



Pre-formulation study of Bisoprolol as fast Dissolve Sublingual Tablet

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ABSTRACT

Fast dissolving drug delivery systems offer a solution for patients having difficulty in swallowing tablets. In this study, an attempt had been made to perform pre-formulation studies of bisoprolol as fast dissolve sublingual tablet, an antihypertensive by direct compression methods using sodium-starch-glycolate, croscarmellose-sodium, & crospovidone as superdisintegrant agent. The basic purpose of the pre-formulation activity is to provide a basis for the formulation approaches, to maximize the chances of success in formulating an acceptable product, optimizing drug product quality and performance. Preformulating activity including drug melting point; analytical wavelength (λ max) detections, drug-excipients physical & chemical compatibility by FT-IR, and Calibration curve of Bisoprolol were studied. It was discovered that the melting point was 100°C, and the UV spectral analysis revealed that the maximum value of λ was between 224 and 273 nm. The physicochemical compatibility studies results indicate that there was no interaction between bisoprolol and the excipients. Strong linear relationship obtained from calibration curve. Based on results, fast dissolving sublingual tablets of Bisoprolol can be prepared successfully by direct compression.

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1. Introductions:

1.1. Oral rout of administration:

Drug Delivery Systems (DDS) are methods used to administer therapeutic agents to patients. DDS can help expand markets and generate opportunities in the pharmaceutical industry, and despite advancements in drug delivery, the oral route remains the preferred method due to its low

cost, ease of administration, accurate dosage, and high patient adherence. [1]

Approximately 50–60% of all dose forms are tablets and capsules, making them the most often utilized drug forms. Tablets are widely used because to their portability, accuracy in manufacturing, and ease of usage. Because they

are more convenient to self-administer than other medications, they are recommended. [2]

1.2. Characterized of ideal properties of Fast Dissolve Tablets:

Fast dissolved tablets (FDTs), as a novel dosage form, have several characteristics to distinguish them from the more traditional dosage forms. Traditional tablet formulations generally don't require taste masking, because it is assumed that the dosage form will not dissolve until passing the oral cavity. Many oral suspensions, syrups, and chewable tablets simply contain flavors, sugars, and other sweeteners to overcome the bitter taste of the drug. [3] In fast dissolving/disintegrating tablets include sweeteners and flavors for taste-masking but many bitter drugs are not masked by taste masking agent. The primary methods of taste-masking include adsorption onto or complexation with carriers and spray coating of drug particles. [2]

1.3. Criteria for an active pharmaceutical ingredient (API) to be formulated into Fast Dissolve Tablets dosage form:

- The drugs could not cause irritations in the oral cavity, especially for long term treatment.[4, 5]
- It should have a pleasant taste or be compatible with taste masking agent. [4, 6]
- The drug should leave no residue in the mouth after oral administration.
- The maximum weight of the end product should be ≤ 500 mg. High loading of drug substance may affect the end product and prolongs the disintegration time. [4, 7]

1.4. Bisoprolol overview:

Bisoprolol Fumarate (BF) is selective beta blocking agent, which is used for the management of hypertension & prophylaxis treatment angina pectoris and heart failure [8, 9]. At therapeutic dosages, bisoprolol lacks intrinsic sympathomimetic activity (ISA) and membrane-stabilizing qualities. It is a synthetic β 1-selective (cardio selective) adrenoceptor blocking drug. Its

affinity for the β 2-receptor found in adipose cells, bronchial smooth muscles, and blood vessels is modest. It has no effects mediated by β 2 receptors at lower dosages. In addition to lowering cardiac output and heart rate, bisoprolol also prevents the kidneys from releasing renin. Many older persons have trouble swallowing pills due to their diminished capacity to do so. [10]

Bisoprolol is classified as a Class I API according to the current Biopharmaceutics Classification System (BCS). [11]

By contrast, the free base form of Bisoprolol has low aqueous solubility and its water solubility at 25°C was reported as 2.24 mg/ml. [12, 13]

Bisoprolol fumarate is marginally soluble in acetone and ethyl acetate, but it is highly soluble in water and methyl alcohol. It is also easily soluble in alcohol, chloroform, and glacial acetic acid. Bisoprolol and bisoprolol fumarate were shown to have partition coefficients of 0.93 and -1.10, respectively. A log P value for Bisoprolol also was reported as 2.15. [10]

Bisoprolol fumarate chemical name:(e)-but-2-enedioic acid;1-(propan-2-ylamino)-3-[4-(2-propan yloxyethoxy methyl) phenoxy]propan-2-ol. [10]

appeared as a slightly hygroscopic, white or nearly white powder. [10]

1.5. Super disintegrant (SD):

Disintegrating agents are compounds that are frequently added to tablet formulations to help break apart the compacted mass into the fundamental particles to make it easier for the active ingredients to dissolve or release when the tablet is placed in a fluid environment. They support the tablet matrix's penetration and dispersion by moisture. SD are new materials that have recently been discovered to enhance disintegration processes. Another type of super-absorbing substance with specifically designed swelling qualities is SD. These materials are intended to swell quickly rather than to absorb a sizable volume of water or other aqueous fluids.

They are physically scattered throughout the dosage form's matrix and will enlarge when exposed to a moist environment. These more recent compounds have increased mechanical strength and disintegration efficiency, making them more efficient at lower concentrations. SD are primarily employed in solid dosage forms at low concentrations, approximately 1–10% by weight of the dosage unit's total weight. They typically have small, porous particles, allowing for quick tablet dissolution in the mouth without unpleasant gelling or large particle sensation. Additionally compressible, the particles increase the tablet's hardness and friability. Effective SD improve the compressibility and compatibility of formulations containing high dose medications while having no negative effects on their mechanical strength. In general, 10–40 g of water or another aqueous media can be absorbed by 1 g of SD. Following absorption, swelling pressure and isotropic swelling of the SD particles produce stress-concentrated regions where a gradient of mechanical characteristics exists, causing the entire structure to shatter a part. [14, 15]

1.5.1. Advantages of Super disintegrant:

- Required in less concentration.
- Compatible with many drugs and excipients.
- Does not affect compressibility and flowability [16].

