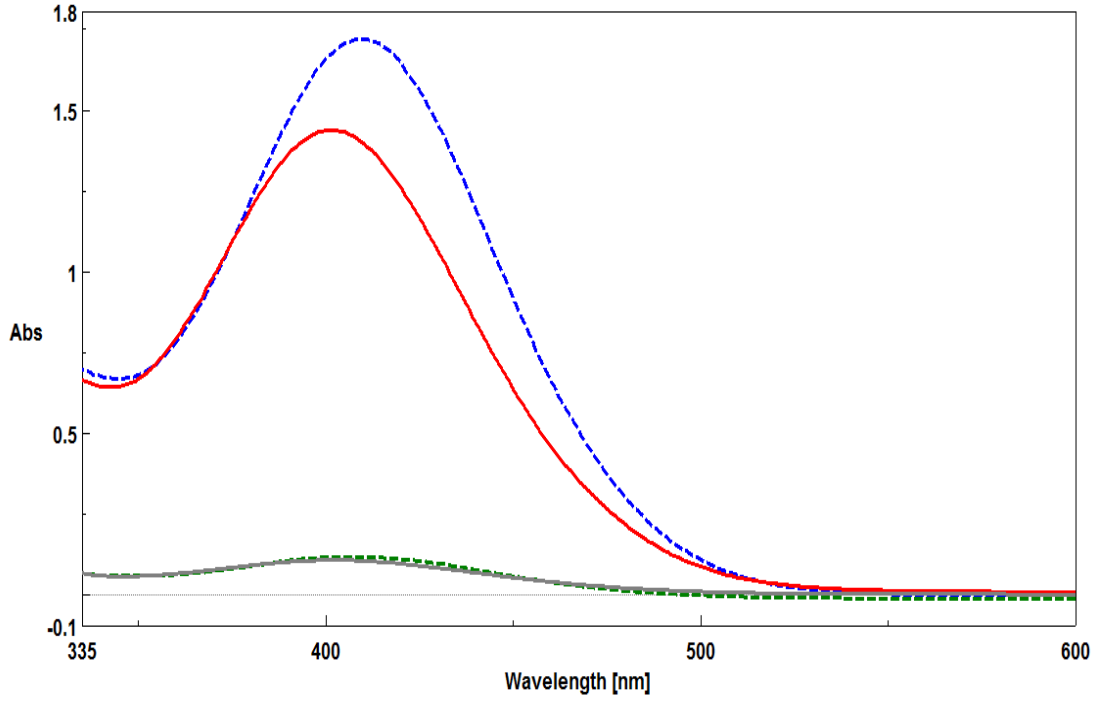


Fig. 2 Absorbance spectra of reaction products of TRP (32.5 µg/mL) with BTB (red) and BCG (blue) in acetone. BTB and BCG reagents blank against acetone are in grey and green color, respectively.

3.2. Mechanism of Reaction

The direct reaction of amino drugs with acidic sulphonephathalien dyes (such as BTB and BCG) in organic solvents was being explained by couples of models in the literature:

