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Application of Bromocresol Green and Bromothymol Blue for the Extractive Spectrophotometric Determination of Anti-hypertensive Drugs

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ABSTRACT

Simple, selective and highly sensitive spectrophotometric methods are proposed for the rapid and accurate determination of anti-hypertensive drugs namely telmisartan (TEL), propranolol (PRO), bisoprolol (BIS) and carvedilol (CRV) in tablets and biological fluids using bromocressol green (BCG) and bromothymol blue (BTB). The developed methods involve formation of stable yellow colored dichloromethane extractable ion-pair complexes of the amino derivative of four antihypertensive drugs such as TEL, PRO, BIS and CRV with two sulphonphthalein acid dyes, namely; BCG and BTB in acidic buffer. The effect of optimum conditions *via* pH on the ion-pair formation, reagent concentration, time and temperature and solvent was studied. The composition of the ion-pairs was found 1: 1 by Job's method. The established methods having high sensitivity and good selectivity could be applied to the determination of the studied drugs in pharmaceutical, urine and blood serum samples with satisfactory results. The results obtained are good agreement with experimental data. The reaction mechanism was also discussed.

INTRODUCTION

Telmisartan (TEL, Fig. 1a) is a highly selective angiotensin II type 1 receptor antagonist, widely used in the treatment of hypertension and heart failure (Yusuf *et al.*, 2008; Pitt and Konstam, 1998). It can selectively block the angiotensin type 1 receptor without affecting other receptor systems involved in cardiovascular regulation. Literature survey reveals several methods for determination of TEL individually in biological fluids and formulation like LC (Babu *et al.*, 2012; Gupta *et al.*, 2011; Rao *et al.*, 2011; Jyothi and Nalluri, 2012), HPLC (Seelam *et al.*, 2010; Zhang *et al.*, 2009), voltammetry (Alarfaj, 2013), spectrophotometry and derivative spectrophotometry (Ilango and Kumar, 2012; Qin *et al.*, 2009). Propranolol (PRO, Fig. 1b) is one of common *β*-blockers, which is widely used in clinical treatment of cardiovascular diseases such as angina, hypertension arrhythmia and so on (Sweetman, 2002). Its structure is shown in Fig.1. Several methods for the analytical determination of PRO in pharmaceutical formulations have been reported in the literature, by spectrophotometry (El-Didamony, 2010; Basavaiah *et al.*, 2004; Zahálka *et al.*, 2013), spectrofluorometry (Rekhi *et al.*, 1995) and HPLC (Šatínský *et al.*, 2013; Salman *et al.*, 2010; El-Sahart, 2003; Abdel-Hamid, 2000). Carvedilol (CRV, Fig. 1c) is a non-selective and β-adrenergic antagonist with no intrinsic sympatomimetic activity and is widely used to treat essential hypertension and angina pectoris (Anderson, 2002; Moffat *et al.*, 2004).

Carvedilol is also indicated for the treatment of mild to severe chronic heart failure, Left ventricular dysfunction following myocardial infarction in clinically stable patients and hypertension. β-blockers affect the heart and blood circulation (Flanagan, 1998). Analytical methods such as HPLC (Belal *et al.*, 2013; Machida *et al.*, 2003; Zarghi *et al.*, 2007), differential pulse voltammetry (Dogan and Ozkan, 2005) and spectrofuorimetry (Önal, 2011; Cardoso *et al.*, 2007) have been used for the determination of CRV.

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Bisoprolol (BIS, Fig. 1d) is a second-generation selective beta-blocker without intrinsic sympathetic activity. It is effective in reducing blood pressure (Dubach *et al.*, 2002). Several analytical methods have been studied for the determination of BIS in biological fluids.