1.5.2. Types of Super disintegrants:

The super disintegrants can be classified into two categories based on their availability:

- Natural super disintegrants.
- Synthetic super disintegrants. [17, 18]

The disintegration of dosage forms depends upon various physical factors of disintegrants/super disintegrants. [19]

2. Aim of work:

The main aim of the work is to study the physicochemical properties of materials that enter in formulation of bisoprolol as fast dissolve sublingual tablet.

3. Material and methods:

Bisoprolol Fumarate as an active pharmaceutical ingredient. The Super disintegrant as Croscopvedone, Croscarmellose Sodium, and Sodium starch glycolate, Avicel PH102, D (-) Mannitol, Magnesium stearate, Aerosol 200. All materials were obtained as a gift sample from Yemen Egyptian Pharmaceutical Company (YEPHCO), Sanaa, Yemen. Other materials used in the study were of pharmaceutical grade. Equipment's used for the research work UV-VIS. Spectrophotometer, HPLC, Analytical Balance, Oven Binder, Centrifuge Hettich, Shaker Platform, PH Meter, Heat – Stir, Tab Density Tester, Homogenizer Machine, Volumetric Flask, Magnetic rod, Pipette, and Melting point detectors. Other Equipment's used in the study were of pharmaceutical grade.

3.1.Melting point:

The melting point of a drug was determined using a melting point apparatus (Bibby/UK), and the resultant number was contrasted with the drug's official melting point value [1].

3.2.Finding the bisoprolol's analytical wavelength (λ max):

Accurately weighed 20 mg of bisoprolol fumarate were dissolved in water in a 100 ml volumetric flask to create a standard stock solution of 200 μ g/ml. The volume was then increased to 100 ml with water. Four milliliters (ml) were pipetted into a 100 ml volumetric flask from the standard stock solution. With water, the volume was increased to 100 ml. The final solution, which contained 8 μ g/ml, was scanned using a UV-VIS Spectrophotometer from SHIMADZU business between 200 and 400 nm. [1]

3.3.Studies on the physical compatibility of drugs and drug-excipients:

By making solid admixtures of the drug and excipients in a 1:1 ratio, the physical compatibility of various formulation excipients with the drug component bisoprolol was examined. Every ten days, the admixtures were checked for color changes in sealed glass vials

kept in a stability chamber at room temperature and $30 \pm 20^\circ\text{C}/65 \pm 5\% \text{RH}$. This preformulating study aids in determining how excipients affect the characteristics and formulation design of the finished product [1].

3.4. Studies on chemical compatibility using FT-IR:

The drug's and the excipients' IR spectra were examined using FT-IR and the KBr pellet method. The spectra were scanned between $4000\text{-}500\text{ cm}^{-1}$ at a modest pace in order to determine the peak values and functional groups that were present in the samples. To ascertain whether the medication and the excipients were chemically compatible, the findings were compared to standard values. [1]

3.5. Calibration curve:

In this work, the calibration curve was used to determine the linearity of the HPLC method for the determination of Bisoprolol in standard powder. The curve was obtained by plotting the peak area of Bisoprolol standard against its concentration in the range of $8\text{-}100\text{ }\mu\text{g/mL}$, and the linearity was evaluated by calculating the regression equation and correlation coefficient [20].

Standard solution preparation:

The standard solution was prepared by dissolved 100 mg Bisoprolol Fumarate (reference substance) in 25 mL methanol, and after complete dissolution (about 5 min in an ultrasonic bath) it was diluted with the mobile phase to a volume of 100 ml to obtain a solution with a concentration of 1 mg/mL ($1000\text{ }\mu\text{g/ml}$). The obtained solution was diluted with the mobile phase to obtain concentrations in the range of 8 to $100\text{ }\mu\text{g/ml}$. All working solutions were prepared by diluting the stock solution with the mobile phase [20].

Analytical determination:

The analytical analysis was conducted using a chromatographic column, specifically the BDS Hypersil C8 ($150\text{ mm} \times 4.6\text{ mm}$, 5μ). The ratio of methanol, triethylamine, and water (v/v/v) is the mobile phase utilized in the HPLC technique

development for the analysis of bisoprolol in standard powder. The mobile phase flow rate was 1 mL/min , UV detection being carried out at a wavelength of 225 nm [20, 21].

4. Results and Discussion:

4.1. Melting point:

The melting point of Bisoprolol, a drug used to treat cardiovascular disease, was determined to be 100°C using a capillary method. This value falls within the range specified in official limits, indicating that the drug can be formulated into stable and bioavailable dosage forms that can be mass produced.

4.2. Finding the bisoprolol's analytical wavelength (λ_{max}):

Figure (1) displays the UV absorption spectra of 20 ppm bisoprolol in acetonitrile. With a pair of matching, 3.5 ml quartz cuvettes, the Shimadzu UV-VIS Spectrophotometer was used to record the UV spectra of BF in acetonitrile. The drug's and the blank's absorption spectra were measured between $200\text{ and }400\text{ nm}$ in wavelength. At 224.20 and 273.80 nm , the molar absorptivity of BF was $17,572.5$ and $2362.13\text{ Lmol}^{-1}\text{cm}^{-1}$, respectively.

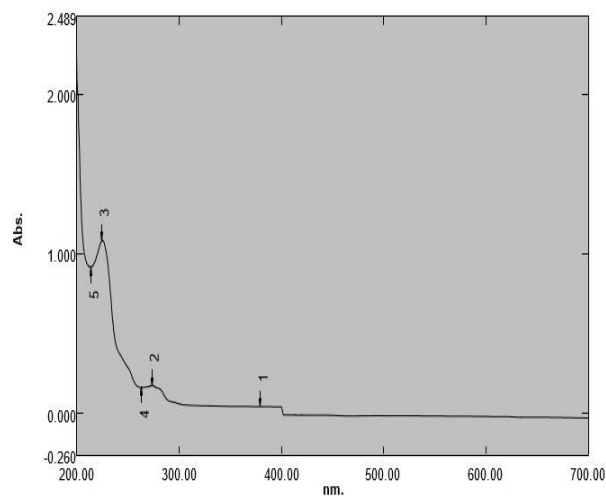


Figure (1). absorption spectrum of bisoprolol fumarate dissolved in acetonitrile.

