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Spectrophotometric Determination of Oxidative Coupling Reactions of Nebivolol and Trandolapril

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Simple and sensitive spectrophotometric methods (M_1-M_3) by the application of oxidative coupling reactions for the assay of nebivolol and trandolapril have been described. Methods M_1, M_2 and M_3 involve the oxidative coupling reactions of nebivolol with (2,3- dimethoxystri-cychridin-10-one) (Brucine) (Bru) (Method M_1, λ_{max} 520 nm) or 3-methyl-2-benzothiozolinone hydrazone (MBTH) (Method M_2, λ_{max} 620 nm) in the presence of periodate. Method M_3 is based on the oxidative coupling of trandolapril with Brucine (Method M_3, λ_{max} 520 nm) in the presence of periodate. Regression analysis of Beer's law plot showed good correlation in the concentration range of 6-36, 2-12, 6-36 µg/mL for methods M_1, M_2 and M_3, respectively. The molar absorptivities lie within the range of 0.0728×10^5–0.2118×10^5 1 mol^{-1} cm^{-1} and reproducible with an accuracy of ± 1 %.

Key Words: Nebivolol, Trandolapril, 3-Methyl-2-benzothiazolinone hydrazone, 2,3-Dimethoxystri-cychridin-10-one, Sodium/meta-periodate, Spectrophtometry.

INTRODUCTION

Nebivolol (NEB)[1] is an antihypertensive for oral administration and chemically known as a-a[imino*bis*-methylene)]*bis*[6-fluoro-3,4-dihydro-2*H*-1- benzopyran-2-methanol]. It is a cardio selective β-blocker licensed for the treatment of hypertension. It has beneficial effects on left ventricular function in patients with hypertension and heart failure. Literature survey revealed that less attention was paid in developing visible spectrophotometric methods. The analytically important functional groups imino ol and aliphatic secondary amine in NEB[2-11] have not been exploited so far and hence there is a need to develop sensitive and flexible spectrophotometric method to exploit them. In trandolapril (TRA)[12,13], the aliphatic secondary amine is exploited. The oxidative coupling procedure involving the use of couplers MBTH[14-22] or brucine in the presence of an appropriate oxidant to form highly coloured species were explored for the assay of drugs possessing functional groups imino ol or secondary amine. This paper describes the applications of oxidative coupling reactions by using couplers (brucine or MBTH) in presence of periodate for the assay of NEB and TRA. The results for these methods are statistically validated.

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EXPERIMENTAL

An ELICO, UV-visible digital spectrophotometer with 1 cm matched quartz cells were used for the spectral and absorbance measurements. An ELlCO L1-120 digital pH meter was used for pH measurements.

All the chemicals and reagents used were of analytical grade and the solutions were freshly prepared with double distilled water.

Brucine solution (Loba, 0.2 %, 5.067 × 10^{-3} M): Prepared by dissolving 200 mg of brucine initially in minimum amount of 0.16 M H_2SO_4 and then made up to 100 mL with distilled water.

$NaIO_4$ solution (BDH, 0.2 %, 9.35 × 10^{-3} M): Prepared by dissolving 200 mg of sodium meta-periodate in 100 mL distilled water and standardized iodometrically.

H_2SO_4 solution (Qualigens, 1.2 M): Prepared by diluting 126 mL of concentrated H_2SO_4 to 100 mL distilled water initially, followed by diluting to 1000 mL with distilled water.

Standard drug solutions: A 1mg/mL stock solution of NEB was prepared by dissolving 100 mg of pure NEB in 100 mL aldehyde free methanol and this stock solution was diluted stepwise to obtain the working standard solutions of concentrations of 300 µg/mL for method M_1 and 100 µg/mL for method M_2.

A 1 mg/mL stock solution of TRA was prepared by dissolving 100 mg of pure drug (TRA) in 100mL 0.1 N HCl. This solution was diluted stepwise with distilled water to obtain the working standard solution of 300 µg/mL for method M_3.

Recommended procedures

For Pure form

Methods M_1 and M_3 for NEB and TRA: Aliquots of standard (0.5-2.5 mL, 300 µg/mL) solution, 3.0 mL (1.52 × 10^{-3} M) brucine, 1.5 mL of (1.402 × 10^{-3} M) $NaIO_4$ solution and 2.0 mL of (1.2 M) sulfuric acid were added successively into 25 mL calibrated tubes. The volume was brought up to 10 mL with distilled water and kept in boiling water bath for 15 min. The solutions were cooled to room temperature and kept in boiling water bath for 15 min. The solutions were cooled to room temperature and the volume was made up to the mark with distilled water. The absorbances were measured at 520 nm against a similar reagent blank with in 0.5 h. The amounts of drugs in the sample solution were computed from its calibration graph.

Method M_2 for NEB: Aliquots of standard NEB (0.5-3.0 mL, 100 µg/mL) solution, 1 mL each of (3.740 × 10^{-4} M) $NaIO_4$ and (1.396 × 10^{-1} M) acetic acid were delivered into a series of 25 mL calibrated tubes. The total volume in each tube was brought to 10 mL with distilled water and kept in boiling water bath for 40 min. After cooling to the room temperature, 1 mL (3.424 × 10^{-4} M) MBTH solution was added. After 20 min the solution in each tube was diluted to 25 mL with distilled water. The absorbance was measured at 620 nm against a reagent blank and the amount of drug was calculated from its calibration graph.

