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UV SPECTROPHOTOMETRIC AREA UNDER CURVE METHOD FOR THE SIMULTANEOUS DETERMINATION OF BISOPROLOL FUMARATE AND CILNIDIPINE IN PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

It is new precise, rapid, accurate UV spectroscopic method. In that area under curve method involved measurement of integrated area between selected wavelength ranges. For measurement of area wavelength range was found to be 222.20 -232.40nm (ƛ1-ƛ2) and 231-254.80nm (ƛ3-ƛ4) for Bisoprolol Fumarate and Cilnidipine respectively. UV Spectroscopic Area under Curve method was performed by using methanol: water (80:20) as a solvent system in Bulk as well as pharmaceutical dosage form. For that analyzed method linearity range were found to be 5-15µg/ml & 10-30µg/ml for Bisoprolol Fumarate and Cilnidipine respectively and it has regression coefficient was found to be 0.999 for both drug. This proposed method according to ICH guideline.

KEYWORD: Bisoprolol Fumarate, Cilnidipine, Area under Curve method and Validation.

INTRODUCTION

Besicor-C5 Tablet is combination of Bisoprolol Fumarate and Cilnidipine medicine used for treatment of high blood pressure. Bisoprolol Fumarate is beta adrenoreceptor blocker. It is a white crystalline powder. Beta-blocker are competitive antagonists at beta-adrenergic receptor site and are used in management of hypertension, angina pectoris, heart failure.[1,2]

Cilnidipine is a novel and unique fourth-generation dihydropyridine calcium channel blocker that possesses a slow-onset, long-lasting vasodilating effect. It blocks the influx of calcium

ions into both vascular smooth muscle at the level of L-type calcium channels and neuronal cells at the level of N-type calcium channels so it is used as antihypertensive.[1,2,3]

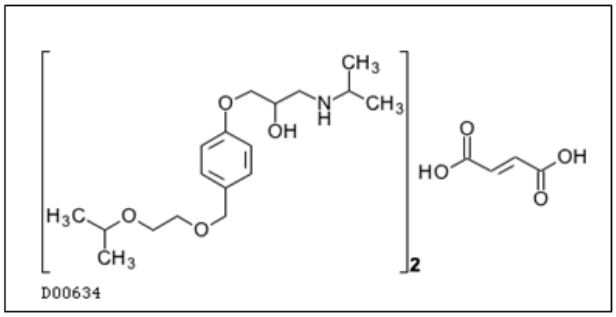

Fig.1 Structure of Bisoprolol Fumarate.

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

Molecular Weight: 767.0 g/mol.

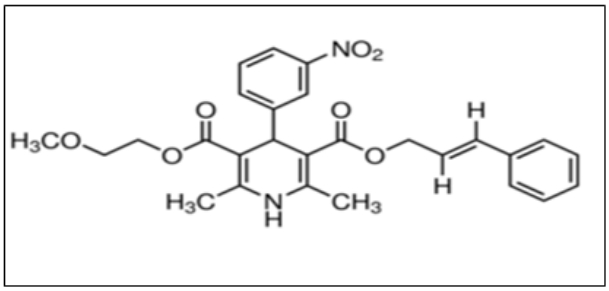

Fig: 2 Structure of Cilnidipine.

Molecular Formula: $C_{27}H_{28}N_2O_7$.

Molecular Weight: 492.5g/mol.

Literature review revealed enormous analytical methods were reported for the estimation of Bisoprolol Fumarate and Cilnidipine individually or in combination with other drugs. There is no UV spectrophotometric Area under Curve method available in the literature for Simultaneous estimation Bisoprolol Fumarate and Cilnidipine. So our aim is to develop and validate a new simple, rapid, accurate, specific and highly sensitive and economical UV spectrophotometric Area under Curve method for estimation of Bisoprolol Fumarate and Cilnidipine.[3,5,6.7]

MATERIALS AND METHODS

Chemical and reagent

Bisoprolol Fumarate [bulk drug] used were of analytical reagent grade purchased from Unichem laboratories Ltd, Pharmaceutical Company in Goa Industrial Estate, Goa, India.

Cilnidipine was gifted by J.B. chemical and pharmaceutical Pvt. Ltd., Mumbai. Methanol (AR grade) was purchased from Research lab finechem. Industries Mumbai and double distilled water was used throughout the analysis.

Instrumentation

A shimadzu1800UV/VIS double beam spectrophotometer with 1cm matched quartz cells was used for all spectral measurements.

Preparation of standard stock solution

10mg of Bisoprolol fumarate and 10mg of Cilnidipine were weighed accurately and transferred to a separate 10ml volumetric flask, dissolved in sufficient quantity of mobile phase then sonicated for 15min and diluted to 10ml with the same solvent so as to get the concentration of 1000µg/ml. From the above standard stock solution, working standard solution was prepared containing 5-15µg/ml of Bisoprolol fumarate and 10-30µg/ml of Cilnidipine separately in mobile phase.