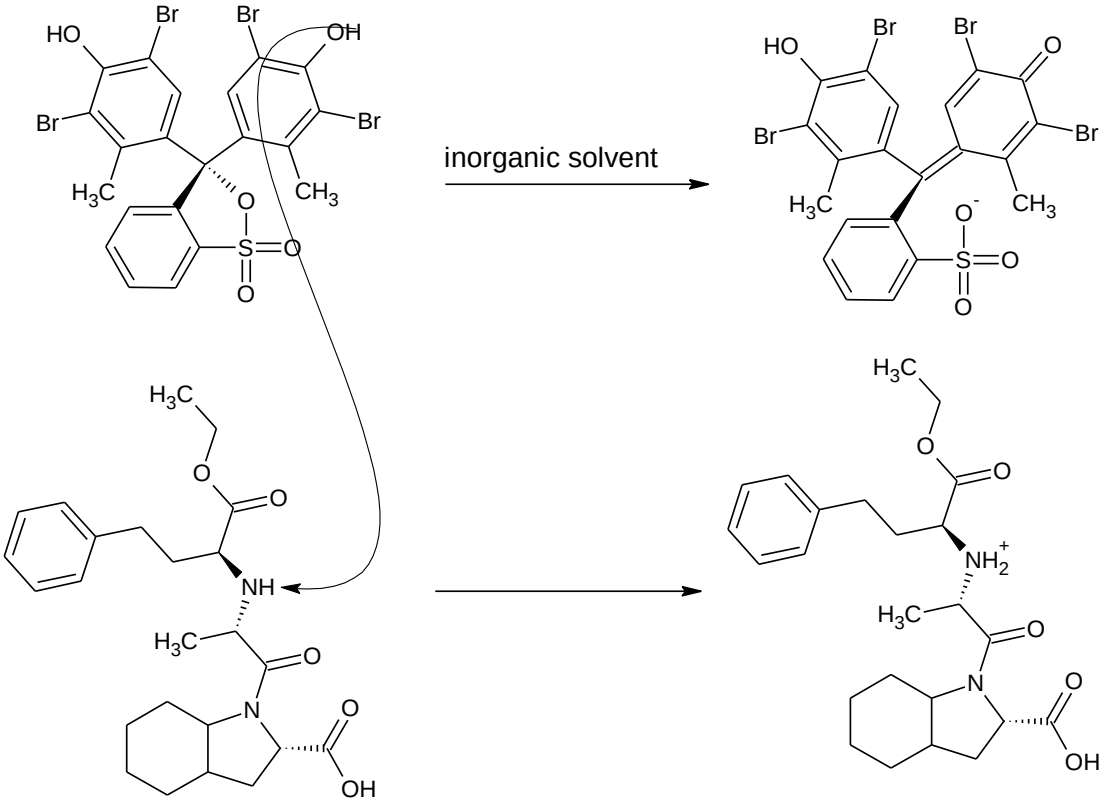
1- Ion pair formation [21-24]: implies that the color of BTB and BCG is due to opening of lactoid ring and formation of quinoid group. However, in an organic solvent (such as acetone, chloroform or dichloromethane), the amine group in drug abstracts the proton of the phenolic group of the dye,

resulting in an opening of the lactoid ring which is followed by formation of a complex between the protonated amine drug and the anion of the dye. A schematic proposal of the reaction pathway between TRP and BCG as an example of this mechanism is given in scheme 1.

2- Charge transfer reaction [25-27]: suggests that amino drug molecule acts as n-electron donor, whereas the sulphonephathalien dyes behave as strong electron acceptors due to the presence of the strong electron withdrawing sulphonic acid group conjugated with the aromatic ring system. Therefore, the drug reacts with electron acceptors to form charge transfer complexes or radical anions according to the polarity of the solvent used.

$$\underset{\text{Donor}}{D^{\cdot\cdot}} + \underset{\text{Acceptor}}{A} \rightarrow \underset{\text{DA complex}}{[D^{\cdot\cdot}\rightarrow A]} \rightarrow D^{\cdot+} + \underset{\text{radical anion}}{A^{\cdot-}}$$

However, these two illustrations are both accepted from scientific point of view, and both can be applied to explain our case in this work.



Scheme 1: Schematic illustration of reaction between trandolapril and BCG as an example for ion pair formation.

3.3. Optimum Reaction Conditions

3.3.1. Effect of Solvent

Effect of solvent polarity on the complex formation was investigated using fixed concentration of trandolapril. Diverse organic solvents with different polarities (methanol, ethanol, isopropanol, acetonitrile, acetone, dimethyl sulfoxide, dichloromethane and chloroform) were tested for each reagent. Interestingly, the polar aprotic solvents, acetone and acetonitrile, were found to be the best solvents for both reagents, while less sensitivity was achieved with dichloromethane and chloroform. All other examined solvents either were not

suitable for complex formation or showed high blank signal. Since acetone is cheaper than acetonitrile, it was selected for continuing the study.