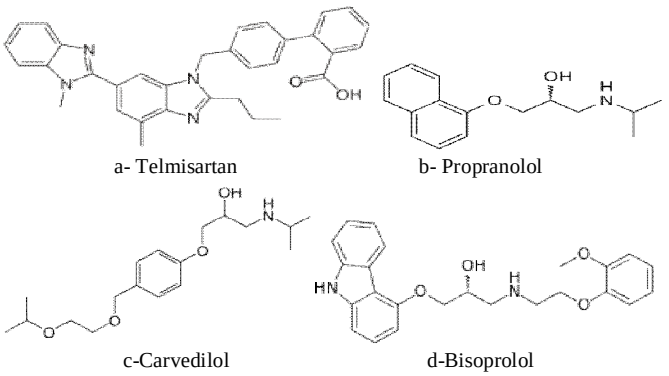

Fig. 1: Chemical structure of the studied drugs.

Among these methods, HPLC (Joshi *et al.*, 2010; Tutunji *et al.*, 2009; Shaikh *et al.*, 2008; Patel *et al.*, 2006), LC–MS-MS (Peste *et al.*, 2010; Ding *et al.*, 2007; Caudron *et al.*, 2004) have been utilized for the determination of BIS. Some methods have also been reported for the determination of BIS in pharmaceutical preparations. These articles include voltammetry (Goyal *et al.*, 2008) and spectrophotometry (Sahu and Patel, 2006; El-Didamony *et al.*, 2012; El-Didamony and Shehatab, 2014).

Hypertension is a major cause of morbidity and mortality worldwide. Anti–hypertensive medication is effective in reducing blood pressure. Therefore, this paper proposes two simple and sensitive extractive spectrophotometric methods for the determination of four antihypertensive drugs. The methods are based on ion-pair complexes of drugs with dyestuffs such as bromocresol green (BCG) and bromothymol blue (BTB) and subsequent extraction into dichloromethane under reaction conditions used.

MATERIALS AND METHODS

Apparatus

All the absorbance spectral measurements were made using Shimadzu spectrophotometer model: 1800-240V, made in Japan, spectral bandwidth 2.0 nm, with 10 mm matched quartz cells. The pH values of buffer solutions were measured using Jenway instrument pH-meter (combined electrode).

Reagents and Solutions

All of the chemicals used were of analytical or pharmaceutical grade and used without further purification. Double distilled de-ionized water was used to prepare all solutions.

i. Pharmaceutical grade of TEL, PRO, CRV and BIS certified to be 99.85% pure was obtained as gift were kindly supplied from Egyptian International Pharmaceutical Industries Company (EIPICo), Egypt. Stock solutions of pure TEL, PRO, CAR and BIS were prepared separately by dissolving accurately weighed 20 mg of each drug in a 100 ml calibrated flask. Working solutions of lower concentrations were freshly prepared by appropriate dilution with water.

ii. A 1.0×10^{-3} M of bromothymolol blue and bromcresol green (Aldrich Co., Ltd., Gillingham-Dorst, Germany), were prepared by dissolving accurate weight from each dye in 2 ml methanol then, add 20 ml distilled water and diluted to 100 ml in a calibrated flask with distilled water to the mark.

iii. Commercial dosage forms of TEL (Micardis 40mg, Boehringer Ingelheim Co., Germany), PRO (Inderal 10 mg, EIPICo 10^{th} of Ramadan, Egypt), CRV (Carvid 7.5mg Multi-apex, Badr-city, Cairo) and BIS (10 mg/tablet Concor, product of Amoun Pharmaceutical Co., El-Obour city, Egypt) .

iv. Series of buffer solutions of KCl-HCl (pH 1.0-2.2), NaOAc-HCl (1.99-4.92) and NaOAc-AcOH (3.4-5.6) pH were prepared by standard methods.

General Recommended Procedures

Ion-pair Method Using BCG

Into a series of separated funnels, accurately measured aliquots of TEL, PRO, CRV and BIS in the concentration range shown in (Table 1) were pitted out. A volume of 2.0 ml of 1.0×10^{-3}M BCG was added. Then, 2.0 ml of the buffer solution of pH = 2 for TEL or CRV and pH = 4 for PRO or BIS were added in each case and the volume was completed to 10 ml with distilled water. The contents were extracted with 10 ml dichloromethane and the organic layer was dried over anhydrous sodium sulfate. The absorbance of the yellow colored complexes was measured at 402 against a reagent blank prepared similarly. Calibration plots were drawn to calculate the amount of drugs in unknown analyte samples.