4.3. Studies on the physical compatibility of drugs and drug-excipients:

Physical compatibility studies are important for ensuring that a solid dosage form of a drug is stable and effective. These studies are performed

visually and examine whether the drug and other components, such as excipients, are physically compatible with each other. The study's findings, which are shown in table No. (1), show that the physical description of the medicine and excipients remained constant throughout the

investigation, indicating that they were physically compatible.

Table (1). Studies of the drug's physical compatibility with the excipients

Drug + Excipients	An explanation on the first day	RT, 35±20C/65±5% RH IN days		
		10th	20th	30th
BISO	Crystalline white powder	NS	NS	NS
CP	Crystalline white powder	NS	NS	NS
CCS	White or greyish white powder	NS	NS	NS
SSG	White, free-flowing hygroscopic powder	NS	NS	NS
MNT	Free flowing white crystalline powder	NS	NS	NS
AVI	Crystalline white powder	NS	NS	NS
AER	Crystalline white powder	NS	NS	NS
Mg S	Crystalline white powder	NS	NS	NS
BISO + CP	Powdery off-white to yellow	NS	NS	NS
BISO + CCS	Powdery off-white to yellow	NS	NS	NS
BISO + SSG	Powdery off-white to yellow	NS	NS	NS
BISO + MNT	Powdery off-white to yellow	NS	NS	NS
BISO + ALL	Off white to yellow free flowing powder	NS	NS	NS

BISO – Bisoprolol, CP – Crosspovidone, CCS – Croscarmellose sodium, SSG – Sodium starch glycolate, MNT – Mannitol, AVI –Avicel PH 102, AER–Aerosel 200, Mg, S– Magnesium stearate, NS – Nothing Shifts.

4.4. Studies on chemical compatibility using FT-IR:

The study describes a chemical compatibility study of Bisoprolol, a drug, and other excipients using an IR spectral analysis method. The study's findings, which are displayed in Figs. (2) through (15), demonstrate that there was no interaction between Bisoprolol and the excipients because

all of the distinctive peaks for the drug's pure form and its physical mixture were present. This implies that the medicine and excipients are compatible with each other both chemically and physically, which is crucial for the solid dosage form's durability and potency.