3.3.2. Effect of reagents concentration

The optimal final reagents concentration that gives maximum absorbance was also investigated. As shown in Fig. 3, a volume of 1 mL of BTB solution (1×10^{-3} M), or BCG solution (1×10^{-3} M) was found to be sufficient for producing a maximum, steady and reproducible color intensity with low blank absorbance value. Using 1 ml of each reagent gives a final concentration of 2.0×10^{-4} M of BTB and BCG which preserves a molar ratio of more than 2.5 reagent/drug at the highest concentration of TRP determined in both methods. However, higher concentration of reagents did not affect the color intensity.

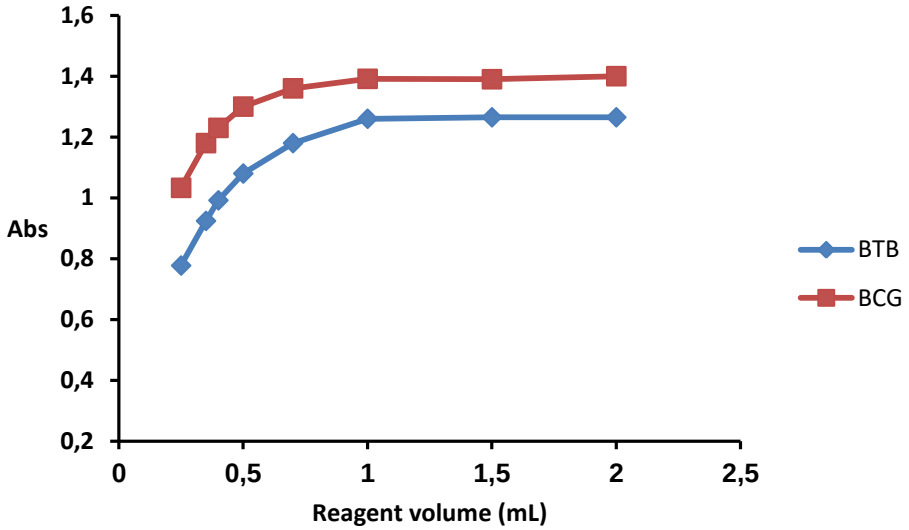


Fig. 3 Effect of the volume added of BTB and BCG on the complex formation with TRP (20 µg/mL).

3.3.3. Effect of Time

The effect of reaction time on trandolapril-reagent system was studied by following the color intensity at optimum wavelengths at ambient temperature (25 ± 2°C). It was observed that the complexes got stabilized immediately after mixing and absorbance value remained stable for at least 24 hours with BTB and BCG (Fig. 4).

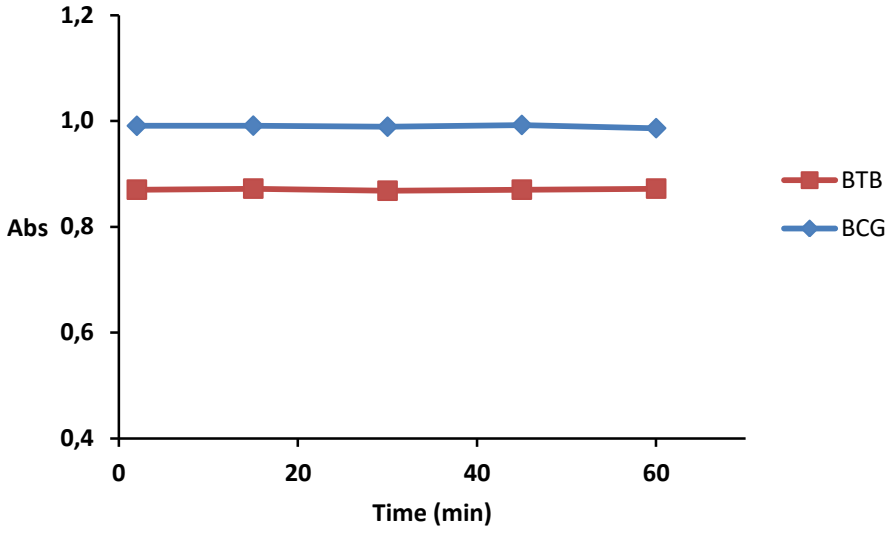


Fig. 4 Stability of TRP (20 µg/mL) reaction product with BTB and BCG over time.

