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Simultaneous Determination of Bisoprolol Fumarate and Telmisartan by Area under Curve UV Spectrophotometric Method

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ABSTRACT

Area under curve UV spectrophotometric method has been developed for the simultaneous determination of Bisoprolol fumarate and Telmisartan using methanol as solvent. Both drugs follow Beer-Lambert's law over the concentration range of 1-5µg/ml for Bisoprolol fumarate and 8-40µg/ml for Telmisartan. Area selected between 219-229nm for determination of Bisoprolol fumarate and 287-304nm for determination of Telmisartan. The percentage recovery was found to be in range of 97% to 102% at three different levels. Validation of the proposed method was carried out for its accuracy, precision, and specificity according to ICH guidelines.

I INTRODUCTION

Bisoprolol fumarate is chemically 2- propanol,-[4-[[2-(1-methylethoxy) ethoxy] methyl] phenoxy]-3-[(1-methylethyl) amino]-, (±)-, (E)-2-butenedioate (Fig.1)[1-4]. Bisoprolol is a cardio-selective beta-blocker. It is used as an antihypertensive drug. Bisoprolol fumarate was used for the treatment of heart attacks and kidney problems.[4-11]

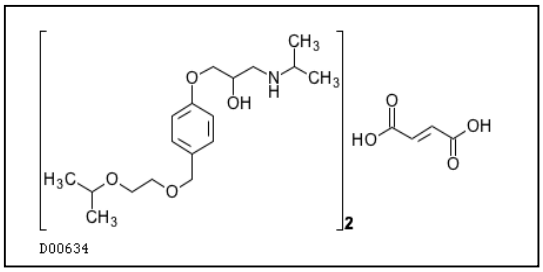

Figure No.1: Structure of Bisoprolol fumarate

Molecular Formula: $(C_{18}H_{31}NO_4)_2.C_4H_4O_4$

Molecular Weight: 767.0 g/mol

Telmisartan is 4'-{[4-methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl] methyl}-2-biphenyl-carboxylic acid (Fig.2).[1] Telmisartan is a drug used to treat hypertension by blocking the angiotensin II receptors. It is used as an antihypertensive and antidiabetic.[12]

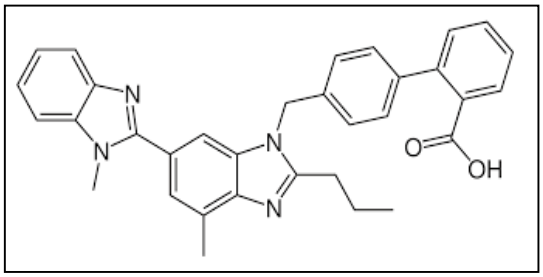

Figure No. 2: Structure of Telmisartan

Molecular Formula: $C_{33}H_{30}N_4O_2$.

Molecular Weight: 514 g/mol.

Literature surveys revealed that one UV spectrophotometry and RP-HPLC method have been reported for determination of Bisoprolol fumarate and Telmisartan are available in combined tablet dosage form. This combination used for treatment of hypertension. To our notice, so far no UV- spectrophotometric method using Area under Curve (AUC) has been reported for the determination of this combination. This successful attempt has been made to estimate the two drugs simultaneously by Area under Curve (AUC) method. This method describes simple, rapid, accurate, reproducible and economical methods for the simultaneous determination of Bisoprolol fumarate and Telmisartan in tablet formulations using Area under Curve (AUC) method.[6-10]

II. MATERIALS AND METHODS

Chemical and reagents

Bisoprolol fumarate and Telmisartan[bulk drug] used were of analytical reagent grade purchased from Unichem laboratories Ltd, Pharmaceutical Company in Goa Industrial Estate, Goa, India. Methanol (AR grade) was purchased from Research lab fine chem. Industries Mumbai and double distilled water was used throughout the analysis.

Instrumentation

A shimadzu1800 UV/VIS double beam spectrophotometer with 1cm matched quartz cells was used for all spectral measurements.

Selection of solvent

Solubility of both drugs was checked in water, methanol and chloroform. As compare to other solvent methanol shows good result. So; Methanol is used as mobile phase for this method.

Preparation of standard stock solution

Accurately weighed portion of Bisoprolol fumarate (10 mg) and Telmisartan (10 mg) was transferred separately in two 10 ml volumetric flasks, dissolved, sonicated and diluted to the mark with methanol to obtain standard solution (1000µg/ml) of both drug.

