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# STABILITY ASSESSMENT OF BISOPROLOL FUMARATE UNDER DIFFERENT STRESS CONDITIONS

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## ABSTRACT

***Objective:*** To assess the stability of Bisoprolol Fumarate under different stress conditions. ***Methods:*** Different samples of Bisoprolol Fumarate standard were subjected to a variety of stress conditions as a temperature, a combination of temperature and relative humidity, direct sunlight, acid/base hydrolysis, and oxidation were subsequently analysed. The analysis was carried out using RPHPLC system equipped with UV/vis detector. ***Results:*** Bisoprolol Fumarate was stable in diluent when exposed for 72 hrs (at room temperature). The results of analysis showed that the drug standard was 99.50% which proves that no degradation. When the drug was subjected to 75°C for 6 hours (Dry Temperature), there was no change in drug potency. No change in the assay content when Bisoprolol Fumarate was exposed to a temperature of 105°C for one hour. Upon exposure to sunlight in a temperature recorded between (35-40°C) for 72 hours, Bisoprolol Fumarate was unstable, the drug content decreased to 95.73%. The effect of heat and relative humidity was a decreased in drug assay (i.e. from 99.69% to 93.78%) for one month. Bisoprolol Fumarate was affected by acid and base hydrolysis (0.1M), the drug content was decreased from 99.69% to 94.72% and 91.60% respectively. Moreover, the drug was affected by oxidation (30% $H_2O_2$) and the drug content decreased from 99. 69% to 96.91%. ***Conclusion:*** Bisoprolol Fumarate stability was effected when exposed to different stress conditions.

**KEYWORDS:** Stability, Bisoprolol Fumarate, Stress conditions.

## INTRODUCTION

Drug stability is a critical element in the accurate and appropriate delivery of the drug therapy to patients.[1] Both the therapeutic adequacy of the treatment and safety of the therapy can be adversely affected by drug instability.[2] The purpose of stability testing is to provide evidence on how the quality of a drug substance or product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, to establish a retest period or shelf life for the product and to provide the recommended storage conditions.[3]Stability of a pharmaceutical product may be defined as the capability of a particular formulation in a specific container closure system, to remain within its physical, chemical, microbiological therapeutic and toxicological specification. Pharmaceutical products are expected to meet their specification for identity, purity, quality, and strength throughout their defined storage period at specific storage conditions.[4]

Forced degradation is a process that involves degradation of drug products and drug substances at conditions more severe than accelerated conditions and thus generating degradation products that can be studied to determine the stability of the drug. It also known as stress testing, stress studies, stress decomposition studies or forced decomposition studies.[2] Stability study programs like long and accelerated stability studies would take a long time to produce and study degradation products like their separation, identification and quantitation. In contrast to stability studies, forced degradation studies help to generate degradants in a much shorter span of time, mostly a few weeks.[5]

### *Chemical and reagents*

All chemical and reagents used were analytical grade or HPLC grade and were used without any further purification. Bisoprolol Fumarate working standard potency 99.69% was a gift from Azal Pharmaceutical Company, Khartoum-Sudan (water content 0.18%), acetonitrile (HPLC grade), heptafluorobutyric acid, distilled water (HPLC grade), sodium hydroxide, hydrochloric acid, and hydrogen peroxide.

### Instruments

High Performance Liquid Chromatography (HPLC) system, Model: LC-20AB prominence, the analytical column was phenomenx ® C18, 4.6 mm, 12.5 mm

particle size UV/vis Spectrophotometer detector Model SPD-20AV prominence, Manual sampler Model: SIL-20A prominence. Degasser Model: DGU-20A3R prominence, Holder Reservoir Model: TRAY20 prominence**,** the data processing systems was run with software for HPL-LC solution for LC on Pentium computer.

- Analytical balance, Model: ED22458, horizontal flow oven, Model WOF-155, Wise oven.
- Water purefaction system, Model: NW10UV Heal force.

## METHOD

The researchers used United States Pharmacopeia and National Formulary method.[6] The analysis was carried out using High performance liquid.

