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FORMULATION AND EVALUATION OF SUBLINGUAL TABLET OF BISOPROLOL FUMARATE FOR THE TREATMENT OF HYPERTENSION

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Abstract

Bisoprolol fumarate is a selective β1-blocker used in the treatment of hypertension. The present study focuses on the formulation and evaluation of sublingual tablets to provide rapid onset of action and avoid first-pass metabolism. Tablets were prepared by direct compression using suitable superdisintegrants. The formulations were evaluated for pre- and post-compression parameters such as flow properties, hardness, friability, drug content, wetting time, and disintegration time. All formulations showed acceptable results within pharmacopeial limits. The optimized batch exhibited rapid disintegration and faster drug release in dissolution studies, indicating improved bioavailability. Thus, sublingual tablets of bisoprolol fumarate offer an effective alternative to conventional oral dosage forms for quick management of hypertension..

Keywords: Bisoprolol fumarate, Sublingual tablets, Hypertension, Direct compression.

1. Introduction

Sublingual Tablet's that disintegrate or dissolve rapidly in the patient's mouth are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where potable liquids are not available. Because the drug can be absorbed completely or in part into the circulatory system from blood vessels located in the sublingual mucosa, the sublingual route skips the hepatic first-pass metabolic processes and results in a rapid onset of effect. The sublingual routes is suitable for medications with short delivery times, as well as those that are rendered inactive by the GI tract's proteolytic enzymes or first-pass intestinal or hepatic metabolism [1].

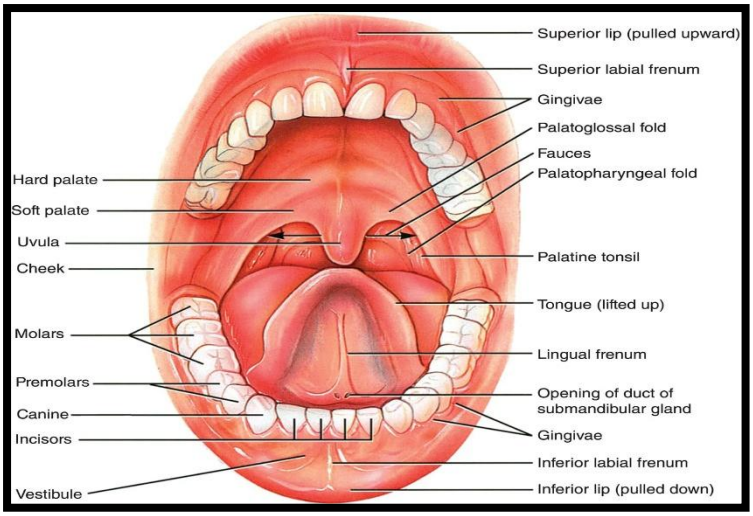
The positive aspect of the sublingual drug administration method is that the medicine can enter the circulatory system right way, avoiding the breakdown of enzymes in the gut and liver. Patients who are young and elderly benefit most from these formulations [2]. Additionally, great drug penetration is made possible by the sublingual mucosa and the amount of blood supply in the sublingual area, which results in high plasma drug concentrations with quick onset of action [3].

Sublingual tablets are defined by the US Food and Drug Administration (FDA) as "a solid dosage form carrying medicinal substance or active ingredient which disintegrates rapidly usually within a period of seconds when placed upon the tongue [4]. A very thin oral strip that is simply placed on the patient's tongue or any oral mucosa tissue is used to distribute the dosage. The film is quickly hydrated by the saliva, adheres to the application site, and then quickly disintegrates and dissolves for releasing the medication for oral cavity absorption. This will preserve the quick dissolving characteristic and enable gastrointestinal absorption to be performed when swallowed [5].

A systolic blood pressure of 140 mmHg or higher and a diastolic blood pressure of 90 mmHg or higher considered as Hypertension. It blocks the renin angiotensin system by inhibiting the effects of angiotensin II at its receptors. The renin-angiotensin system is thought to be particularly important in hypertension and plays an important role in blood pressure regulation. It has been shown that losartan is better than earlier peptide receptors antagonists and angiotensin converting enzyme (ACE) inhibitors due to their improved tolerance, selectivity, and specificity. Bisoprolol fumarate is typically

used to treat essential hypertension because it has less adverse effects, such as cough. It is easily absorbed and quickly metabolized by the cytochrome P-450 system in the liver to produce the active metabolite EXP-3174 [6].

