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METHOD DEVELOPMENT AND VALIDATION FOR ESTIMATION OF BRISOPROLOL FUMERATE IN BULK AND PHARMACEUTICAL DOSAGE FORM BY UV SPECTROMETRIC METHOD USING WATER AS SOLVENT

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ABSTRACT

A rapid, simple, selective and precise UV- Visible Spectrophotometric method has been developed for the determination of Brisoprolol Fumerate in bulk forms and tablet dosage formulations. The spectrophotometric detection was as per carried out at an absorption maximum of 223 nm using water as solvent. The method was validated for specificity, linearity, accuracy, precision, robustness and ruggedness. The detector response for was linear over the selected concentration range 10-50 ug/ml with a correlation coefficient(R^2) of 0.9981. The accuracy was carried out as per recovery study and found between 99.65%% to 100.45%. The results demonstrated that the excipients in the tablets did not interfere with the method and can be conveniently employed for routine quality control analysis of metformin in bulk and formulation.

KEYWORDS: UV Spectroscopy; Method Development; Validation; Brisoprolol Fumerate and ICH Guideline.

1. INTRODUCTION

A spectroscopy method is the branch of science dealing with the study of interaction between Electromagnetic radiation and matter. It is a most powerful tool available for the study of atomic and molecular structure/s and is used in the analysis of wide range of samples. Ultraviolet-Visible spectrophotometry.[1] UV-Visible spectrophotometry is one of the most frequently employed techniques in pharmaceutical analysis.

Analytical method development is the process of selecting an accurate assay procedure to determine the composition of a formulation. It is the process of proving that an analytical method is acceptable for use in laboratory to measure the concentration of subsequent samples Analytical methods should be used within GMP and GLP environments and must be developed using the protocols and acceptance criteria set out in the ICH guidelines Q2(R1).[1,2]

The important parameters that may be evaluated during method development are specificity, linearity, limits of detection (LOD) and quantitation limits (LOQ), range, accuracy and precision. During early stages of method development, the robustness of methods should be evaluated because this characteristic ultimately helps to decide which method will be approved.

Analytical procedures developments are primarily based on a combination of mechanistic understanding of the basic methodology and prior experiences. Experimental data from early procedures can be used to guide further development.

The life cycle of an analytical method is brief as shown in Figure 1. The common steps followed in the method development are as follows:

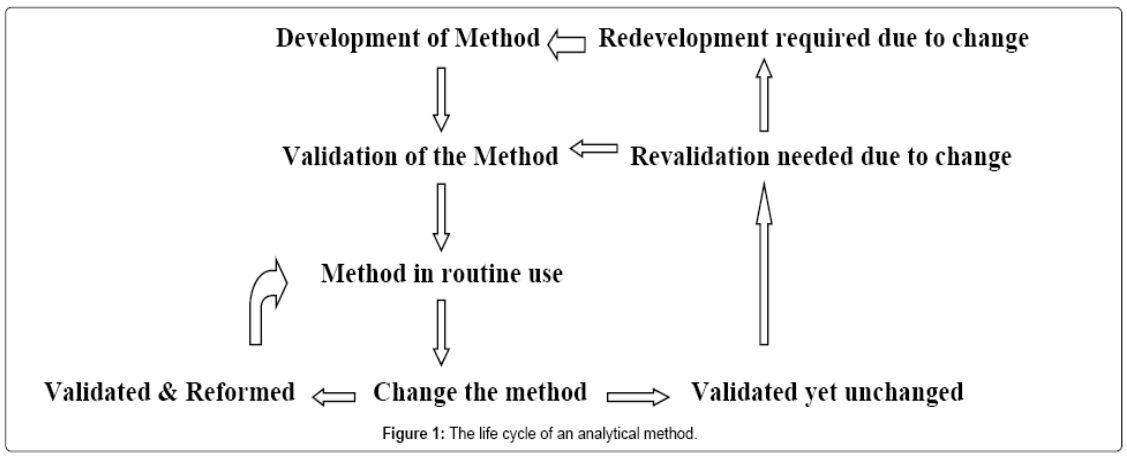

Figure 1: The life cycle of an analytical method.

The ability to provide accurate, reliable and consistent data is the motive of the analytical chemist. This may include: preparation of samples, standards and reagents; use of apparatus; generation of the calibration curve, use of the formulae for the calculation etc.

Nowadays, there are several international renowned organisations offering guidelines on method validation and related topics.