Temperature effect has been also investigated at 30, 40, 50, and 60 °C. However, stable absorbance values were obtained over the studied range. Thus, the reaction was carried at laboratory temperature.

3.3.4. Stoichiometric Ratio

Under the described conditions, the stoichiometry ratio of the reactants was studied by Job's method of continuous variation, and molar ratio method. As shown in Figures 5 and 6, the stoichiometry of the reaction was found to be 1:1 ratio (reagent:drug). This finding supports that the interaction of TRP and the reagents used takes place at one site, which was the secondary amino group in TRP.

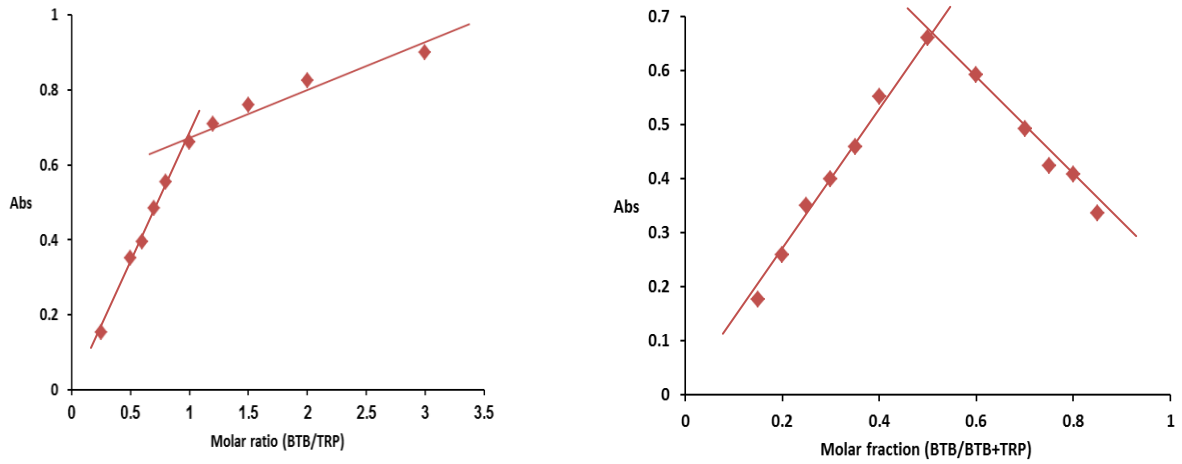


Fig. 5 Molar ratio and molar fraction plots for the stoichiometric relation between TRP and BTB.