Ion-pair Method Using BTB

Suitable aliquots of the stock solution of TEL, PRO, CRV and BIS in the concentration range shown in (Table 1) were transferred into a series of 25 ml separated funnels. Then, 2.0 ml of the buffer solution of pH = 2 for TEL or CRV and pH 4 for PRO or BIS were added in each case and the volume was completed to 10 ml with distilled water. The contents were extracted with 10 ml dichloromethane and the organic layer was dried over anhydrous sodium sulfate. The absorbance of each solution was measured at 402 nm against a reagent blank after 5 min. A linear equation for each standard curve was calculated by linear regression.

Procedure for Tablets

Ten tablets of each commercial pharmaceutical formulation for TEL, PRO, CRV and BIS were crushed, powdered, weighed out and the average weight of one tablet was determined. An accurate weight equivalent to 10 mg each drug and

then active component was transferred into a 100 ml measuring flask. About 25 ml of distilled water was added and the mixture was shaken thoroughly for about 5 min. Then, it was diluted up to the mark with distilled water, mixed well and filtered using filter paper. An aliquot of this solution was diluted appropriately to obtain the working concentrations and analyzed as described under the standard procedure.

Procedures for Human Serum and Urine

The proposed methods were applied to the determination of the studied drugs in spiked urine and serum provided from several healthy volunteers. Spiked urine was 50-fold diluted with distilled water. A 10 ml of serum sample was deproteinzed by adding 5ml of acetonitrile in a centrifuge for 5 min at 1000 rpm. The supernatant was used to investigate recovery. Add an aliquot of standard aqueous solution of each drug to 1.0 ml of diluted urine or serum. Proceed as described above. A blank value was determined by treating drug-free urine and drug -free serum in the same way. The absolute recovery was determined for each drug by comparing the representative absorbance of the treated urine or serum samples with the absorbance of the standard drug at the same concentration.

RESULTS AND DISCISSION

Absorption Spectra

According to the experimental methods, the absorption spectra of PRO solution, the reagent solution (mixed solution of BCG and buffer solution), PRO-BCG complex (against dichloromethane) and dichloromethane were obtained in the wavelength range of 200~600 nm (Fig. 2).

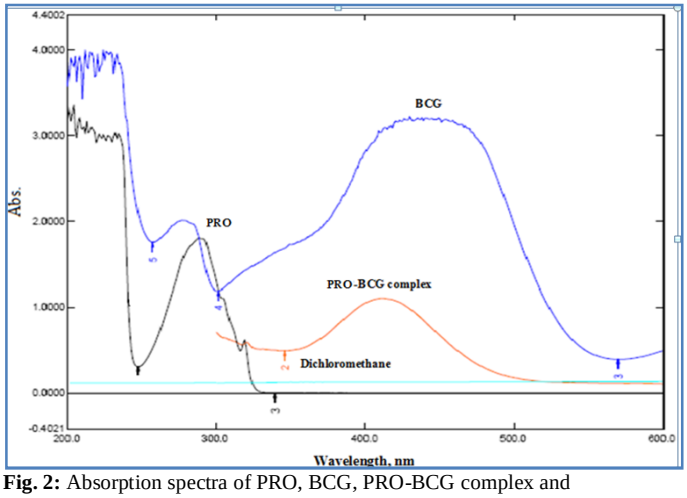

Fig. 2: Absorption spectra of PRO, BCG, PRO-BCG complex and dichloromethane.

