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DEVELOPMENT AND VALIDATION OF BISOPROLOL FUMARATE IN BULK AND PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

UV Spectroscopy is a widely used analytical technique that involves the absorption of ultraviolet radiation by molecules, leading to electronic transitions. The aim of the presented work is to develop and validate a simple, rapid, accurate, precise and effective UV-spectroscopy method for the estimation of bisoprolol, an anti- hypertensive drug. Ethanol is used as the solvent for the preparation of stock solution as it shows good solubility when compared with the other solvents. The wavelength at maximum absorption (λ max) was found to be 273nm. The drug bisoprolol shows the linearity concentration range 20-180µg\ml with the correlation coefficient value of 0.9961and a regression equation y =0.004x+ 0.0311. Then a graph was plotted by taking the concentration x- axis and absorbance on y-axis which gives straight line percentage assay of bisoprolol in pharmaceutical formulation was found to be 99.58%. The LOD and LOQ was found to be 0.284 & 0.863 respectively.Precision studies show acceptable results with intraday precision and interday precision as %RSD <2 method validation was carried out in accordance with international council of harmonization guidelines.

KEYWORDS: Bisoprolol, Anti- hypertensive drug, UV spectrophotometric method, Validation.

1. INTRODUCTION

Bisoprolol is a highly selective β_1- adrenergic receptor blocking agent used extensively in the treatment of cardiovascular diseases such as hypertension, angina pectoris, and chronic heart failure. By selectively inhibiting β_1-receptors in cardiac tissue, bisoprolol decreases heart rate, myocardial contractility, and cardiac output, leading to a reduction in blood pressure and myocardial oxygen consumption. Its high β_2-receptor blockade, particularly broncho constriction and peripheral vasoconstriction.

Bisoprolol exhibits favorable pharmacokinetic properties, including good oral absorption, low first-pass metabolism, and a relatively long elimination half- life, allowing once daily dosing. It is eliminated through both hepatic metabolism and renal excretion, making dose adjustment minimal in patients with mild to moderate organ impairment. Due to its efficacy, tolerability, and cardio- selective profile, bisoprolol is widely recommended in clinical guidelines for cardiovascular disease management.

2. DRUG PROFILE

DRUG NAME

- Bisoprolol

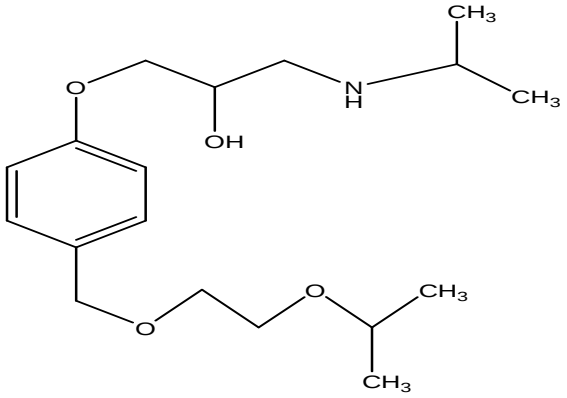
SYNONYMS

- Concor
- Zebeta
- Cardicor
- Biselect
- Bisotab

DESCRIPTION

- **Colour –** White or off-white crystalline powder
- **Odour –** Odourless
- **Taste –** Slightly bitter.
- **PH** – 4.0 - 6.0

STRUCTURE



STRUCTURE OF BISOPROLOL

CHEMICAL FORMULA

C_{18} H_{31} NO_4.

MOLECULAR WEIGHT

325.4g/mol.

IUPAC NAME

1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(methylethyl)amino]-2-propanol.

CATEGORY

It is in a class of medications called anti hypertension.

DOSE

5-10 mg orally once daily (depends on indication).

MELTING POINT

Approximately 142 - 145°C.

SOLUBLITY

Soluble in organic solvents like ethanol and methanol. Sparingly soluble in water.

STORAGE

Store at normal room temperature.