For pharmaceutical formulations: A weighed amount of tablet powder equivalent to 100 mg of NEB or TRA was extracted with chloroform (3 × 25 mL) and filtered. The filtrate was evaporated to dryness and the residue was dissolved in 100 mL distilled water to achieve a concentration of 1 mg/mL. The solution was further diluted stepwise to get working standard solutions and analyzed under procedures described for bulk samples. The UV methods were chosen as the reference methods for ascertaining the accuracy of the proposed methods.

RESULTS AND DISCUSSION

The optimum conditions for the colour development in each method were established by varying the parameters one at a time keeping the others fixed and observing the effect produced on the absorbance of the coloured species.

The optical characteristics such as Beer's law limits molar absorptivity and sandell's sensitivity for the methods are given in Table-1. Regression analysis using the method of least squares was made to evaluate the slope (b), intercept (a) and correlation coefficient (r) for each method are presented in Table-1. The accuracy of the methods was ascertained by comparing the results by proposed and reference methods (UV). Statistically by the t-tests and F-tests (Table-2). This comparison shows that there is no significant difference between the results of proposed methods and those of the reference ones. The additives and excipients that are

TABLE-1
OPTICAL, REGRESSION CHARACTERISTICS, PRECISION AND ACCURACY OF THE PROPOSED METHODS FOR NEB AND TRA

Parameter	MBTH	Bru-IO_4^-	
	NEB	NEB	TRA
λ_{max} (nm)	620	520	520
Beer's law limits (?g/mL)	2-12	6-36	6-36
Detection limits (?g/mL)	0.2979	0.9661	1.1415
Molar absorptivity (1 mol^{-1} cm^{-1})	0.2118×10^{5}	0.0728×10^{5}	0.0738×10^{4}
Sandell's sensitivity (µg cm^{-2}/0.001 absorbance unit)	0.0191	0.0696	0.0538
Optimum photometric range (µg/mL)	3-10	13-32	13-63
Regression equation (Y = a + bx)			
i) Slope (b)	0.0524	0.0181	0.0164
ii) Standard deviation on slope (S_b)	3.4993×10^{-5}	4.3730×10^{-5}	4.15×10^{-5}
iii) Intercept (a)	-6.000×10^{-4}	-3.73×10^{-3}	-0.041×10^{-3}
iv) Standard deviation on intercept (S_a)	5.2×10^{-3}	5.8486×10^{-2}	0.0555
v) Standard Error of Estimation (S_e)	2.9277×10^{-4}	1.0972×10^{-3}	1.042×10^{-3}
vi) Correlation co-efficient (r)	0.99999	0.99998	0.99999
vii) Relative standard deviation (%)*	0.4470	0.5364	0.5976
% Range of error (confidence limits)*			
i) 0.05 level	0.4692	05631	0.4547
ii) 0.01 level	0.7358	0.8830	0.6837
% Error in bulk samples**	0.3159	0.2145	-0.2564

*Average of six determinations; **Average of three determinations.

TABLE-2
DETERMINATION OF NEB IN PHARMACEUTICAL FORMULATIONS

Sample	Labeled amount (mg)	Amount found by proposed method*		Ref.	% Recovery by proposed method**	
		NEB			NEB	
		Bru-IO_4^-	MBTH		Bru-IO_4^-	MBTH
Tablet I	25	2.475±0.013 F=1.69 t=0.7873	2.48±0.019 F=3.61 t=1.332	2.47±0.010	98.12±0.17	99.82±0.35
Tablet II	5	4.99 ± 0.031 F=1.986 t= 0.642	5.01±0.026 F=1.397 t=2.165	4.98±0.022	99.87±0.63	100.22±0.52
Tablet III	5	4.985 ± 0.014 F=1.96 t= 0.7217	4.98±0.017 F=2.89 t=1.237	4.99±0.010	99.9±0.67	99.97±0.2
		TRA			TRA	
		Bru-IO_4^-			Bru-IO_4^-	
Tablet I	4	4.03±0.54 F=1.378 t=0.83		3.79±0.46	99.81±0.33	
Tablet II	2	1.98±0.012 F=1.440 t=1.732		1.99±0.01	99.81±0.37	
Tablet III	1	1.01±0.24 F=1.5956 t=0.1506		0.99±0.19	99.81±0.37	

Tablets from four different pharmaceutical companies. **Average ± standard deviation of six determinations, the t-and F-test values refer to comparison of the proposed method with the reference method. Theoretical values at 95 % confidence limit, F=5.05, t=2.57. ***Recovery of 10 mg added to the preanalysed pharmaceutical formulations (average of 3 determinations).

usually present in tablets do not interfere in the assay of proposed methods. Recovery experiments were performed by adding a fixed amount of the drug to the pre analyzed formulations. The percentage recovery was calculated in the usual way.

Interference studies: Nebivolol or trandolapril exists in its pharmaceutical formulations either singly or in combination with other active or inactive ingredients *e.g.*, methyl cellulose, lactose, *etc*. Results of the analysis of the former type reveal that the proposed methods are suitable for their analysis with virtually no interference of the usual additives. However in the latter type, the interference can also be minimized by separating it from NEB or TRA with appropriate solvent.

Conclusion

The proposed methods exploit the various functional groups in nebivolol or trandolapril. The aspect of spectrophotometric analysis is of major interest in analytical pharmacy since it offers distinct possibilities in the assay of a particular component in a complex dosage formulation. The methods are simple, rapid and have reasonable precision and accuracy.

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