The colorless blanks have practically negligible absorbance. The absorption maximum of the reagent solution was at 430 nm. When PRO was added into the reagent solution, BCG reacted with PRO to form ion-pair complex, the color of the solution changed and the maximum absorbance wavelength was 402 nm; compared with the maximum absorbance wavelength of the reagent solution, hypsochromic shift was 28 nm. So 402 nm were chose as the determination wavelength against dichloromethane.

Optimization of the Reaction Conditions

A number of preliminary experiments established optimum conditions necessary for rapid and quantitative formation of colored ion-paired complexes to 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.

Effect of Buffer Type and pH

The effect of pH was studied by extracting the colored complexes in the presence of KCl-HCl buffer (pH 1.0–2.2) and NaOAc–HCl (pH 1.99-4.92). It was evident that the maximum color intensity and constant absorbance were observed in KCl-HCl buffer of pH 2.0 for TEL or CRV with BCG or BTB and in NaOAc–HCl buffer of pH 4.0 for PRO or BIS with BCG or BTB. Buffer volume was determined by applying the same experiment and variation the volume regularly (0.5-4.0 ml). The higher absorbance value obtained at using 2.0 ml of buffer solutions.

Effect of Reagent Concentration

The effect of the amount of reagents on the intensity of the color development was examined by measuring the absorbance of the solutions containing a fixed concentration of the drugs and varied amounts of the respective reagent. It was found that 2.0 ml of 1.0×10^{-3}M BCG or BTB was sufficient for maximum absorbance. So any excess of reagents has no effect on the determination of the drugs.

Choice of Organic Solvents

Several organic solvents, such as chloroform, carbon tetrachloride, and ethyl acetate, in addition to dichloromethane were examined for their ability to extract the drug-dye ion-pairs. The latter was found to be the most suitable solvent in terms of extraction efficiency for both methods and considerably lower extraction ability for the reagent blank and shortest time to reach the equilibrium between both phases.

Shaking Time and Stability of the Ion-pair Complexes

Shaking time ranging from 0.5-4.0 min was tested to ascertain the extraction of the complex. Maximum and constant absorbance value was obtained when extracted after 2.0 min shaking. The stability of the ion-pair complexes formed between the studied drugs and BCG or BTB was evaluated. Although the ion-pairs were obtained instantaneously, constant absorbance readings were obtained after not less than 5.0 min of standing at room temperature (25±2 °C). Ion-pairs were stable for at least 24 h without any change in color intensity or in λ_{max}.

Composition of Ion-pair Complexes

Anionic dyes such as BCG or BTB forms ion-pair complex with the positively charged drugs. The drug–dye

stoichiometric ratios were established by Job's method of continuous variation (Job, 1928). In this method, 1.0×10^{-3} M solutions of drugs and reagents were mixed in varying volume ratios in such a way that the total volume of each mixture was the same.

The absorbance of each solution was measured and plotted against the mole fraction of the drug (Fig. 3). This procedure showed the formation of 1: 1 ion-pair. The suggested reaction pathway for the reaction product of PRO-BCG ion–pair complex formation for example, is given in Fig. 4. These complexes were probably formed via electrostatic interaction between the most basic center in the drug molecule (amino group) and the sulphonic acid group of the dye.

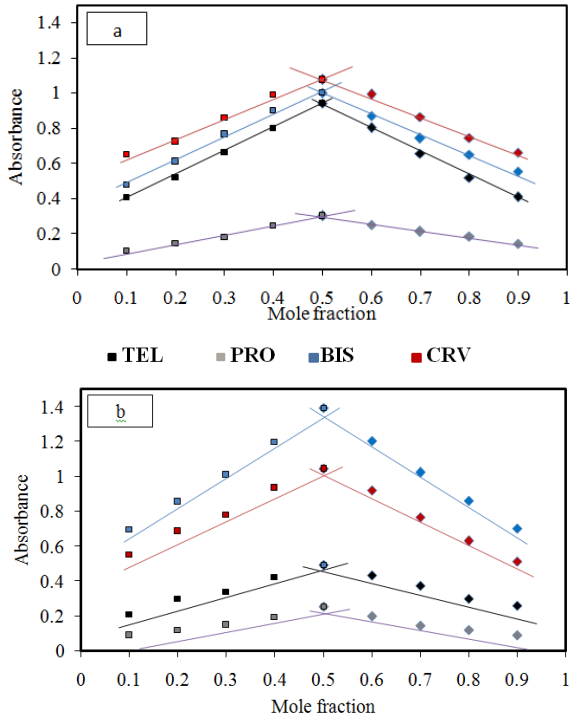

Fig. 3: Continuous variations method applied for (a) BCG and (b) BTB with each drugs.