PHARMACOKINETIC PROPERTY

Bisoprolol has high oral bioavailability (80 – 90%), reaches peak levels in 2 – 4 hours, and attains steady state in about 5 days. It shows low protein binding and low lipophilicity, with hepatic metabolism mainly by CYP3A4. Elimination is primarily renal, with 50% excreted unchanged and 50% as inactive metabolites, and negligible fecal excretion.

MECHANISM OF ACTION

Bisoprolol selectively blocks β_1- adrenergic receptors in the heart, reducing heart rate, cardiac workload, and oxygen demand. It also decreases renin release from the kidneys, helping to lower the blood pressure.

USES

- Hypertension
- Angina pectoris
- Treatment of chronic stable heart failure
- Control of heart rate in certain cardiac arrythmias
- Reduce cardiac work load

ADVERSE EFFECT

- Bradycardia
- Hypotension
- Fatigue
- Cold extremities
- Sleep disturbances

3. MATERIALS AND METHODS

MATERIALS USED

Drugs

Bisoprolol raw material was bought from local market.

Formulation

Concor 10mg was purchased from local market.

Reagents and chemicals

All the chemicals and solvents used were of analytical grade. The solvent used for this study is Ethanol.

Instruments used

The instruments used for the present work are.

- Digital balance (1mg sensitive)-**Kingslab.**
- **Shimadzu-1900i** double beam UV-visible spectrophotometer with a pair of matched quartz cells.
- Sonicator.

SPECIFICATION OF INSTRUMENTS

Instrument No. 1: Digital balance (**1mg** sensitive)

- **Model** **:** PGB220
- **Manufacture:** Kings lab.

Instrument No.2: SHIMADZU- 1900i Double Beam UV-Visible Spectrophotometer.

METHOD

In the present work, an attempt was made to develop and validate simple, precise and accurate methods for the estimation of bisoprolol in pure and in tablet dosage form by UV-Visible Spectroscopy.

UV Spectroscopic Method

Selection of solvent

The solubility of bisoprolol was determined in variety of solvents. In this study, from the solubility data ethanol was selected as solvent for the analysis of bisoprolol.

Preparation of standard stock solution

The amount of 0.01g of standard substance bisoprolol was weighted and transferred into 10ml Standard flask, dissolved in 10ml of ethanol, the primary stock solution was prepared. From the primary stock solution 0.7ml was taken and transferred into 10ml Volumetric flask and made up to the volume with ethanol.

Selection of wavelength

The standard stock solution was further diluted with ethanol to get the concentration of 70µg/ml and the solution was scanned between 200-400nm using ethanol as blank. From the spectra λ max was found.

Preparation of calibration graph

From the standard stock solution 0.2 - 1.8ml were transferred into a series of 10ml Volumetric flask and made up to the volume with ethanol. The absorbance of different concentration solution were measured. The calibration curve was constructed by plotting concentration Vs absorbance. Bisoprolol was linear with the concentration range of 20-180µg/ml.

RESULT AND DISCUSSION

LINEARITY

Different aliquots of bisoprolol fumarate were prepared for this study, the calibration curve was plotted against various concentration vs absorbance prepared by diluting with ethanol. Further the sample solutions are scanned between the range of 200-400nm against ethanol as blank. The absorbance of sample solution is recorbered and to construct the calibration curve by using the readings. On plotting the calibration curve the correlation co-efficient was found to be $R^2 = 0.996$, and the regression equation was found to be $y = 0.004x + 0.031$.

Table no 1: linearity of bisoprolol at selected wavelength.

S.NO	CONCENTRATION(µg/ml)	ABSORBANCE at 273nm
01	0	0.000
02	20	0.086
03	40	0.197
04	60	0.278
05	80	0.363
06	100	0.432
07	120	0.496
08	140	0.606
09	160	0.644
10	180	0.735