Selection of Wavelength

5µg/ml of Bisoprolol fumarate and 40 µg/ml Telmisartan was scanned in the UV-region i.e. 400 to 200 nm. In UV – Spectrophotometric method wavelength range 219-229nm and 287-304nm has been selected for determination of the Area under Curve [AUC] of Bisoprolol fumarate and Telmisartan respectively (Fig.3 and 4).

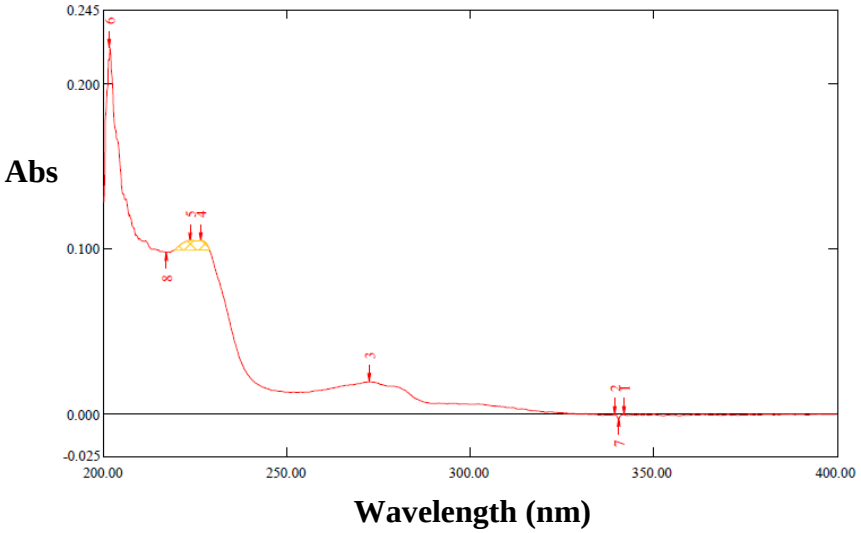

Figure No. 3: AUC spectrum of Bisoprolol fumarate in Methanol

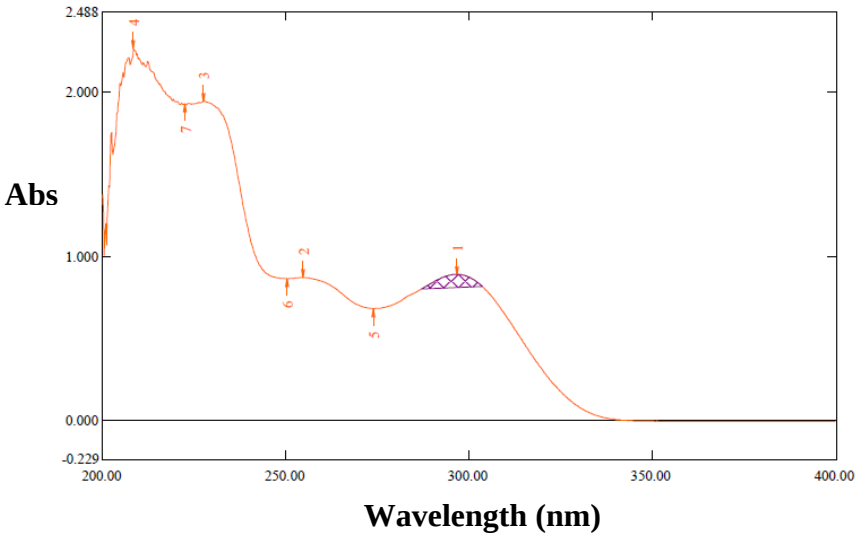

Figure No. 4: AUC spectrum of Telmisartan in Methanol

Area under Curve Method

The principle for AUC method is "the area under two points on the mixture spectra is directly proportional to the concentration of the component of interest." AUC method is applicable where there is no sharp peak or when broad spectra are obtained. It involves the calculation of integrated value of absorbance with respect to the wavelength between the two selected wavelengths $\lambda_1$and λ_2.The calibration curve was constructed by plotting concentration versus AUC.

Analysis of marketed formulation

Ten Tablets of brand name besicor T 5 were weighed and powdered. Average weight of content was determined. The powder equivalent to 5 mg of Bisoprolol fumarate or 40 mg of Telmisartan has been transferred to a 10 ml volumetric flask, dissolved and diluted up to the mark with methanol. Aliquots of 0.1 ml of this solution were diluted to 10 ml with methanol six times. AUC determined in the wavelength range between 219-229nm and 287-304nm for estimation of bisoprolol fumarate and Telmisartan respectively. The concentration of each drug was calculated using "Cramers and Matrix rule" equation.