Selection of wavelength and solvent

For Area under Curve method, the sampling wavelength ranges selected for estimation of Bisoprolol Fumarate and Cilnidipine were 222.20-232.40nm (λ1-λ2) and 231-254.80 nm (λ3-λ4) respectively (Figure 3 & 4). For determining the concentration of drugs by AUC method, by using methanol: water (80:20) as solvent system.

Selection of Wavelength Range

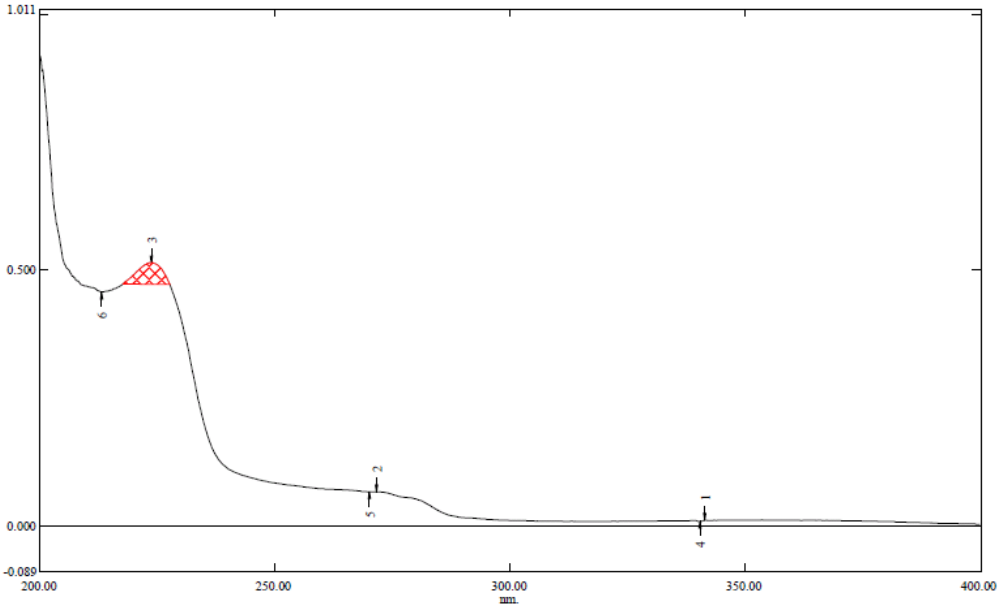

Fig. 3: AUC spectra of Bisoprolol Fumarate(222.20-232.40nm).

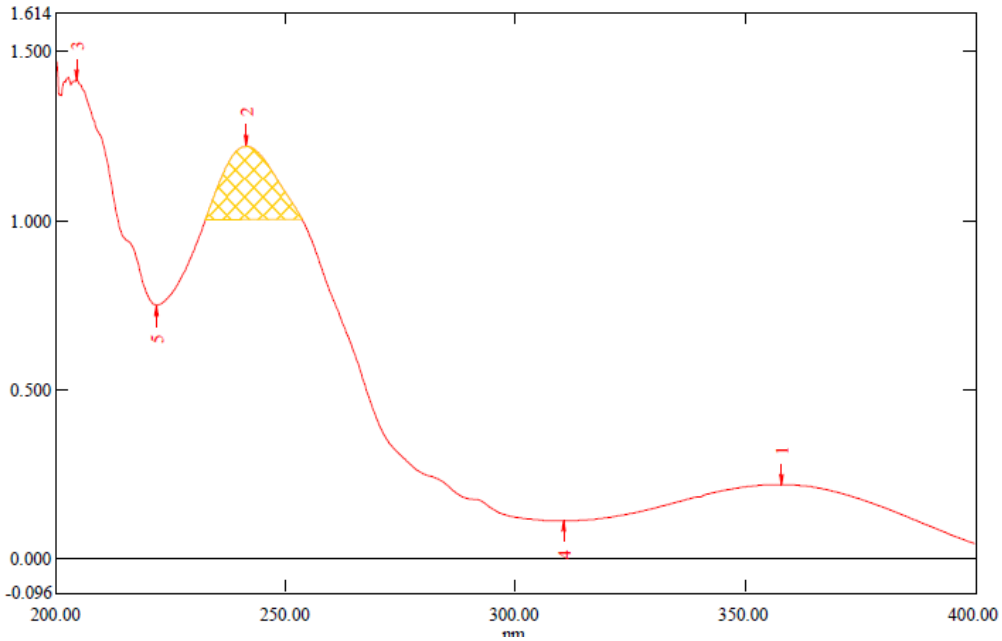

Fig. 4: AUC spectra of Cilnidipine (231-254.80nm).