Studies on chemical compatibility using FT-I

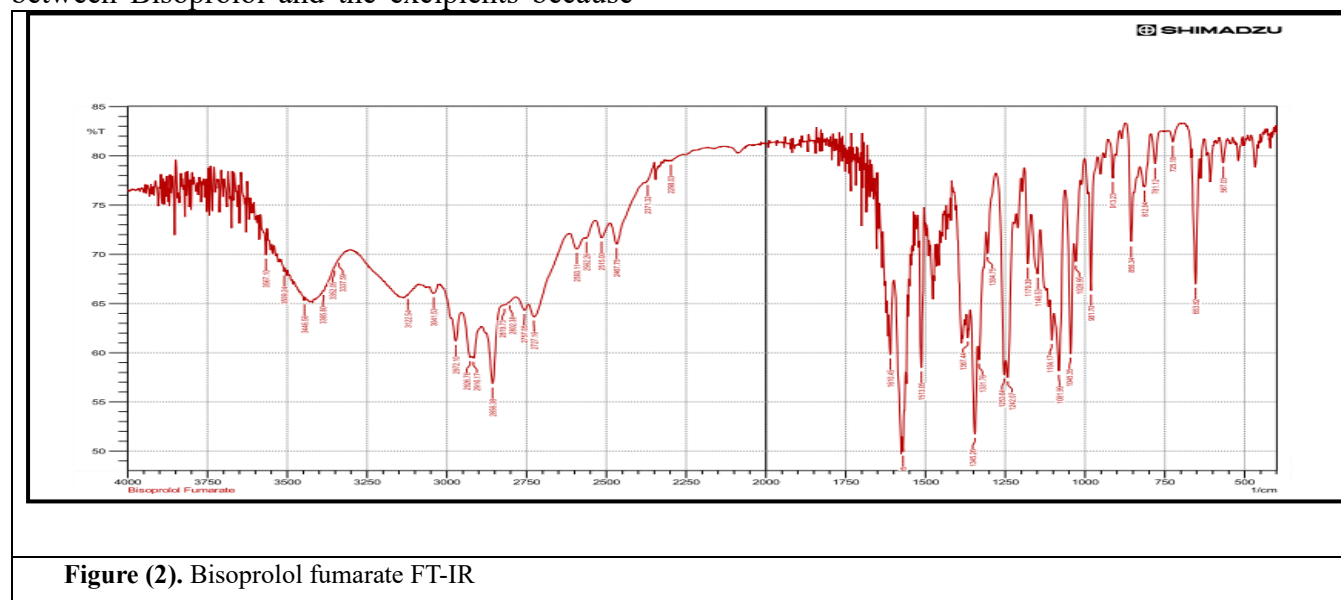


Figure (2). Bisoprolol fumarate FT-IR

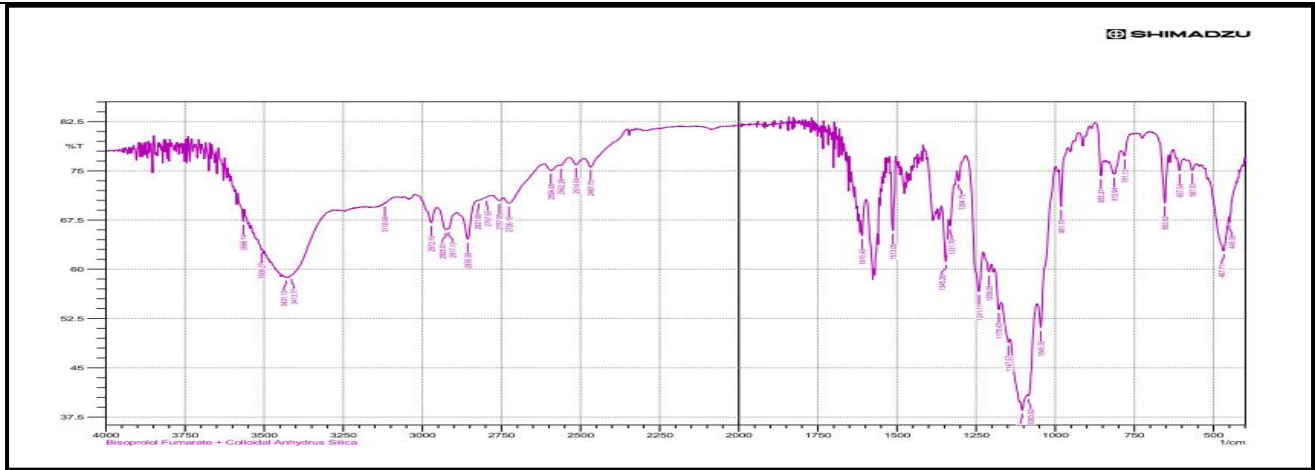


Figure (3), Bisoprolol fumarate + colloidal anhydrous silica

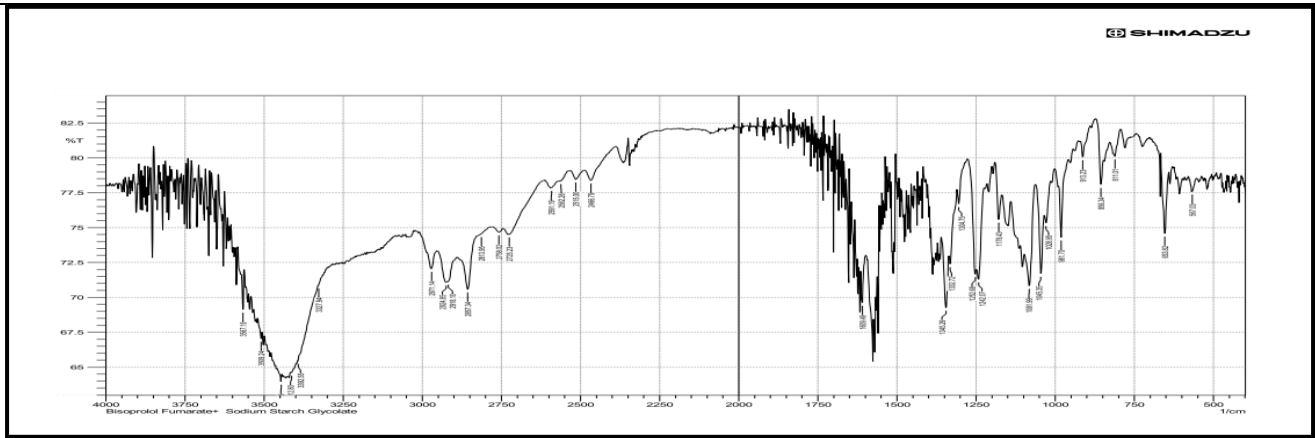


Figure (4), Bisoprolol + sodium starch glycolate

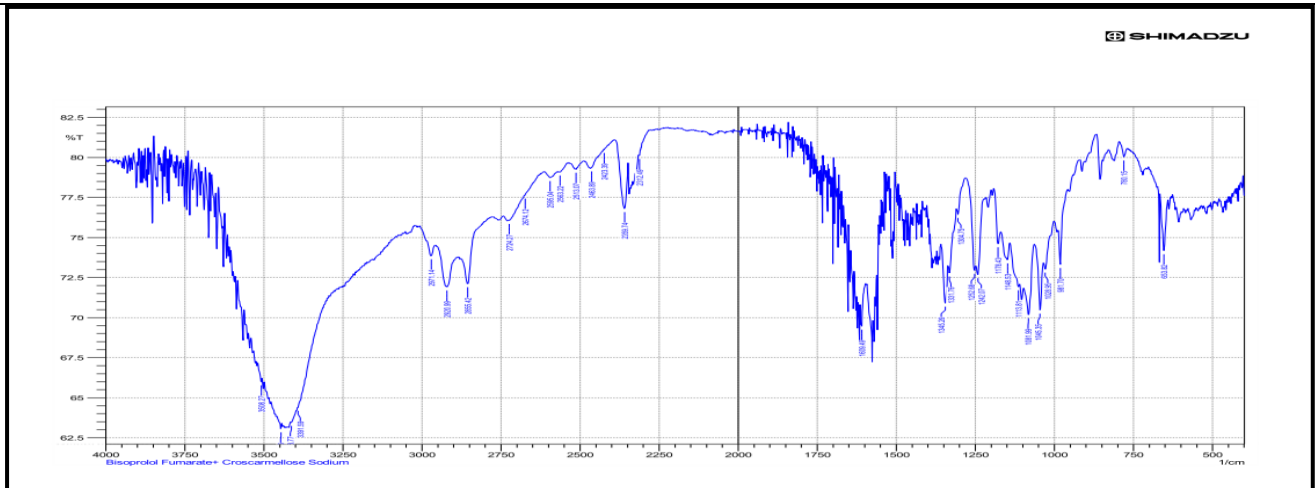


Figure (5), Bisoprolol + croscarmellose sodium FT- IR

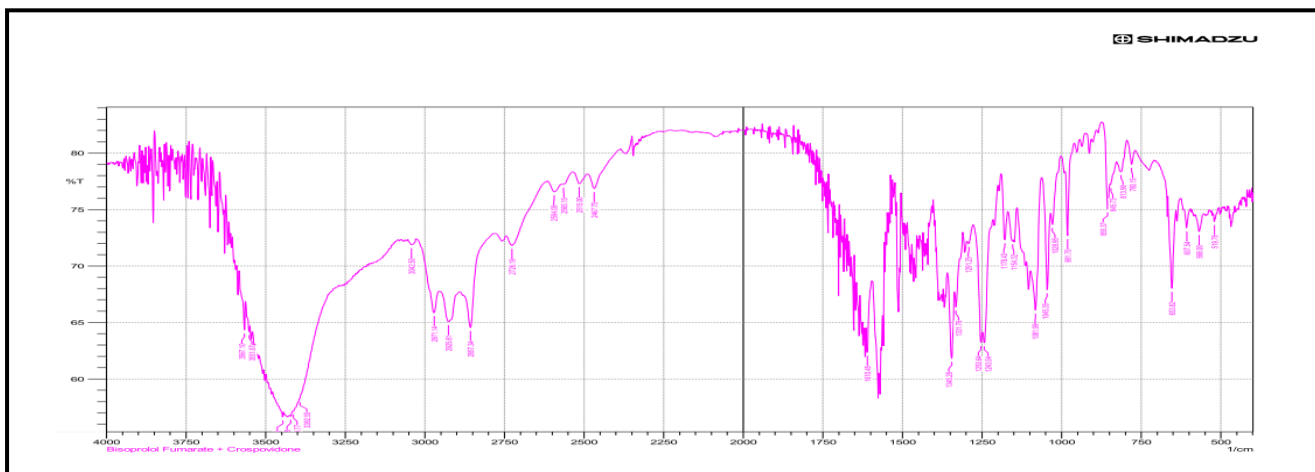


Figure (6), Bisoprolol + crospovidone FT-IR

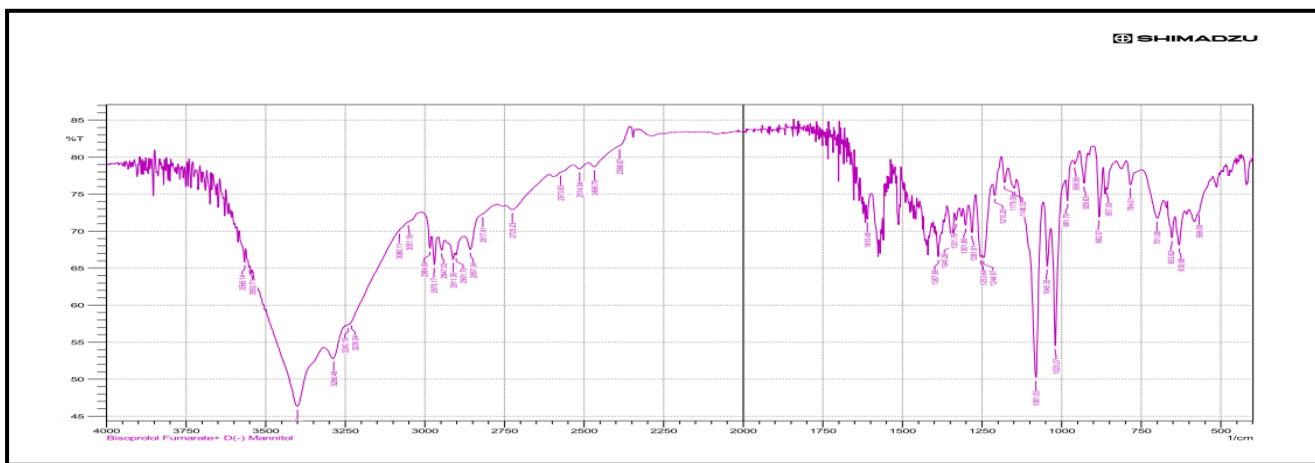


Figure (7), Bisoprolol + D (-) Mannitol FT-IR

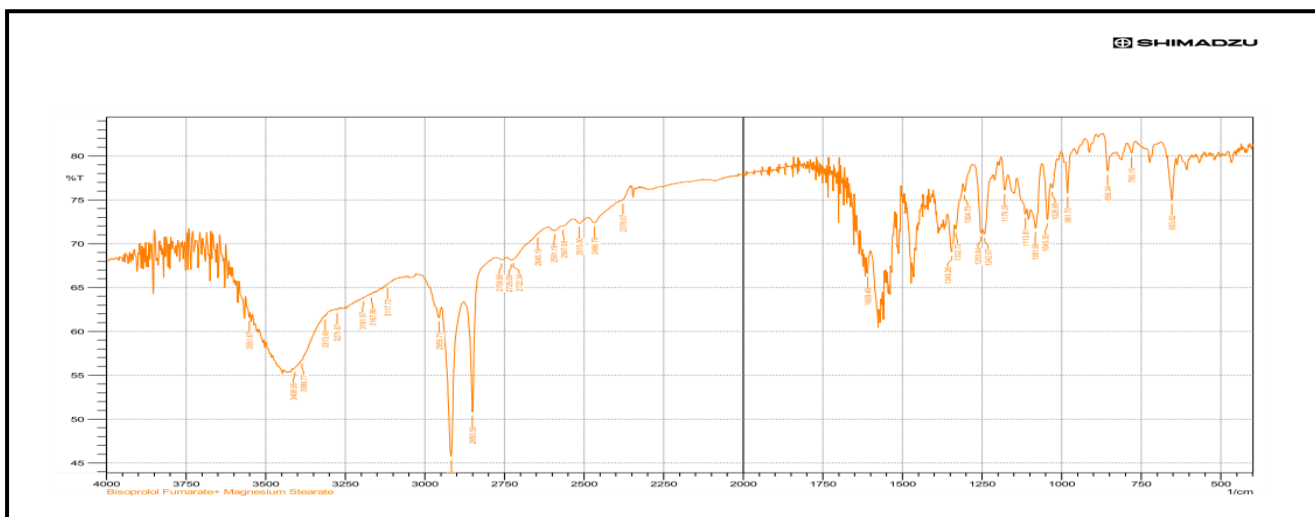


Figure (8), Bisoprolol + Magnesium stearate FT-IR

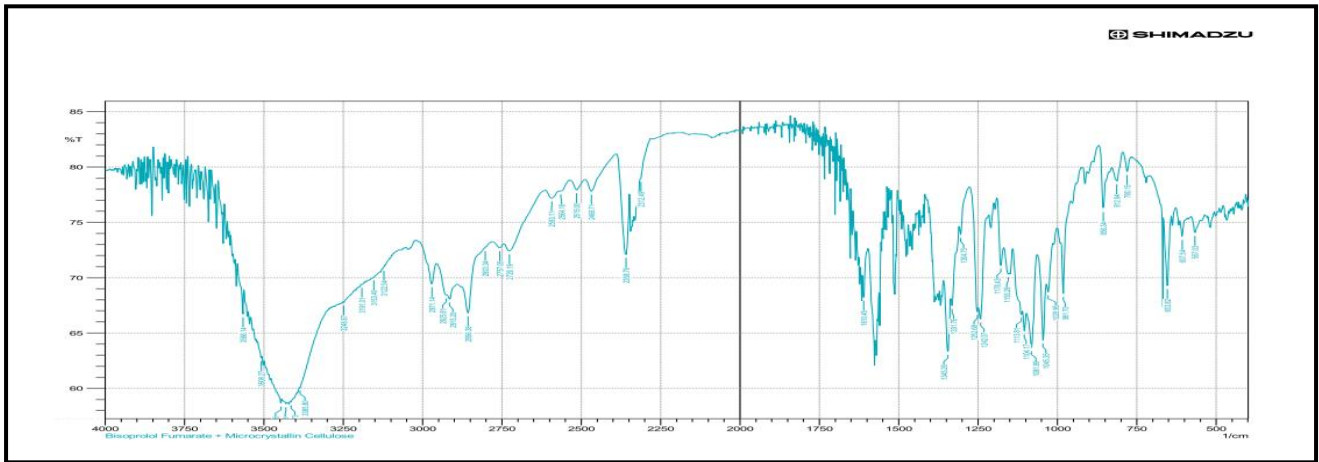