Fig 1. Schematic Representation of Sublingual Tablet.



NEED FOR DEVELOPMENT FOR SUBLINGUAL TABLET:

Patient who struggle to chew and swallow.

Patient's non-compliance because they are afraid of choking.

Elderly depressed individuals who could have trouble swallowing solid dosage forms.

A patient with limited access to water or who travels a lot [7].

ADVANTAGES OF SUBLINGUAL TABLET:

Easy administration to patients, including children, the elderly, and people with mental illnesses, who refuse to take a tablet.

Accurate dosing and ease of drug administration in contrast to liquid formulations.

Patients who are travelling and do not have rapid access to water will find it advantageous since the dosage form can be swallowed without water.

The "bitter pill" perception of medications is altered by the good moth feel feature, especially for young patients [8].

Rapid drug absorption and dissolution, leading to a prompt onset of action [9].

DISADVANTAGES OF SUBLINGUAL TABLET:

Sublingual drug administration is generally regarded as undesirable for long-term administration since it affects with consuming food, drinking beverages, and speaking.

Despite this, sustained delivery systems are not a good fit for this location [10].

When a patient is unconscious or uncooperative, sublingual medication are not administered.

Since smoking narrows blood vessels, the patient should refrain from smoking when using sublingual medicine. This will reduce the medication's absorption [11].

MATERIAL AND METHODS:

Materials: Core Analyticals Pvt.Ltd supplied the API Bisoprolol Fumarate; mannitol we used as a directly compressible material; microcrystalline cellulose served as a diluent and disintegrating agent; crosspovidone was a major super disintegrating agent; starch was used as a binder; sodium saccharine was used as a sweetening agent to mask the bitter taste; and talc was used to lubrication. The sublingual formulation was created using the direct compression method using the given substances [12].

Methods: Direct Compression was used to create Bisoprolol Fumarate or dispersible pills. 20mg of the medication were mixed and homogenously triturated until a homogenous mixture was discovered. A tablet punching machine was used to crush the resulting slurry into tablets in 8mm die cavities. Five distinct formulas, table, and quantity were used to create 15 formulations which are listed below [13].

Table 1. Formulation of Bisoprolol Fumarate Tablet.

Ingredients	F1	F2	F3	F4	F5
Bisoprolol Fumarate	20	20	20	20	20
Mannitol	129	129	129	129	129
MCC	36	32	30	28	26
Crosspovidone	4	8	10	12	14
Starch	5	5	5	5	5
Sod. Saccharine	3	3	3	3	3
Talc	3	3	3	3	3
Total (mg)	200	200	200	200	200

EVALUATION PARAMETERS:

Triturated or homogenous blend formulation's micromeretic characteristics.

Preformulation Study of Homogenous Powder:

FTIR: FT-IR and the KBr Pellet method were used to analyse the IR spectra of the medication and the excipients. To identify the high point values and functional groups that existed in the samples, the spectra were scanned t as moderate speed between 4000 and 500 cm^{-1}. The results were when compared to standard values in order to determine whether the drug and the excipients were chemically compatible. The outcome is shown in Fig.4 & 5 [14].

Flow Parameter of Powder: Numerous factors, including bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio, were used to calculate the flow properties.

Bulk Density: 5gm of Bisoprolol Fumarate and an excipient mixture were added to a 10ml measuring cylinder. The sample's volume and weight were computed. The following formula was used to calculate the powder's bulk volume and weight. The outcome shown in table 3 [15].

$$Bulk\ Density = \frac{Mass}{Bulk\ Volume}$$

Tapped Density: A 10ml a measuring cylinder was filled with 5g of Bisoprolol Fumarate and an excipients combination. It was tapped 100 times, and the formula was used to determine the change in volume and weight. The outcome shown in Table 3 [16].

$$Tapped\ Density = \frac{Mass}{Tapped\ Volume}$$

Angle of Repose: The funnel method was used to ascertain it. The funnel was filled with a precisely weighed 5gm powder of Bisoprolol Fumarate and additional excipients, with its tips positioned around 2cm (h) above the surface. The mixture was released from the funnel until the bottom of the funnel was touched by the tip of the powder pile. The formula was used to obtain the mean diameter (®), height, and angle of repose (°). The outcome shown in table 3 [17].

$$Angle\ Of\ Repose\ (\emptyset) = tan - \frac{1h}{r}$$

Carr's Index: The following formula is used to calculate Carr's Index: [18]. The outcome shown in Table 4.