Table No. 1: Analysis of marketed formulation

Sr. No.	Bisoprolol fumarate			Telmisartan		
	Area	Amount Recovered (µg/ml)	% Recovery	Area	Amount Recovered (µg/ml)	% Recovery
1	0.055	5	100	1.625	39.97	99.93
2	0.054	4.909	98.18	1.624	39.95	99.87
3	0.055	5	100	1.626	40	100
4	0.056	5.0909	101.81	1.623	39.92	99.81
5	0.054	4.909	98.181	1.628	40.05	100.12
6	0.056	5.090	101.81	1.622	39.9	99.75
Mean	0.055	5	100	1.624	39.96	99.91
%RSD	1.626	1.6262	1.626	0.1329	0.1351	0.1351

Validation of the Method [3 5 13 14]

1. Linearity

The linearity for Bisoprolol fumarate and Telmisartan were assessed by analysis of combined standard solution in the range of 1-5µg/ml and 8-40µg/ml respectively. Calibration curves were

plotted using concentration Vs area and the slop, intercept and correlation coefficient were calculated. The linearity values were shown in Table 2 (Fig. 5and 6).

Table No. 2: Linearity values of Bisoprolol fumarate and Telmisartan

Parameter	Bisoprolol fumarate	Telmisartan
Range	1-5µg/ml	8-40µg/ml
Slop	0.011	0.040
Intercept	-0.000	0.026
Correlation coefficient	0.999	0.998

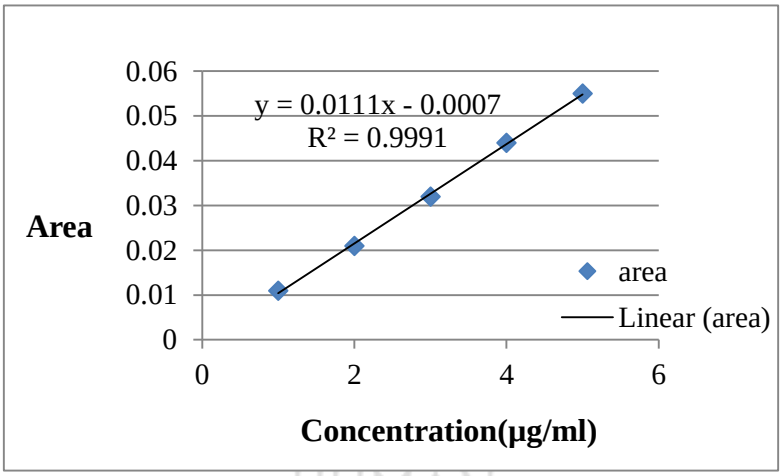

Figure No. 5: Linearity graph of Bisoprolol fumarate

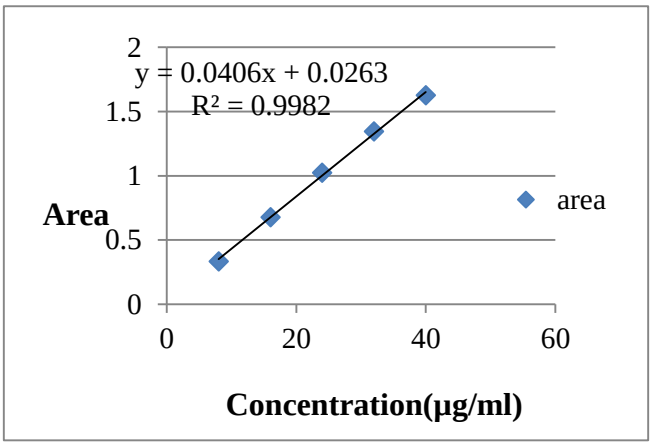

Figure No. 6: Linearity graph of Telmisartan

2. Precision

The precision of the method was evaluated by inter day and intraday variation studies. The % Relative Standard Deviation (%RSD) values were found to be less than 2, which indicate that the method is accurate and reproducible. The results for intra-day precision are shown in (Table No.3 and 4) and for inter-day precision are shown in (Table No. 5 and 6).