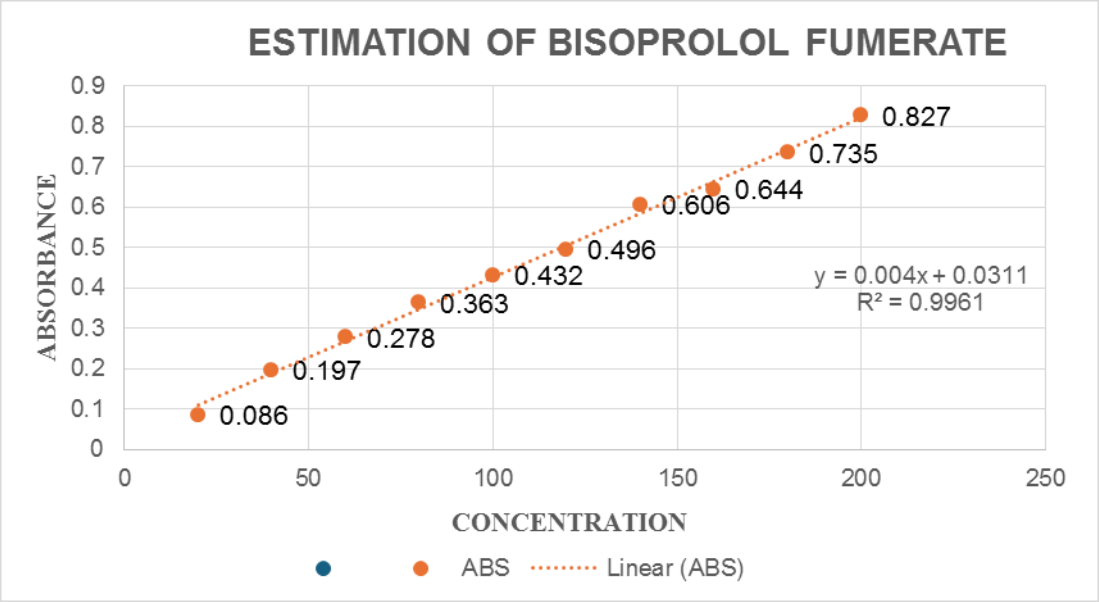


Fig. no. 1: linearity of bisoprolol fumarate.

PRECISION

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. For interday precision the samples of bisoprolol fumarate were analyzed for three times on three consecutive days, while for intraday analysis the samples are taken and analyzed three times within same day. And to validate by calculating mean, SD, and %RSD.

Table no 2: Interday precision of bisoprolol fumarate.

CONCENTRATION	ABSORBANCE		
	SAMPLE 1	SAMPLE 2	SAMPLE 3
70µg/ml	0.341	0.336	0.332
	0.335	0.342	0.340
	0.346	0.331	0.341
MEAN	0.320	0.336	0.337
SD	0.0057	0.0053	0.0049
%RSD	1.72	1.63	1.46

Table no 3: intraday precision of bisoprolol fumarate.

CONCENTRATION	ABSORBANCE		
	SAMPLE 1	SAMPLE 2	SAMPLE 3
70µg/ml	0.334	0.327	0.325
	0.336	0.330	0.335
	0.334	0.328	0.325
MEAN	0.334	0.328	0.328
SD	0.00115	0.00153	0.0057
%RSD	0.345	0.465	1.758

LOD and LOQ

The limit of detection (LOD) is the lowest concentration at which the results still satisfy some predetermined acceptance criteria. Below the LOD, the results fail to meet these criteria (analysis is not feasible).

It may expressed as LOD = 3.3× σ/S

Where, standard deviation of response

S slope of calibration curve

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy.

The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and degradation products.

LOQ = 10 × σ /S

Where,

σ = standard deviation of response

S = slope of the calibration curve

Table no 4: LOD & LOQ of bisoprolol fumarate.

DRUG	PARAMETER	
	LOD	LOQ
BISOPROLOL FUMARATE	0.284	0.863

ASSAY

The assay provide an exact result which allows an accurate statement of the content or potency of the analyte in a sample. The assay of bisoprolol fumarate was performed by tablet

powder of Bisoprolol 0.1717mg was weighed accurately and transferred into 100ml Standard flask. Added about 100ml of ethanol to dissolve the substance and the solution was sonicated for 10 minutes. The solution was filtered through Whatmann filter paper grade no:1. From the clear solution, further dilutions were made by diluting 7ml was pipetted out into a series of six 10ml volumetric flask and made upto the mark with distilled water to get the concentration of 70µg/ml of Bisoprolol. The absorbance of six solutions were measured and the amount was calculated by using regression equation.