Carr's Index (%) $= \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} \times 100$

Hausner's Ratio: This serves as an intermediary for powder flow ease. It is calculated by following formula. The outcome shown in Table 3 [19]:

$$Hausner'sRatio = \frac{Tapped\ Density}{Bulk\ Density}$$

Physical Evaluation Test:

Solubility, pH, appearance, thickness, and diameter, hardness, friability, weight fluctuation, wetting time, water absorption ratio, dissolution, and disintegration were among the post-compression quality control tests performed on the tablets The outcomes was given in Table 4,5,6.

Solubility: Soluble in both organic and inorganic solvents, including water and methanol.

Appearance: Shape, colour, and odour of the tablets were assessed [20].

Thickness & Diameter: Vernier calipers were used to measure the tablet sizes [21].

Hardness Test: The purpose of this test was to ascertain whether the tablets would be able to endure the rigors of handling and transit encountered in the manufacturing facility, in the drug distribution systems, and in the field through the hands of end users (patients/consumers). A digital hardness tester was used to measure the hardness of 5 randomly chosen tablets from each batch. The average hardness value was noted [22].

Friability Test: 5 different formulations of tablets were already weighed and placed in a friabilator to conduct this test. Roche friabilator and spin for 4 minutes at 25rpm. The percentage of friability was computed after the tablet size was decreased and reweighed.

$$Friability\ (\%) = \frac{W1 - W2}{W1} \times 100$$

Where:

W1 = Initial weight of tablets before test

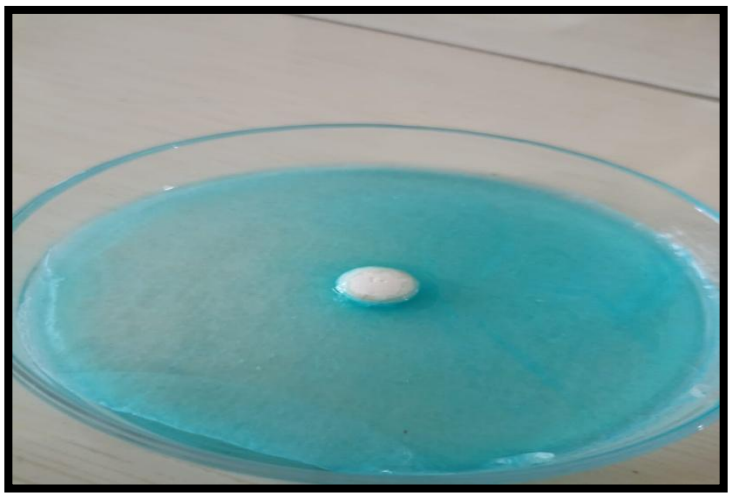
W2 = Final weight of tablets after test (after dust removal)

Weight Variation: From each formulation, twenty pills were chosen at random, weighed separately, and the average weight was computed [23].

$$Percentage\ Deviation = \frac{Individual\ Weight - Average\ Weight}{Average\ Weight} \times 100$$

Wetting Time: The tablet was positioned in the middle of a dish that was filled with 2 layers of absorbent paper. The excess water was drained out of the dish after the paper had been properly wetted with saline phosphate buffer (pH- 6.8). A stopwatch was then used to record how long it took for the water to permeate the entire tablet from the wetted absorbent paper. The outcomes are displayed in Fig2.

Fig 2: Representation of wetting time.



Water Absorption Ratio: 6ml of saline phosphate buffer (pH 6.8) were added to a tiny petri dish along with a piece of tissue paper that has been folded twice. After placing a tablet on the tissue paper, it was let to get totally saturated. After that, the tablet was weighed. The following formula was used to calculate the water absorption ratio, or R [24].

$$R = \frac{Wa - Wb}{Wb} \times 100$$

Where:

Wb = Weight of the tablet **before** water absorption.