Figure (9), Bisoprolol + Microcrystalline Cellulose FT-IR

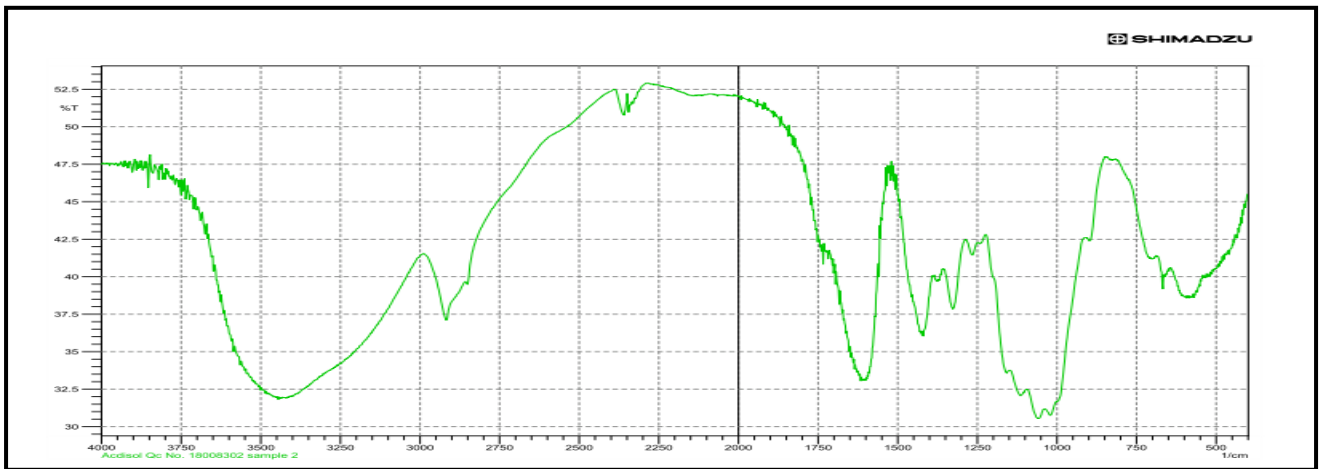


Figure (10), crosscarmellose FT-IR

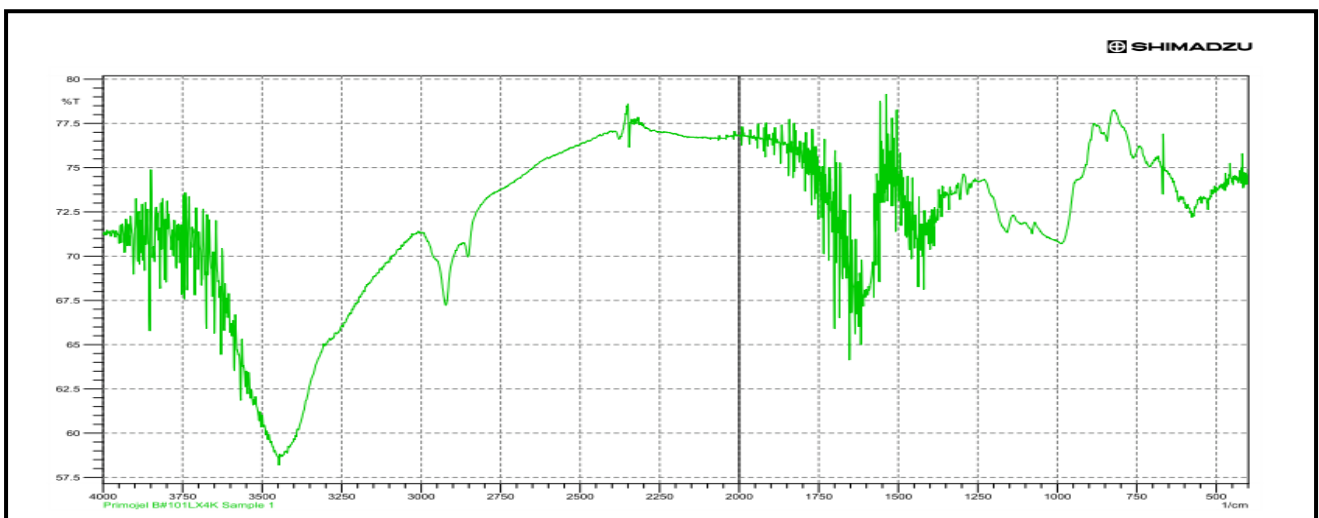


Figure (11), Sodium starch glycolate FT-IR

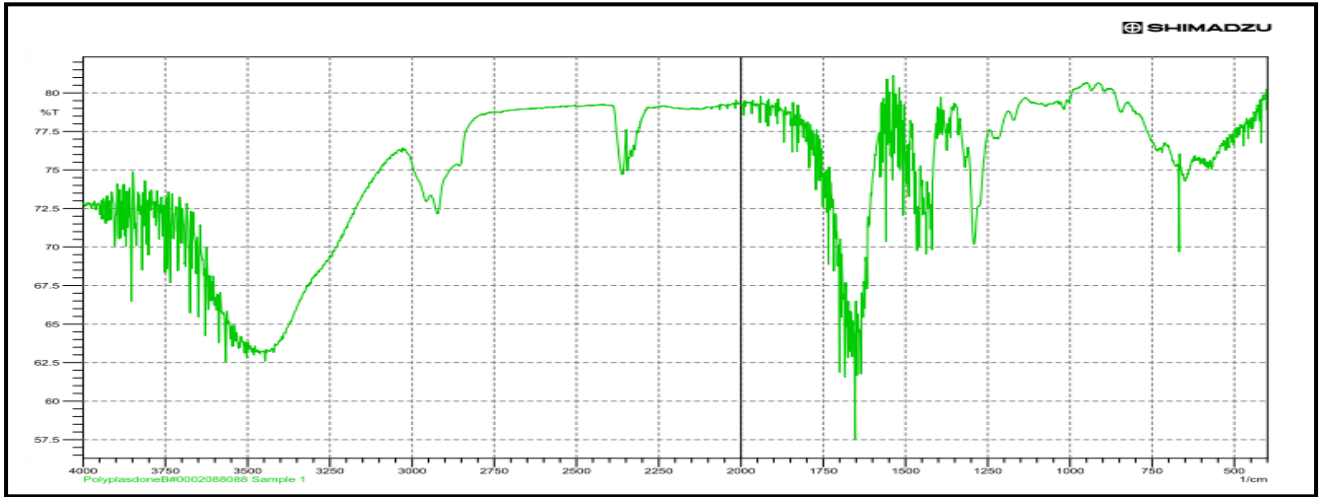


Figure (12), Crospividone FT-IR

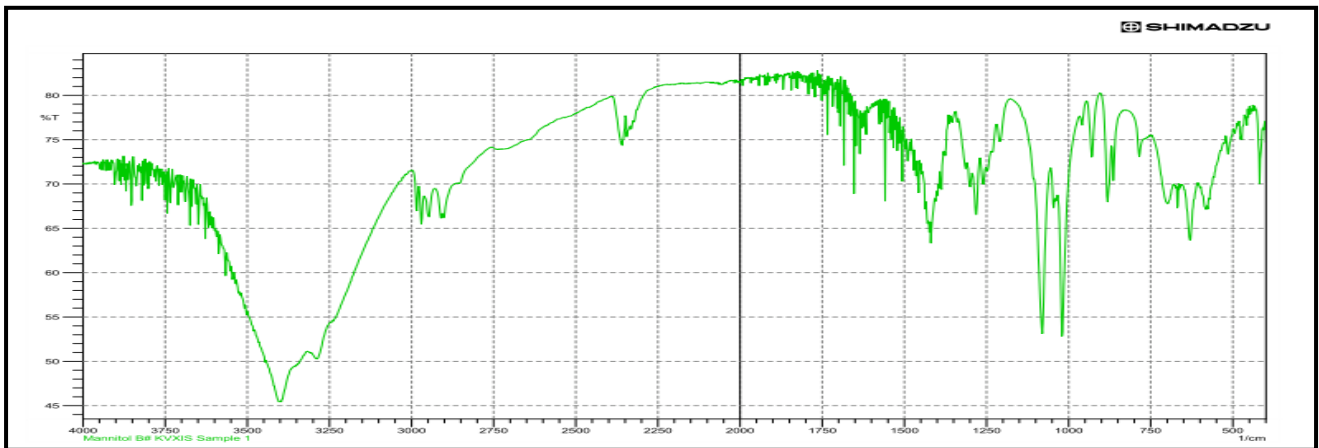


Figure (13), Mannitol FT-IR

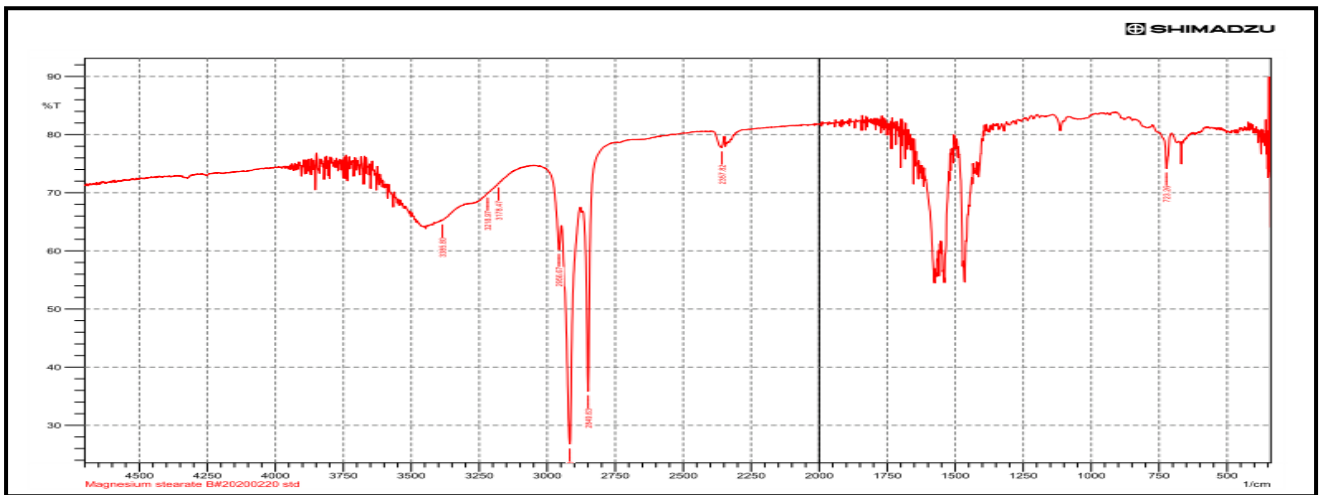


Figure (14), Aerosol FT-IR

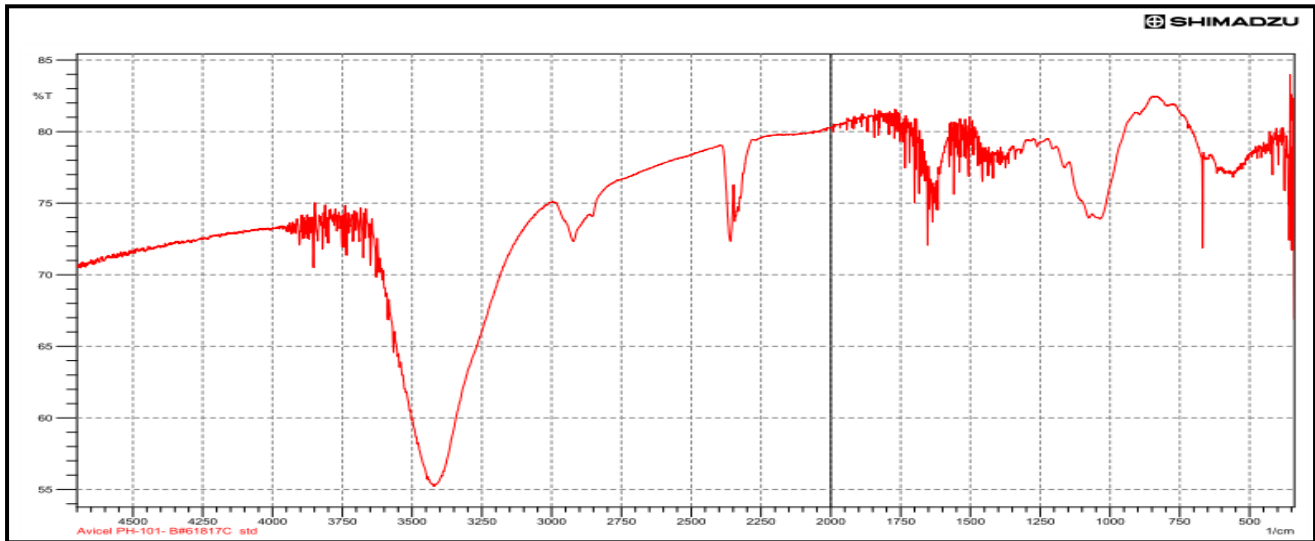


Figure (15), Avicel FT-IR

5. Conclusion:

- Based on the results obtained from the pre-formulation study: the melting point of Bisoprolol was determined to be 100°C. This value falls within the range specified in official limits, indicating that the drug was pure.