### Mobile phase preparation

Diluent: Exactly 650 mL of deionized water was added to 350 mL of acetonitrile (HPLC grade). Mobile phase: to 1-L of diluent 5 mL hepta-fluorobutyric acid, 5 mL of diethylamine, and 2.5 mL of formic acid were added, mixed, filtered and degased.

### Preparation of Samples

***Acid degradation***

Exactly 25 mg of Bisoprolol Fumarate were weighed and transferred to 25 mL volumetric flasks. 5 mL (0.1M HCl). The sample was left at room temperature for one hour and then the volume was completed with the diluents and analysed.

***Base Hydrolysis***

Exactly 25 mg of the drug were weighed and transferred to 25 mL volumetric flasks. 5 mL of NaOH (0.1M)**,** the sample was left at room temperature for one hour and then the volume was completed with the diluents and analysed.

***Oxidative Degradation***

An amount of 25mg of the drug was weighed accurately and transferred to a 25ml volumetric flask. 1.25 mL of $H_2O_2$ (30%). The sample was left at room temperature for one hour and then the volume was completed with the diluents and analysed.

In all these preparations, the final drug concentration was1mg/ml.

***Photo Degradation***

Bisoprolol Fumarate (50 mg) were exposed to direct sunlight for 72 hours during this period the temperature was recorded between (35-40ºC). 25 mg of Bisoprolol Fumarate were weighed and transferred to 25 mL volumetric flasks. 15 mL of diluent were added and sonicated for 60s and completed to volume by diluent up to the mark with concentration of 1mg/ml.

***Thermal Degradation***

A weight 50 mg of the drug were exposed to 40°C temperature and relative humidity 75% RH (dishes were kept in open Petri dish for one month). A weight of 25 mg of Bisoprolol Fumarate, transferred to serial 25 mL volumetric flasks and 15 mL of diluent was added to each one and sonicated for 60s and completed to volume by diluent up to the mark with concentration of 1mg/ml.

***Dry heat degradation***

Approximately 100 mg Bisoprolol Fumarate powder were kept in an oven at105°C for one hour and another 100 mg in 75°C for 6 hours. Then about 25 mg sample (in 105°C) and 25 mg in 75°C of Bisoprolol Fumarate were weighted then transferred to volumetric flasks. 15 mL of diluent was added to each one and then sonicated for 60s and completed to volume by diluent to give a concentration of 1mg/mL.

## RESULTS AND DISCUSSION

As mentioned previously, the main aim of this study is to investigate the effect of various stress parameters on the stability of Bisoprolol Fumarate and to evaluate the effect of each parameter. The following formula was used to calculate recovery percentage of Bisoprolol Fumarate.

The retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the assay.[6]

### Chromatographic system

According to the method for system suitability Bisoprolol Fumarate retention time should not be less than 7.0 min and tailing factor was not more than two. Bisoprolol Fumarate contains not less than 97.5% and not more than 102.0%.**[6]** The obtained chromatogram in this study satisfies this condition as shown in figure 1.

$$Q\% = \frac{Ru}{Rs} x \frac{Cs}{Cu} x \frac{P}{100} x \frac{(100 - Wc)}{100} x 100$$

Where

| | |
|---|---|
| **Ru** | Peak response from the sample solution |
| **Rs** | Peak response from the standard solution |
| **Cs** | Concentration of Bisoprolol Fumarate RS in the standard solution (mg/mL) |
| **Cu** | Nominal concentration of Bisoprolol Fumarate in the sample solution (mg/mL) |
| **P** | Potency of Bisoprolol Fumarate RS |
| **Wc** | Water content of Bisoprolol Fumarate RS |