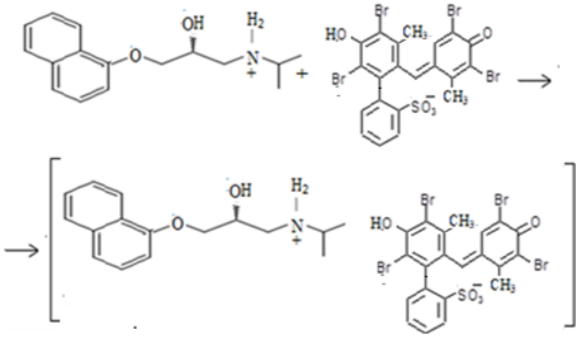

Fig. 4: Suggested mechanism of PRO-BCG ion-pair complex formation.

Calibration Curves

Under the described experimental conditions, calibration curves for proposed methods were constructed (Fig. 5). The regression parameters given in the regression equation calculated from the calibration graphs along with the standard deviations of the slope (S_b) and the intercept (S_a) are also given in Table 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, Sandell sensitivity, limits of detection and quantification of all the methods were also calculated (Miller and Miller, 2005) and recorded in Table 1. Only it could be concluded that best sensitivity was achieved with BCG.

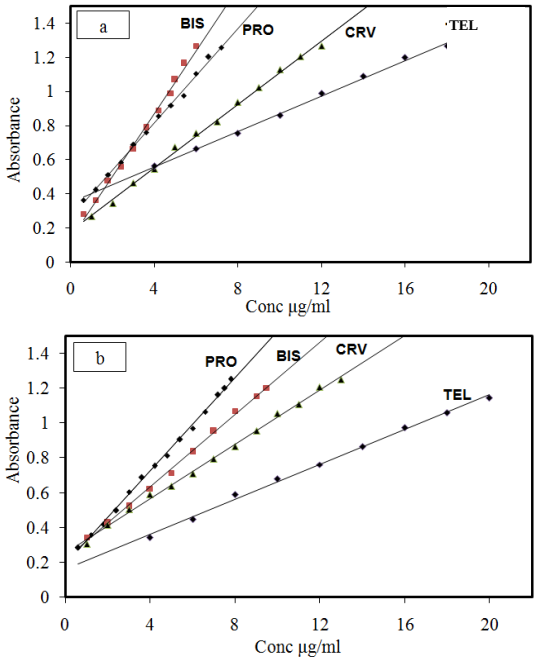

Fig. 5: Calibration curves of ion-pair complexes with: (a) BCG and (b) BTB.

Accuracy and Precision

In order to determine the accuracy and precision of the proposed methods, pure drug solutions at three different concentration levels (within the working range) were prepared and analyzed in seven replicates during the same day (intra-day precision) and on five consecutive days (inter-day precision) and the results are presented in Table 2, 3.

Precision and accuracy were based on the calculated relative standard deviation (RSD, %) and relative error (RE, %) of the found concentration compared to the theoretical one, respectively and indicate that the proposed method is highly accurate and reproducible repeatability and usefulness of the proposed methods in the routine analysis.

Analysis of Dosage Forms

To evaluate the validity and reproducibility of the methods, known amounts of the studied drugs were added to the previously analyzed pharmaceutical preparations and the mixtures were analyzed by the proposed methods. The percent recoveries are given in Table 4. Interference studies revealed that the common excipients and other additives such as lactose, starch, gelatin, talc and magnesium trisilicate, that are usually present in the tablet dosage forms did not interfere at their regularly added levels.