- American Society for Testing and Material (ASTM)
- Codex Committee on Methods of Analysis and Sampling (CCMAS)
- European Committee for Normalization (CEN)
- Cooperation on International Traceability in Analytical Chemistry (CITAC)
- European Cooperation for Accreditation (EA)
- Food and Agricultural Organization (FAO)
- United States Food and Drug Administration (FDA)
- International Conference on Harmonization (ICH). ICH Guidelines (ICH Q2R1) for nalytical procedure and validation
- Current Good Manufacturing Practice (cGMP) regulations
- Good Laboratory Practice (GLP) regulations.
- The Pharmaceutical Inspection Cooperation Scheme's (PIC/S)
- World Health Organization (WHO)

When some changes are made in the validated nonstandard methods, the influence of such changes should be documented and a new validation should be carried out. If standard methods are available for a specific sample test, the most recent edition should be used. Validation includes specification of requirements, determination of method characteristics, a check that the requirements can be fulfilled by using the method, a statement on validity.[3-6.]

Method validation is a vast area which includes many validation parameters with different approaches for different level of requirements based on intended use of analytical method. Validated method elucidates the unpredicted or unknown problem during the course of routine usage. Validated method has limited level of confidence. After method development it needs to be validated as per requirement that gives certain level of confidence for its intended use.[7]

Typical validation parameters recommended by FDA, USP, and ICH are as follows.[8-9]

1. Specificity
2. Linearity and Range
3. Precision

A) Method precision (Repeatability)

B) Intermediate precision (Ruggedness)

4. Accuracy
5. Solution stability
6. Limit of Detection (LOD)
7. Limit of Quantification (LOQ)
8. Robustness

Bisoprolol fumarate has a molecular weight of 766.97. It is a white crystalline powder which is approximately equally hydrophilic and lipophilic, and is readily soluble in water, methanol, ethanol, and chloroform. Bisoprolol fumarate is a selective β1-adrenergic receptor blockers. No intrinsic sympathomimetic activity and membrane stabilizing effect. Animal experiments of different models show that affinity for β1-receptor is 11 to 34-fold larger than β2-receptor. The selectivity for β1 receptor is four times of the similar drugs Atenolol. This product plays the role for a long time (24 hours or more), continual application takes good control of symptoms without tolerance phenomenon, with minimal side effects on the respiratory system, no effects on metabolism of fat. it also has a certain degree of block effect for bronchial β2 receptors, but it may only occur at high doses, usually it has no obvious clinical significance.

2. MATERIALS AND METHODS

2.1 Instruments: The analysis was performed by using the analytical balance (Mettler), pH meter (Cyber scan), UV spectrophotometer (UV-Lambda 25, Perkin Elmer equipped with variable wavelength detector and data integration software).

2.2 Reagents and Solutions: Brisoprolol Fumerate, distilled water, Whatman filter paper were used.

2.3. Method development

2.3.1. Selection of solvent: Bisoprolol fumarate a white crystalline powder which is approximately equally hydrophilic and lipophilic, and is readily soluble in water.

2.3.2. Spectral study: The final solution of Brisoprolol Fumerate in water scanned in UV spectrophotometer over the range 200- 400nm (Figure 3.1)

2.3.3. Preparation of standard stock solution bisoprolol fumarate: Weigh accurately about 10 mg drug dissolving in water in 100 ml volumetric flasks and then make up to volume distilled water. Take into different concentration from 10 -50 µg/ml. Observation was

recorded Table 3.1 and calibration curve (Figure 3.2.) was prepared by plotting absorbance v/s concentration of Bisoprolol Fumarate.

2.4. Method of validation[10]

The developed method was validated according to ICH guidelines.

2.4.1 Linearity and Range: The stock solution of drug i.e. 10-50µg/ml were transferred into 10ml standard flask and make volume by distilled water and the absorbance of the solution of different concentration was measured 223 nm.

2.4.2. Limit of detection (LOD): LOD is the lowest amount of analyte in sample that can be easily but not necessarily quantified. LOD was calculated by following formula It was calculated by using following formula,

DL =3.3α/S

Where α: standard deviation. S: slop of calibration curve.

2.4.3. Limit of quantity (LOQ): LOQ is the lowest amount of analyte in sample that can be easily detected and quantified with suitable precision and accuracy. LOD was calculated by following formula. It was calculated by using following formula,

QL =10 α/S

Where α: standard of deviation. S: slop of calibration curve.

2.4.4. Precision: To evaluate repeatability of the method, pure drug of solution within working limit was analyses and being six times. Precision of method was also demonstrated by intraday and inter day variation studies. Intraday studies repeated requirement of standard and sample solution are made in day and % RSD were calculated. Inter day studies are repeated measurement of standard and sample solution were made on 3 consecutive days and % RSD were calculated. The RSD % is not less than 2.0 and indicated high precision for proposed method.

2.4.5. Accuracy and recovery study: To ensure the accuracy known the amount of pure drug were added to solvent and these samples are reanalyse by the proposed method and % recovery was studied.