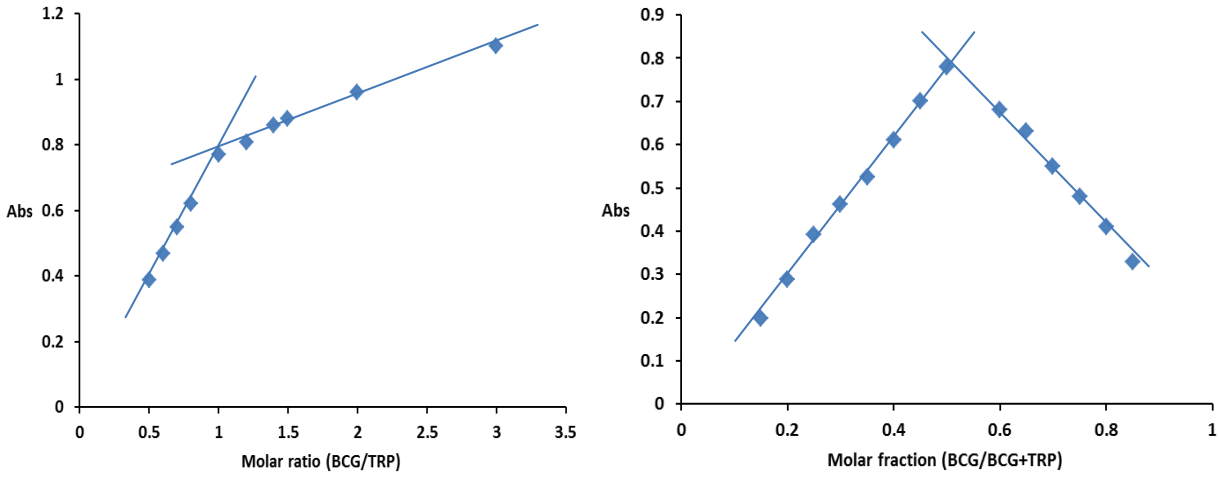


Fig. 6 Molar ratio and molar fraction plots for the stoichiometric relation between TRP and BCG.

3.4. Validation of the Proposed Method

3.4.1. Linearity

Under the optimal selected conditions, standard calibration curve was constructed by plotting absorbance intensity versus trandolapril concentration. The relationship between the absorbance and concentration was quite linear in the concentration ranges given in Table 1. The intercept, slope, correlation coefficient, molar absorptivities, detection limit (DL), and quantitation limit (QL) are summarized in Table 1. Values of DL and QL were calculated according to ICH Q2B [28] using the equations: LOQ = 10 σ/S, LOD = 3.3 σ/S. Where σ is the standard deviation of intercept of regression line and S is the slope of the calibration curve. Based on these equations, the detection limits were found to be as small as 0.230 µg/mL and 0.216 µg/mL using BTB and BCG, respectively. Whereas, the quantification limits were found to be 0.699 µg/mL and 0.654 µg/mL using BTB and BCG, respectively.

Table 1. Statistics and analytical parameters of trandolapril determination using BTB and BCG

Parameter	**BTB**	**BCG**
Wavelength λ_{max} (nm)	401	408
Linearity range (µg/mL)	2.0 – 26.0	2.0 – 30.0
Molar absorptivity ($M^{-1}cm^{-1}$)	18108	21314
Slope	0.0421	0.0495
Standard deviation in the slope	0.0002	0.00018
Intercept	0.0266	0.0019
Standard deviation in the intercept	0.0029	0.0032
Correlation coefficient	0.9999	0.9999
Limit of detection (µg/mL)	0.230	0.216
Limit of quantification (µg/mL)	0.699	0.654

3.4.2. Selectivity

The effects of some common excipients used in pharmaceutical preparations were studied by analyzing solutions contain suggested amounts of each excipient using BTB and BCG. Frequently encountered excipients or additives were studied such as lactose, microcrystalline cellulose, starch, polyvinylpyrrolidone k30, talc, and

magnesium stearate. None of the studied excipients has given a significant absorbance at the selected wavelengths and the maximum interference did not exceed 0.9%. So, the proposed methods were proven to be suitable for analysis of TRP in its dosage forms and application in quality control laboratories.

3.4.3. Precision

The repeatability of proposed method was estimated by measuring five replicate samples of each concentration of trandolapril prepared in one laboratory on the same day. Percent relative standard deviations (RSD%) were of acceptable values and did not exceed 2.85% and 3.19% for BTB and BCG method, respectively, which indicating good precision (Table 2).