Table no 5: Assay of bisoprolol fumarate.

SAMPLE	TAKEN AMOUNT (µg/ml)	AMOUNT FOUND (µg/ml)	% obtained	AVERAGE %	S.D.	%RSD
1	70	68.72	100.87			
2	70	68.97	100.51			
3	70	72.22	96.89			
4	70	68.22	101.61	99.58%	1.8455	1.850
5	70	68.97	100.51			
6	70	70.72	98.02			

Ruggedness

Ruggedness of method was confirmed by the analysis of formulation was done by using different instruments and different analysts. The amount was calculated. The %RSD were calculated.

Table no 6: ruggedness study of bisoprolol fumarate.

CONDITION	LABELED AMOUNT(µg/tab)	AMOUNT FOUND (µg/tab)	PERCENTAGE OBTAINED	MEAN	SD	%RSD
Analyst 1	10	9.5	99%	100.43%	1.2897	1.284
		10.3	101.5%			
		9.65	100.8%			
Analyst 2	10	9.82	98.5%	99.63%	1.2055	1.209
		9.9	97.5%			
		10.2	100.9%			

ROBUSTNESS

The developed method was validated for Robustness. It refers to the analysis should be done in different wavelength like 272 nm, 273 nm, 274nm. The percentage RSD value for those three wavelength were found to be 1.09 and 1.49 and 1.54 respectively. The low % RSD values indicate that the method was more robusted. The results are shown in table 7.

Table no 7: robustness study of bisoprolol fumarate.

WAVELENGTH	ABSORBANCE		
	SAMPLE 1	SAMPLE 2	SAMPLE 3
272	0.317	0.263	0.354
273	0.324	0.271	0.361
274	0.320	0.267	0.365
MEAN	0.32	0.267	0.360
SD	0.0032	0.0004	0.0055
%RSD	1.09	1.49	1.54

ACCURACY

The accuracy of the method was confirmed by recovery studies. To the pre-analyzed formulation a known quantity of bisoprolol raw material solution was added at three different concentrations. The concentration of standard raw material added were 56, 70 and 84µg/ml of the sample concentration. The absorbance was measured and the percentage recovery was calculated. The results were shown in table 8.

Table 8: accuracy study for bisoprolol fumarate.

%	AMOUNT PRESENT (µg/ml)	AMOUNT ADDED (µg/ml)	AMOUNT ESTIMATED (µg/ml)	AMOUNT RECOVERED (µg/ml)	% Recovery	SD	%RSD
80%	70	56	126	126.22	100.17%	0.305505	0.304784
	70	56	126	126.72	100.57%		
	70	56	126	125.91	99.97%		
100%	70	70	140	139.72	99.8%	0.556507	0.5549531
	70	70	140	140.22	100.15%		
	70	70	140	141.25	100.89%		
120%	70	84	154	154.72	100.46%	0.407308	0.403915
	70	84	154	155.22	100.79%		
	70	84	154	155.97	101.27%		

CONCLUSION

A Simple, accurate, and precise UV spectrophotometric method was succefully developed and validated for the estimation of bisoprolol fumarate in both API and pharmaceutical dosage form. The method is developed and validated in accordance with ICH guidelines. This method shows good linearity over the selected concentration range from 2 - 18µg/ml, with a high correlation coefficient of 0.996 and a regression equation y = 0.004x + 0.031 which indicates a relationship between absorbance and concentration at 273nm. The limit of detection (LOD) and limit of quantification of bisoprolol was found to be 0.284 and 0.863 at 273nm respectively, which indicates that the method is suitable for routine analysis. The precision of methd was studied by three repeatability of one measurements of working

standard, and the %RSD values were found to be within the acceptable limits. For both intraday and interday analysis precision study the %RSD values were found to be less than 2%, which shows the method is precise and reproducible as per the acceptance criteria. The assay study was performed using pharmaceutical dosage form which results that the average % assay was found to be in the range of 100.00 to 100.84%, which is in good aggrement to label claim.

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