Table 1: Analytical parameters and optical characteristics for the studied drugs with BCG and BTB.

Parameters	BTB				BCG			
	TEL	PRO	CRV	BIS	TEL	PRO	CRV	BIS
pH	2	4	2	4	2	4	2	4
Beer's law limit, µg/ml	4.0 – 16	0.6-6.6	1.0 – 11	0.6 – 6.6	4.0 – 20	0.6-7.8	1.0 – 12	1.0 – 9
Molar absorptivity, l mol^{-1} cm^{-1}	3.96×10^4	2.75×10^4	5.86×10^4	6.66×10^4	3.01×10^4	2.41×10^4	5.02×10^4	6.58×10^4
Sandell's sensitivity, ng/cm^2	12.97	5.0	6.9	4.8	17.06	5.7	8.08	4.9
Correlation coefficient	0.9972	0.9995	0.9999	0.9955	0.9991	0.9992	0.9978	0.9966
LOD, µg/ml	0.8000	0.2529	0.4980	0.3056	0.9920	0.3773	0.6675	0.4269
LOQ, µg/ml	2.6640	0.8421	1.6583	1.0177	3.3035	1.2566	2.2229	1.4218
Linear regression equation	Y = a +bX, where Y is the absorbance, a is the intercept, b is the slope and X is the concentration in µg/ml.							
Intercept (a)	0.1788	0.0654	0.1432	0.2085	0.1504	0.1980	0.2714	0.1310
Slope (b)	0.0625	0.1977	0.1004	0.1636	0.0504	0.1325	0.0749	0.1171
$S_{y/x}$	10.14×10^{-3}	67.48×10^{-3}	4.90×10^{-3}	57.73×10^{-3}	14.14×10^{-3}	39.58×10^{-3}	8.03×10^{-3}	25.82×10^{-3}
S.D. of slope (S_b)	13.17×10^{-4}	60.56×10^{-3}	8.55×10^{-4}	16.13×10^{-3}	12.7×10^{-4}	6.55×10^{-3}	3.54×10^{-2}	5.4×10^{-3}
S.D. of intercept (S_a)	24.75×10^{-3}	45.49×10^{-4}	11.9×10^{-3}	10.64×10^{-4}	39.59×10^{-3}	58.06×10^{-3}	13.46×10^{-2}	58.03×10^{-3}

Table 2: Evaluation of intra-day accuracy and precision for the studied drugs with BCG and BTB.

Method	drug	Drug taken, µg/ml	Drug found, µg/ml	Recovery[a], %	RSD[b], %	RE[c], %
BCG	TEL	6	5.99	99.999	0.993	-0.001
		10	9.99	99.996	1.826	-0.004
		16	16.01	100.062	0.480	0.062
	PRO	2.4	2.39	99.999	1.459	- 0.001
		4.2	4.19	99.998	1.316	- 0.002
		5.4	5.39	99.997	0.937	- 0.185
	CRV	4	3.99	99.999	1.848	-0.001
		7	6.99	99.998	0.875	-0.002
		10	9.99	99.996	0.419	-0.004
	BIS	3.0	2.99	99.996	0.800	-0.333
		4.2	4.19	99.876	1.093	-0.238
		6.0	5.99	99.999	0.302	-0.166
BTB	TEL	8	7.99	99.999	1.805	-0.001
		12	11.99	99.999	0.812	-0.001
		16	15.99	99.993	0.804	-0.007
	PRO	3.6	3.59	99.999	0.657	- 0.001
		5.4	5.39	99.999	0.655	- 0.001
		6.6	6.59	99.999	0.823	- 0.001
	CRV	4	4.00	100.000	1.142	0.000
		8	7.99	99.999	1.159	-0.001
		11	10.99	99.999	0.827	-0.001
	BIS	3.0	2.99	99.996	1.278	-0.333
		5.0	4.99	99.997	1.177	-0.200
		7.0	6.99	99.999	0.538	-0.142

[a]Mean value of five determinations; [b]Relative standard deviation (%); [c]Relative error (%).