3.4.4. Accuracy

The proposed methods were applied on the available commercial capsules (Gopten® 2mg). However, the methods accuracy were judged by (1) determining the average amount of trandolapril in pure form at several concentration levels, and using a significance test to compare it with actual amount μ [29]

$$t = \frac{|\bar{X} - \mu|}{SD}\sqrt{n}$$

As shown in table 2, the calculated *t*-value is less than tabulated *t*(0.05,4) value (2.78), and thus there is no significant differences between the taken and found concentration at 95% confidence level using BTB and BCG. (2) comparing the results obtained from the presently proposed methods, that have been applied on commercial capsules, with those obtained from a reference method such as HPLC [2]. The resulted values were statistically compared with each other (Table 3) using *t*- and *F*-tests. t_{exp} was calculated using the following equation [29]

$$t_{\text{exp}} = \frac{|\bar{X}_A - \bar{X}_B|}{\sqrt{(S_A^2/n_A) + (S_B^2/n_B)}}$$

Where $\bar{X}_A$ and $\bar{X}_B$ are TRP mean values in each pharmaceutical product using the proposed and reference methods, respectively. S and n are the standard deviation and the number of replicate trials conducted on samples, respectively. With respect to *t*- and *F*-tests, no significant differences were found between the calculated values of both the proposed and the reported methods at 95% confidence level.

IV. CONCLUSION

The present study describes formation of colored ion-pair complexes between trandolapril and two reagents: BTB and BCG. The reaction was favored in acetone for both reagents, and the complexes were instantly formed and found to be highly stable at room temperature. The proposed methods were found to be rapid, simple, accurate, sensitive, and time sparing with no long extraction step. The developed methods were fully validated, and therefore, can be applied for the routine analysis of trandolapril in quality control laboratories.

Table 2. Precision and accuracy for determination of trandolapril in pure form using BTB and BCG.

Using BTB						Using BCG					
Trandolapril (μg/mL)		SD (μg/mL)	RSD%	Recovery %	*t*-test[b]	Trandolapril (μg/mL)		SD (μg/mL)	RSD%	Recovery %	*t*-test[b]
Taken	Found[a]					Taken	Found[a]				
2.000	1.995 ± 0.070	0.057	2.85	99.76	0.19	2.000	1.973 ± 0.078	0.063	3.19	98.64	0.96
4.000	4.009 ± 0.118	0.095	2.37	100.23	0.21	4.000	4.026 ± 0.126	0.102	2.53	100.65	0.57
8.000	8.076 ± 0.195	0.157	1.94	100.95	1.08	8.000	7.985 ± 0.124	0.100	1.25	99.82	0.32
12.000	12.070 ± 0.126	0.102	0.84	100.59	1.55	13.000	13.092 ± 0.233	0.188	1.43	100.71	1.09
16.000	16.041 ± 0.167	0.135	0.84	100.26	0.68	17.000	17.137 ± 0.181	0.146	0.85	100.81	2.10
20.000	20.118 ± 0.164	0.132	0.65	100.59	1.99	20.000	20.042 ± 0.084	0.068	0.34	100.21	1.38
26.000	25.956 ± 0.211	0.170	0.65	99.83	0.58	26.000	26.057 ± 0.118	0.095	0.36	100.22	1.34
						30.000	29.928 ± 0.151	0.122	0.40	99.76	1.32

[a] Average of five determinations ± Confidence limit.
[b] The tabulated *t*- value at 95% confidence limit for 4 degrees of freedom (n =5) is 2.78.

Table 3. Precision and accuracy for determination of trandolapril in capsules using BTB and BCG.

Gopten® Capsule	Labeled amount of trandolapril	Trandolapril found (mg)/tablet ± SD[a] (Recovery%)[b]		*t*- and *F*- test[c]
		This work	HPLC [2]	
Using BTB	2.0 mg	2.046 ± 0.018 (102.30)	2.057 ± 0.012 (102.85)	1.05, 2.33
Using BCG	2.0 mg	2.062 ± 0.016 (103.10)	2.057 ± 0.012 (102.85)	0.46, 1.80

[a] Average and standard deviation of five determinations for the proposed method, and three determinations for the reference method
[b] Recoveries were calculated considering the labeled amount reported by the manufacturer.
[c] The tabulated *t* value at 95% confidence limit for 4 degrees of freedom (n =5) is 2.78 and the tabulated *F* value at 95% confidence limit for (4, 2) degrees of freedom for the proposed and reference methods, respectively, is 19.25.

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