Area Under Curve Method

The absorptive values of each of the two drugs were determined at the selected wavelength range in this method. Total area under curve of a mixture at wavelength range is equal to sum of area under individual component at the wavelength range. It involves the calculation of integrated value of absorbance with respect to the wavelength between two selected wavelengths λ1 - λ2 and λ3 – λ4. This wavelength range is selected on the basis of repeated observation so as to get the linearity between area under curve and concentration. The solutions of drugs were scanned in the range of 200-400 nm then area calculated by using UV probe software.[3,4,8]

Assay of Marketed Formulation

Twenty tablets (Besicor c-5) containing 5mg of Bisoprolol Fumarate and 10mg of Cilnidipine weighed, average weight calculated and triturated to fine powder and then weight equivalent to 5 mg of Bisoprolol Fumarate and 10mg of Cilnidipine transferred to 10ml of volumetric flask containing proposed mobile phase, then sonicated for 15 minutes and filtered through Whatman filter paper no. 42 to form 1000µg/ml stock solution and final volume made up to mark with solvent. From that respective stock solution prepare 5µg/ml solution of Bisoprolol Fumarate and 10µg/ml dilution of Cilnidipine, and then measure the absorbance.

Table 1: Assay of marketed formulation.

Sr. No.	Bisoprolol Fumarate			Cilnidipine		
	Area	Amount Recovered (µg/ml)	% Recovery	Area	Amount Recovered (µg/ml)	% Recovery
1	0.669	5.076	101.52	3.285	10.029	101.90
2	0.666	5.047	100.95	3.301	10.097	101.82
3	0.665	5.038	100.76	3.289	10.046	102.07
4	0.664	5.028	100.57	3.306	10.118	102.45
5	0.660	4.990	99.80	3.277	9.995	101.90
6	0.659	4.980	99.61	3.275	9.987	101.44
Mean	0.663	5.026	100.53	3.288	10.04	100.45
%RSD	0.566	0.713	0.713	0.381	0.529	0.529

RESULT AND DISCUSSION

Validation Method

The developed method was validated by using validation parameter like linearity, precision, and accuracy, limit of detection and limit of quantification according to ICH guideline.[9,10]

1. Linearity

Linearity is analytical method it can be measured by analyzing different concentration of standard solution. A calibration curve was build up for each drug by plotting the peak areas on y-axis versus concentration on x-axis. Linear relationship was established in both graphs at the concentration ranging from 5- 15µg/ml for Bisoprolol Fumarate and 10-30µg/ml for Cilnidipine.

Table 2: linearity values for Bisoprolol Fumarate and Cilnidipine.

Parameter	Bisoprolol Fumarate	Cilnidipine
Range	5-15µg/ml	10-30µg/ml
Slop	0.105	0.236
Intercept	0.136	0.918
Correlation coefficient	0.999	0.999

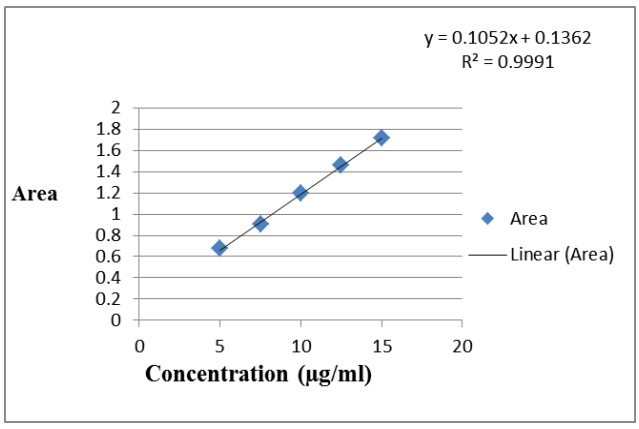

Fig. 5: Calibration curve of Bisoprolol Fumarate.

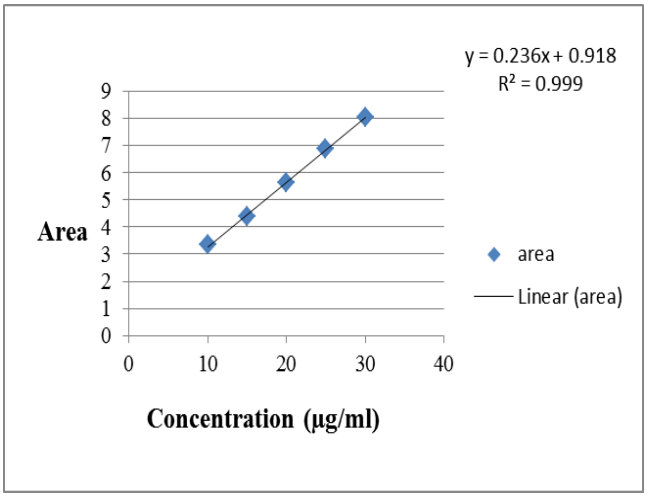

Fig. 6: Calibration curve for Cilnidipine.