Table No. 3: Intraday precision study of Bisoprolol fumarate

Conc. µg/ml	Area			Mean Area	SD	%RSD
	Trial 1	Trial 2	Trial 3			
3	0.032	0.033	0.033	0.032	0.000577	1.767
4	0.044	0.044	0.043	0.043	0.000577	1.322
5	0.055	0.055	0.056	0.055	0.000577	1.043

Table No. 4: Intraday precision study of Telmisartan

Conc. µg/ml	Area			Mean Area	SD	%RSD
	Trial 1	Trial 2	Trial 3			
24	1.026	1.025	1.024	1.025	0.001	0.0975
32	1.345	1.344	1.347	1.345	0.00152	0.1135
40	1.626	1.625	1.625	1.625	0.000577	0.0355

Table No.5: Interday precision study of Bisoprolol fumarate

Conc. µg/ml	Area			Mean Area	SD	%RSD
	Trial 1	Trial 2	Trial 3			
3	0.036	0.035	0.035	0.035	0.000577	1.6340
4	0.046	0.047	0.047	0.046	0.000577	1.2371
5	0.053	0.054	0.053	0.053	0.000577	1.0825

Table No.6: Interday precision study of Telmisartan

Conc. µg/ml	Area			Mean Area	SD	%RSD
	Trial 1	Trial 2	Trial 3			
24	1.03	1.032	1.029	1.030	0.001528	0.1482
32	1.346	1.348	1.345	1.346	0.001528	0.1134
40	1.63	1.628	1.629	1.629	0.001	0.0613

3. Accuracy (Recovery studies)

The accuracy of the method was determined by calculating recoveries of Bisoprolol fumarate and Telmisartan using the standard addition method. Known amount of standard of Bisoprolol fumarate and Telmisartan (50%, 100%, and 150%) were added to the sample solutions of tablet dosage forms. The amounts of Bisoprolol fumarate and Telmisartan were estimated by equations in method. The results are shown in (Table No.7and8).

Table No. 7: Recovery studies of Bisoprolol fumarate

Level	Conc.(µg/ml)		Area	% Recovery	Mean%Recovery ±%RSD
	Sample	Std.			
50%	2	1	0.032	96.97	97.97± 1.758
			0.033	100	
			0.032	96.96	
100%	2	2	0.044	100	98.48± 1.332
			0.043	97.72	
			0.043	97.72	
150%	2	3	0.054	98.18	100± 1.818
			0.056	101.81	
			0.055	100	

Table No. 8: Recovery studies of Telmisartan

Level	Conc.(µg/ml)		Area	% Recovery	Mean%Recovery ±%RSD
	Sample	Std.			
50%	16	8	1	101.45	101.63± 0.782
			0.995	100.93	
			1.01	102.5	
100%	16	16	1.322	101.25	100.70± 0.689
			1.318	100.93	
			1.305	99.92	
150%	16	24	1.626	100	99.93± 0.062
			1.624	99.875	
			1.625	99.937	

4. Limit of detection (LOD) and Limit of Quantification (LOQ)

Limit of detection (LOD) and Limit of Quantification (LOQ) was calculated using the following formula.

- LOD = 3.3 (σ / S)

- LOQ = 10 (σ / S)

Where, S = slope of calibration curve**,** σ = standard deviation of the response.

The LOD and LOQ values of Bisoprolol fumarate and Telmisartan were shown in (Table No. 9).

Table No. 9: LOD & LOQ studies of Bisoprolol fumarate & Telmisartan.

Drugs	**LOD(µg/ml)**	**LOQ(µg/ml)**
Bisoprolol fumarate	0.1816	0.5504
Telmisartan	2.050	6.2133

III. RESULTS AND DISCUSSION

The UV visible spectroscopic method for the Bisoprolol fumarate and Telmisartan by Area under Curve was found to be simple, accurate, reproducible and economical. Two wavelength ranges were selected 219-229nm and 287-304nm for estimation of Bisoprolol fumarate and Telmisartan respectively. Linearity were found to be in range of 1-5 µg/ml (r^2=0.999) for Bisoprolol fumarate and 8-40 µg/ml (r^2=0.998) for Telmisartan. The %RSD for both drug obtained in intraday and interday precision study were less than 2, so method is precise. The % recoveries for Bisoprolol fumarate and Telmisartan obtained in the accuracy study were 97.97-100% and 99.93-101.63% respectively. The LOD for Bisoprolol fumarate and Telmisartan were found to be 0.1816µg/ml and 2.050µg/ml respectively while LOQ for Bisoprolol fumarate and Telmisartan were found to be 0.5504µg/ml and 6.2133µg/ml respectively. The % assay result was found to be 100% for Bisoprolol fumarate and99.91 % for Telmisartan.

IV. CONCLUSION

The simple Area under curve method for simultaneous estimation of Bisoprolol fumarate and Telmisartan in combined dosage form was developed and validated. The method was found to be accurate and precise. The % assay result was found to be 100% for Bisoprolol fumarate and99.91 % for Telmisartan indicate that the developed method can be successfully utilized for routine analysis for simultaneous estimation of Bisoprolol fumarate and Telmisartan in their tablet formulation.

V. ACKNOWLEDGEMENT

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