3. RESULTS AND DISCUSSION

The methods discuss in the present work provide convenient, precise and accurate way for estimation of Bisoprolol Fumarate.in bulk and pharmaceutical dosage form using water as solvent.

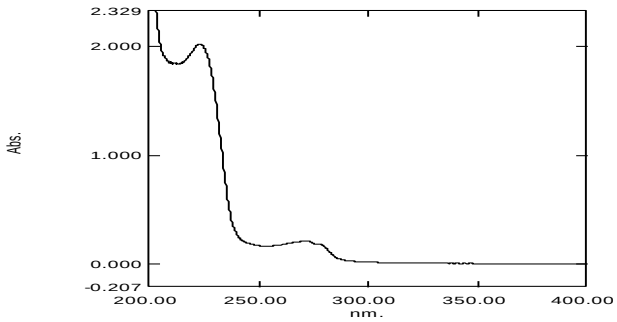

Figure 3.1: UV spectra of bisoprolol fumarate.

The λmax of Bisoprolol Fumarate was found 223 nm which is nearly same as reported in literature (225 nm) and Spectra is shown in Figure.3.1

Table 3.1: Calibration curve in water.

Sr.no	Concentration (ug/ml)	Absorbance
1	10(µg/ml)	0.250
2	20(µg /ml)	0.437
3	30(µg /ml)	0.639
4	40(µg /ml)	0.788
5	50(µg /ml)	0.976

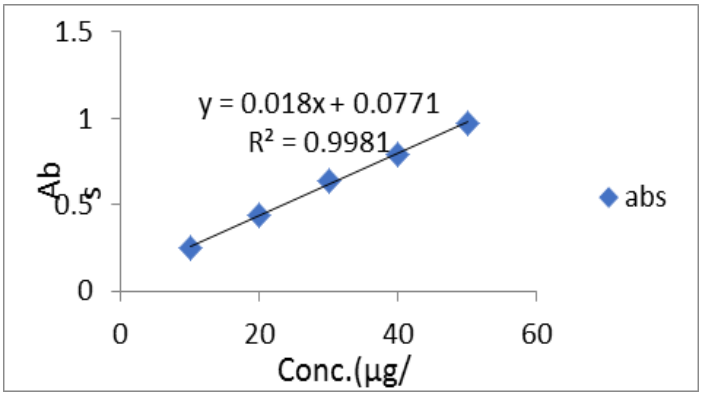

Figure 3.2: Calibration curve of bisoprolol fumarate in water.

Calibration curve of Bisoprolol Fumarate was carried out at λmax 223 nm in water. Regression coefficient of Bisoprolol Fumarate was found to be R^2 0.9981.the standard linear equation was found to be y= 0.018x+0. 0771. Graph shown in Figure 3.2.

Method of validation

The developed method was validated as per ICH guidelines (ICH Q1B, 1996, ICH Q2 R1, 2005) for following parameters. 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.

Precision of the method was determined in terms of repeatability and intraday and interday precisions. Repeatability of the method was determined by analysing six samples of same concentrations of drug. Intraday precision was determined by analysing the drugs at three different concentrations and each concentration for three times, on the same day. Interday precision was determined similarly, but the analysis being carried out daily, for three consecutive days. Accuracy, LOD, LOQ and Sandell's sensitivity are determined and the results are summarized in Table 3.2.

Table 3.2: validation in pH 6.8 phosphate buffer.

Sr. no.	Parameter	Result	ICH Std	Inference
1	Accuracy	99.65%	98%±102%.	Pass
2	Precision			
	a. Interday	0.018		
	b. intraday	0.026	RSD <2	Pass
3	LOD	3.43		
4	LOQ	10.39		
5	Linearity	0.998	>0.997	Pass
6	STD. regression	Y=0.018x+0.077		
7	Range	g/ml		

4. CONCLUSION

The absorption maximum of Bisoprolol Fumarate was selected at 223nm for the analysis. Regression analysis shows linearity over the concentration range of 10-50µg/ml with correlation coefficient R^2 0.9981 (Figure 3.2). The % RSD for repeatability (n=6) precision was found to be less than 2% indicating the precision of method. Accuracy of proposed methods was ascertained by recovery studies and the results are expressed as percentage recovery. Percentage recovery for was found within the range between 98 % to 100.2%. The % RSD value for was found to be less than 2%. In this study estimation of Bisoprolol Fumarate was carried out by UV spectroscopy method and all the validation parameters found satisfactorily. The result of developed method and validation was given in Table 3.2.

The analytical method for estimation of Bisoprolol Fumarate has been developed and validated according to validation protocol of ICH guidelines. All parameters mentioned in the protocol were tested and they fulfilled the requirement of ICH analytical method validation for the drug. The results obtained are well within the set limit; indicates that the described analytical method is suitable for estimation of Bisoprolol Fumarate in bulk as well as formulation.

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