Wa = Weight of the tablet **after** water absorption.

Dissolution Studies: All formulations were subjected to dissolution experiments using the USP paddle method (Apparatus II) with phosphate buffer 6.8 as the dissolving medium (300 ml) at 50rpm. Equivalent volumes of plain dissolving medium were used to replace the samples, which were routinely removed at appropriate intervals. Spectrophotometric analysis of the materials was performed at 250nm.

Disintegration Studies: The traditional tablet test outlined in the pharmacopoeia was used to determine the disintegration time of sublingual tablets. The amount of time needed for the tablets to completely disintegrate that is, to leave no residues on the screen is measured after they are put in the disintegration tubes [25].

RESULTS AND DISCUSSION:

Determination of Absorption Maxima of Bisoprolol Fumarate:

Table 2: Standard Calibration Curve of Bisoprolol Fumarate

Concentration (mg/ml)	Absorbance
0	0
2	0.123
4	0.245
6	0.371
8	0.498
10	0.612

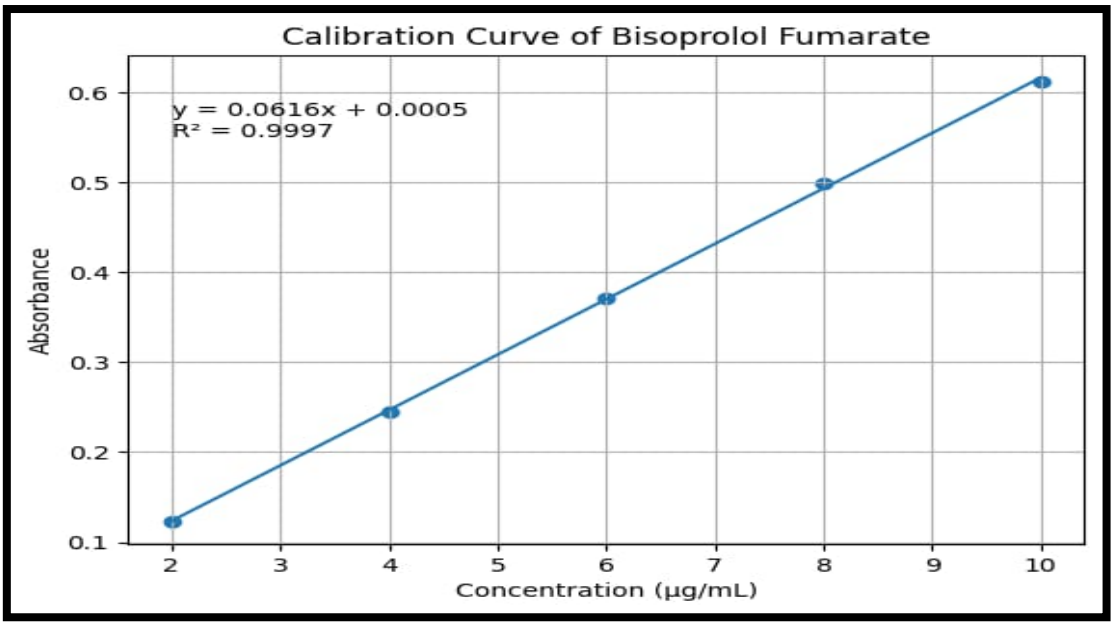


Fig 3: Calibration curve of Bisoprolol Fumarate.

FTIR Studies:

Fig 4: FTIR spectra of Bisoprolol Fumarate pure drug.

Fig 5: FTIR spectra of physical mixture.

Preformulation Study of Homogenous Powder:

Table 3: Preformulation studies of Homogenous Powder

Batch No	Bulk Density (gm/cm³)	Tapped Density (gm/cm³)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (˚)
F1	0.48	0.58	17.24	1.20	27

F2	0.46	0.57	19.30	1.24	29
F3	0.44	0.56	21.43	1.27	31
F4	0.45	0.56	19.64	1.2	29
F5	0.40	0.54	25.93	1.35	34

Physical Evaluation Test:

Table 4: Physical Parameters

Sr.No	Parameters	Observed value Reported Value
1	Colour	White
2	Odour	Odourless
3	Taste	Slightly Bitter
4	Melting Point	101˚C
5	Solubility	Very soluble in water & Methanol.
6	Texture	Powder

Evaluation Parameters:

Table 5: Evaluation Parameters of Tablets.