- Based on the results obtained from the absorption spectra of the Bisoprolol were recorded, with the values of the molar absorptivity were 17572.5 and 2362.13 Lmol⁻¹cm⁻¹ at 224.20 and 273.80nm, respectively.
- Based on the results obtained from the physical compatibility testing show that the medicine and excipients were physically compatible, as evidenced by the fact that the physical description did not alter during the trial. Based on the results obtained from the FT-IR spectral interpretation results show that, generally, there was no influential change of any characteristic peaks, which confirms the absence of chemical interaction between Bisoprolol and Excipients.
- Based on the results obtained from calibration curve preparation indicate a

strong linear relationship between the concentration of Bisoprolol and the corresponding peak area obtained from the HPLC, at λ of 225, analysis.

5.1. Calibration curve of Bisoprolol:

The linearity curve refers to the relationship between the concentration of Bisoprolol and the peak area measured by the HPLC method. The study found that the HPLC method shows area of linearity, with ranges of 8-100 $\mu\text{g/ml}$. The high R² value indicates that the calibration curve generated for Bisoprolol determination is highly reliable and accurate within the concentration range of 8-100 $\mu\text{g/ml}$. The value (R² = 0.9998) refers to the coefficient of determination, which is a statistical measure indicating the goodness of fit of a regression line to the data points. In this case, it suggests a strong linear relationship between the concentration of Bisoprolol and the corresponding peak area obtained from the HPLC, at λ of 225, analysis. As shown in table (2) & Fig. No. (16)

Table (2). The determination of bisoprolol by hplc (clibration curve)

Concentration Range of Bisoprolol $\mu\text{g/ml}$	Peak Area (AUC)
0	0
8	217550.67
10	272697
20	534966.33
30	802881.67
40	1072418
50	1319880.33
60	1588002.33
70	1863763.33
80	2116169.33
90	2389136
100	2700072.33

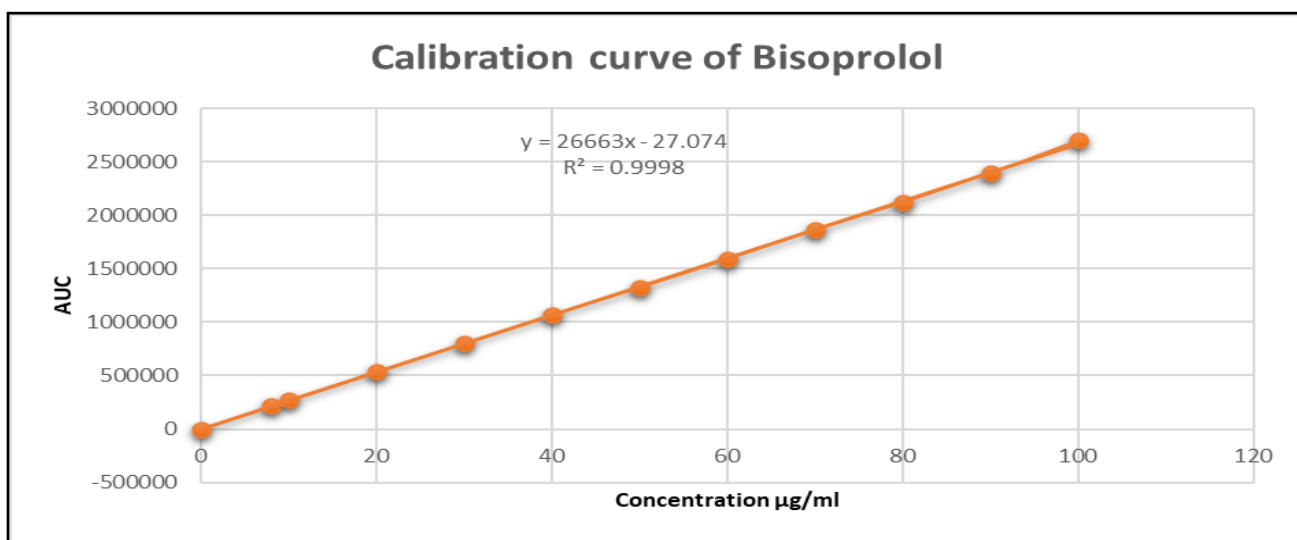


Figure (16). Linearity curve results in the determination of bisoprolol by hplc in the range 8 - 100 $\mu\text{g/ml}$.

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