Table 3: Evaluation of inter-day accuracy and precision for the studied drugs with BCG and BTB.

Method	drug	Drug taken µg/ml	Drug found, µg/ml	Recovery[a], %	RSD[b], %	RE[c], %
BCG	TEL	6	5.99	99.999	1.580	-0.001
		10	9.99	99.999	1.415	-0.001
		16	16.02	100.150	0.389	0.150
	PRO	2.4	2.39	99.995	1.320	- 0.005
		4.2	4.19	99.996	1.158	- 0.004
		5.4	5.39	99.998	0.356	- 0.002
	CRV	4	3.99	99.999	1.141	-0.001
		7	6.98	99.857	0.899	-0.143
		10	9.99	99.998	0.649	-0.002
	BIS	3.0	2.99	99.796	0.892	-0.333
		4.2	4.19	99.888	0.673	-0.238
		6.0	5.99	99.998	0.453	-0.166
BTB	TEL	8	7.99	99.997	0.906	-0.125
		12	11.99	99.999	1.288	-0.036
		16	15.99	99.998	0.558	-0.002
	PRO	3.6	3.59	99.999	0.669	- 0.001
		5.4	5.39	99.999	1.050	- 0.001
		6.6	6.59	99.999	0.260	- 0.001
	CRV	4	3.99	99.997	0.917	-0.003
		8	7.99	99.999	1.036	-0.001
		11	10.99	99.999	0.488	-0.001
	BIS	3.0	2.99	99.999	1.845	-0.333
		5.0	4.99	99.989	0.742	-0.200
		7.0	6.99	99.998	0.804	-0.142

[a]Mean value of five determinations; [b]Relative standard deviation (%); [c]Relative error (%).

Table 4: Recovery of the studied drugs in pharmaceutical formulations with BCG and BTB.

Method	Drug	Drugformulation	Drug taken µg/ml	Drug found, µg/ml	Recovery[a], %	RSD[b], %	RE[c],%
BCG	TEL	Micardis 40mg/tablet	6	5.99	99.996	2.458	-0.004
			10	9.99	99.999	1.685	-0.001
			16	15.99	99.997	1.429	-0.003
	PRO	Inderal 40mg/tablet	2.4	2.39	99.999	1.446	- 0.001
			4.2	4.19	99.999	2.140	- 0.001
			5.4	5.39	99.998	1.748	- 0.002
	CRV	Carvid 7.5mg/tablet	4	3.99	99.994	1.492	-0.006
			7	6.99	99.998	1.881	-0.002
			10	9.99	99.966	0.627	-0.004
	BIS	Concor 10mg/tablet	3.0	2.99	99.996	1.889	-0.004
			4.2	4.19	99.990	0.901	-0.010
			6.0	5.99	99.998	1.345	-0.002
BTB	TEL	Micardis 40mg/tablet	8	7.99	99.999	2.530	-0.001
			12	11.99	99.996	2.592	-0.004
			16	15.99	99.999	2.425	-0.001
	PRO	Inderal 40mg/tablet	3.6	3.59	99.996	1.035	- 0.004
			5.4	5.39	99.852	1.843	- 0.148
			6.6	6.59	99.999	1.736	- 0.001
	CRV	Carvid 7.5mg/tablet	4	3.99	99.999	1.723	-0.001
			8	7.99	99.997	1.327	-0.003
			11	10.99	99.999	0.819	-0.001
	BIS	Concor 10mg/tablet	3.0	2.99	99.999	1.767	-0.001
			5.0	4.99	99.998	1.767	-0.002
			7.0	6.99	99.999	1.121	-0.001

[a]Mean value of five determinations; [b]Relative standard deviation (%); [c]Relative error (%).

Table 5: Recovery of the studied drugs in human serum with BCG and BTB.