2. Precision

The reproducibility of the proposed methods was determined by performing std. drug analysis at different time intervals on same day (Intra-day precision) and on three different days (Inter-day precision). The report of precision study was given in table no. 3, 4, 5, & 6.

Table 3: Intraday Precision for Bisoprolol Fumarate.

Conc. µg/ml	Area			Mean	SD	%RSD
	Trial 1	Trial 2	Trial 3			
5	0.673	0.671	0.672	0.672	0.001	0.148
7.5	0.905	0.904	0.902	0.903	0.0015	0.169
10	1.196	1.196	1.197	1.197	0.001	0.083

Table 4: Interday Precision for Bisoprolol Fumarate.

Conc. µg/ml	Area			Mean	SD	%RSD
	Trial 1	Trial 2	Trial 3			
5	0.672	0.669	0.668	0.669	0.0020	0.310
7.5	0.904	0.903	0.906	0.904	0.0015	0.168
10	1.196	1.192	1.193	1.193	0.0020	0.174

Table 5: Intraday Precision for Cilnidipine.

Conc. µg/ml	Area			Mean	SD	%RSD
	Trial 1	Trial 2	Trial3			
10	3.346	3.345	3.346	3.345	0.0005	0.017
15	4.399	4.397	4.398	4.398	0.001	0.022
20	5.623	5.622	5.625	5.623	0.0015	0.027

Table 6: Interday Precision for Cilnidipine.

Conc. µg/ml	Area			Mean	SD	%RSD
	Trial 1	Trial 2	Trial3			
10	3.346	3.344	3.348	3.346	0.002	0.059
15	4.399	4.394	4.397	4.396	0.0025	0.057
20	5.623	5.620	5.625	5.622	0.0025	0.044

3. Accuracy

The percentage recoveries of drugs from marketed formulation were determined by standard addition of pure drugs at three known concentrations and excellent recoveries were obtained at each level. The percent recoveries for Bisoprolol Fumarate at three levels were found to be 98.03±0.129, 100.98±0.144, 100.21±0.096. The recoveries for Cilnidipine at three level were found to be 98.52±0.059, 99.80±0.127, 100.45±0.063.The result of accuracy study was shown in table no.7 and 8.

Table 7: Accuracy study for Bisoprolol Fumarate.

Level	Conc. µg/ml		Area	% Recovery	Mean %Recovery±RSD
	Sample	Std			
50%	5	2.5	0.907	97.904	98.031 ±0.129
			0.908	98.031	
			0.909	98.158	
100%	5	5	1.196	100.952	100.984 ±0.144
			1.198	101.142	
			1.195	100.857	
150%	5	7.5	1.713	100.127	100.211 ±0.096
			1.714	100.190	
			1.716	100.317	

Table 8: Accuracy study for Cilnidipine.

Level	Conc. µg/ml		Area	% Recovery	Mean% Recovery±RSD
	Sample	Std			
50%	10	5	4.405	98.502	98.521 ±0.059
			4.404	98.474	
			4.408	98.587	
100%	10	10	5.623	99.682	99.802 ±0.127
			5.635	99.936	
			5.628	99.788	
150%	10	15	8.026	100.395	100.457 ±0.063
			8.030	100.452	
			8.035	100.523	

4. LOD & LOQ: (Limit of Detection and Limit of Quantization)

The standard deviation of intercept was calculated by using linearity calibration curve. The LOD and LOQ were calculated by using mathamathetical formula as follow:-

$$LOD = 3.3 \times \sigma/S,$$

Where, σ = the standard deviation of the Intercept

S = Mean slope of the calibration curve

$$LOQ = 10 \times \sigma/S$$

Where, σ = the standard deviation of the Intercept

S = Mean slope of the calibration curve

Table 9: LOD & LOQ data for Bisoprolol Fumarate & Cilnidipine.

Characteristics	Bisoprolol Fumarate	Cilnidipine
Sigma (σ)	0.014249	0.062037
LOD	0.452131	0.867471
LOQ	1.370094	2.628701

CONCLUSION

The area under curve method for simultaneous estimation of Bisoprolol Fumarate and Cilnidipine were new, affordable, dynamic, easy and economic therefore developed method can be suitably analyzed for routine analysis of Bisoprolol Fumarate and Cilnidipine in bulk and combined tablet dosage form. It does not suffer from any interference due to common excipient present in pharmaceutical formulation.

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