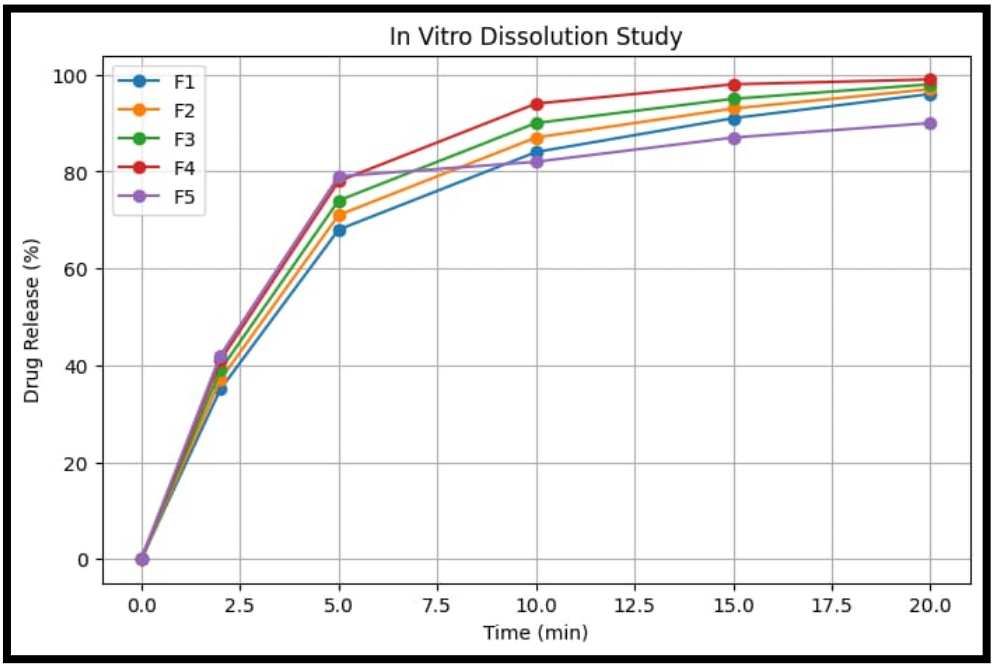
Batch No	**Weight Variation (mg)**	**Thickness (mm)**	**Hardness (kg/cm²)**	**Friability (%)**	**Disintegration Time (sec)**
F1	197.45±2.55	3	3	0.70	32
F2	200±0	3	3.5	0.80	27
F3	196±4.00	3	3.5	0.75	22
F4	199±1.00	3	3	0.60	18
F5	197.25±2.75	3	2.5	0.70	16

Table 6: In vitro Dissolution Study.

Time (min)	**F1 (%)**	**F2 (%)**	**F3 (%)**	**F4 (%)**	**F5 (%)**
0	**0**	**0**	**0**	**0**	**0**
2	**35**	**37**	**39**	**41**	**42**
5	**68**	**71**	**74**	**78**	**79**

10	**84**	**87**	**90**	**94**	**82**
15	**91**	**93**	**95**	**98**	**87**
20	**96**	**97**	**98**	**99**	**90**

Fig 6: In vitro drug release study.



CONCLUSION:

Sublingual tablets of Bisoprolol Fumarate were successfully formulated by direct compression method using crospovidone as a superdisintegrant. The prepared formulations were evaluated for various pre-compression and post-compression parameters including bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio, hardness, friability, weight variation, disintegration time, and in-vitro drug release. All formulations showed acceptable physicochemical characteristics within pharmacopeial limits. The study demonstrated that increase in concentration of crospovidone enhanced the rate of tablet disintegration and drug release. Among all formulations, batch F4 was considered as the optimized batch due to its satisfactory flow properties, acceptable hardness and friability, rapid disintegration time, and better overall drug release profile. The sublingual route also offers the advantage of bypassing first-pass metabolism and improving therapeutic effectiveness. Hence, the study concludes that sublingual tablets of Bisoprolol Fumarate can serve as a promising alternative to conventional oral tablets for rapid antihypertensive therapy.

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