Method	Drug	Drug taken µg/ml	Drug found, µg/ml	Recovery[a], %	RSD[b], %	RE[c], %
BCG	TEL	6	5.99	99.899	0.937	-0.101
		10	9.99	99.996	0.911	-0.004
		16	15.99	99.997	0.448	-0.003
	PRO	2.4	2.39	99.995	3.541	- 0.005
		4.2	4.18	99.666	1.914	-0.334
		5.4	5.40	100.005	2.461	0.005
	CRV	4	3.99	99.998	2.465	-0.002
		7	6.99	99.962	0.876	-0.038
		10	9.99	99.998	1.294	-0.002
	BIS	3	2.99	99.996	2.14	-0.004
		4.2	4.19	99.965	1.722	-0.035
		6	5.99	99.960	1.370	-0.040
BTB	TEL	8	7.99	99.984	2.944	-0.016
		12	11.99	99.996	1.116	-0.004
		16	15.99	99.991	0.613	-0.009
	PRO	3.6	3.59	99.800	1.879	- 0.200
		5.4	5.39	99.999	1.146	- 0.001
		6.6	6.59	99.889	2.613	-0.111
	CRV	4	3.99	99.755	3.560	-0.245
		8	7.99	99.966	1.787	-0.034
		11	11.00	100.004	1.549	0.004
	BIS	3	2.99	99.986	1.147	-0.014
		5	4.96	99.306	1.375	-0.694
		7	6.99	99.999	2.321	-0.001

[a]Mean value of five determinations; [b]Relative standard deviation (%); [c]Relative error (%).

Table 6: Recovery of the studied drugs in urine with BCG and BTB.

Method	Drug	Drug taken µg/ml	Drug found, µg/ml	Recovery[a], %	RSD[b], %	RE[c], %
		6	5.99	99.933	2.966	-0.067
	TEL	10	9.99	99.999	2.413	-0.001
		16	15.99	99.977	1.972	-0.023
		2.4	2.39	99.999	2.144	- 0.001
	PRO	4.2	4.19	99.800	1.799	- 0.200
BCG		5.4	5.39	99.999	1.363	- 0.001
		4	4.00	100.141	2.165	0.141
	CRV	7	6.99	99.999	1.151	-0.001
		10	9.99	99.966	0.764	-0.004
		3.0	2.99	99.996	1.549	-0.004
	BIS	4.2	4.19	99.999	1.152	-0.001
		6.0	5.99	99.999	1.896	-0.001
		8	8.00	100.034	1.280	-0.034
	TEL	12	11.98	99.916	0.991	-0.084
		16	15.99	99.997	2.093	-0.003
		3.6	3.60	100.055	1.951	0.055
	PRO	5.4	5.39	99.999	1.508	- 0.001
BTB		6.6	6.59	99.998	1.038	- 0.002
		4	3.99	99.961	1.881	-0.039
	CRV	8	7.99	99.875	2.067	-0.125
		11	10.99	99.999	0.547	-0.001
		3.0	2.99	99.999	1.388	-0.001
	BIS	5.0	4.99	99.998	2.523	-0.002
		7.0	6.99	99.965	1.501	-0.035

[a]Mean value of five determinations; [b]Relative standard deviation (%); [c]Relative error (%).

Analysis of Biological Fluids

The high sensitivity of the proposed methods, also allowed the in vitro determination of TEL, PRO, CRV and BIS in spiked human serum and urine samples. Thus the proposed methods are sufficient for routine estimation of the drugs in human serum and urine. The results obtained are satisfactorily accurate and precise (Tables 5, 6).

CONCLUSION

The proposed methods are simple, sensitive, accurate, and time saving, thereby encouraging their application in the analysis and quality control of these drugs in their pharmaceutical preparations and biological fluids. Statistical analysis proves that the methods are reproducible and selective for the routine analysis of the said drugs. The performance order of the proposed methods is BCG-drugs more sensitive than BTB-drugs.

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