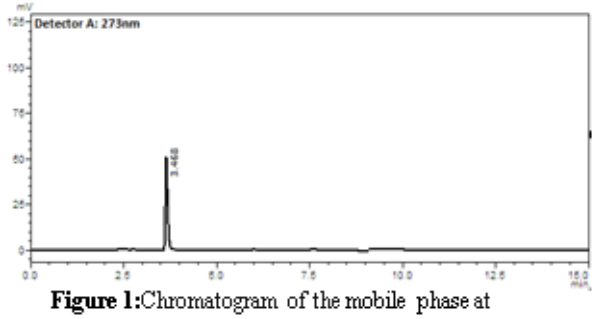


**Figure 1:**Chromatogram of the mobile phase at retention time at 3.46 mints.

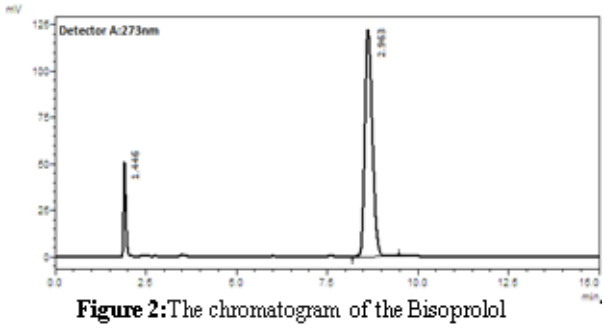


**Figure 2:**The chromatogram of the Bisoprolol Fumarate Standard at retention time 2.96 minutes.

As showen in **table 1**, Bisoprolol Fumarate is stable in diluent when left for 72 hrs and the results of assay was 99.50% which proves that no degradation had taken place.

Bisoprolol Fumarate was not affected when exposed to 75°C for 6 hours, (Dry Temperature). Even subjection of the drug to a temperature of 105°C for one hour causes no change in the assay content. Bisoprolol Fumarate was unstable upon exposure to sunlight for 72 hours, during this period the temperature recorded between (35-40°C) and the drug content was decreased from 99.69% to 95.73%.

Drug degradation was shown upon application of a combination of heat and humidity (40°C and 75% relative humidity) for one month. The drug did not remains stable upon Increment of temperature to 50°C and keeping the relative humidity constant.

Bisoprolol Fumarate was affected by acid hydrolysis (0.1M HCl), base hydrolysis (0.1M NaOH), and Oxidative (30% $H_2O_2$), the drug content was decreased from 99.69% to 94.72%, 99.69% to 91.6% and 99.69% to 96.91% respectively. Bisoprolol Fumarate was affected when subjected to temperature 50ºC and relative humidity 75% kept in open Petri dish for one month, it was observed that the sample was changed in color from white to green as showed in figure 3.

**Table1: The recovery percentage of Bisoprolol Fumarate after was exposed to extreme conditions.**

| Degradation Condition | Q% |
|---|---|
| Stability of Bisoprolol Fumarate in diluent for 72 hours | 99.50% |
| Photo Degradation for 72 hours. | 95.73% |
| **Thermal Degradation** | |
| **Dry Temperature** | |
| Bisoprolol Fumarate subjected to temperature 75ºC for 6 hours. | 99.22% |
| Bisoprolol Fumarate subjected to temperature 105ºC for one hour. | 98.04% |
| **Temperature with relative humidity** | |
| Bisoprolol Fumarate subjected to temperature 40ºC and relative humidity 75% kept in open Petri dish for one month. | 93.78% |
| **Hydrolysis condition** | |
| **Effect of Acid Hydrolysis** | |
| Bisoprolol Fumarate standard subjected to 0.1M Hydrochloric acid at standard condition. | 94.72% |
| Bisoprolol Fumarate standard subjected to 0.1M Hydrochloric acid at standard condition and left one hour. | 94.72% |
| **Effect of Base Hydrolysis** | |
| Bisoprolol Fumarate standard subjected to 0.1M Sodium hydroxide at standard condition. | 91.60% |
| Bisoprolol Fumarate standard subjected to 0.1M Sodium hydroxide at standard condition and left one hour. | 91.60% |
| **Effect of Oxidative Degradation** | |
| Bisoprolol Fumarate standard subjected to 30% hydrogen peroxide at standard condition | 96.91% |
| Bisoprolol Fumarate standard subjected to 30% hydrogen peroxide at standard condition and left one hour. | 96.91% |

**Figure 3: The chromatogram of Bisoprolol fumarate after being exposed to temperature 50°C and relative humidity 75% for one month.**

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