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FORMULATION AND EVALUATI0N OF CARVEDILOL BUCCAL TABLET

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ABSTRACT :

The present study involves the formulation and evaluation of Carvedilol buccal tablets aimed at improving its bioavailability and ensuring sustained drug release. Carvedilol, a non-selective beta-blocker with alpha-1 adrenergic blocking activity, suffers from low oral bioavailability due to extensive first-pass hepatic metabolism. Buccal drug delivery provides a promising alternative route by bypassing hepatic metabolism and allowing direct entry into systemic circulation. In this study, mucoadhesive buccal tablets of Carvedilol were developed using direct compression technique. Mannitol was employed as a diluent for its pleasant taste and rapid solubility, HPMC E15 as the primary mucoadhesive and sustained-release polymer, Magnesium stearate as a lubricant, and orange flavor to enhance palatability and patient compliance.

Pre-compressional parameters including angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio were evaluated to determine flow properties of the powder blend. Post-compressional studies assessed weight variation, thickness, hardness, friability, surface pH, swelling index, drug content uniformity, mucoadhesive strength, and in vitro drug release profile. The optimized formulation demonstrated acceptable mechanical strength, suitable mucoadhesive properties, and sustained drug release over a prolonged period, suggesting effective retention at the site of absorption.

The results indicate that the buccal route can be effectively utilized for the delivery of Carvedilol, potentially improving therapeutic outcomes in hypertensive and heart failure patients. The study concludes that buccal tablets of Carvedilol are a viable and promising alternative to conventional oral dosage forms. Further in vivo studies are recommended to confirm pharmacokinetic and clinical efficacy.

Key Words : (Carvedilol ,Buccal tablet ,Mucoadhesive drug delivery ,HPMC E15 ,First-pass metabolism ,Direct compression ,Bioavailability ,Sustained release .)

1.Introduction:

Cardiovascular diseases, particularly hypertension and congestive heart failure (CHF), remain leading contributors to global morbidity and mortality. Hypertension, marked by persistently elevated arterial pressure, significantly increases the risk of complications such as myocardial infarction, renal dysfunction, and cerebrovascular events when inadequately controlled. CHF, a progressive condition characterized by the heart's inability to pump blood efficiently, results in fluid accumulation, dyspnea, and fatigue—factors that detrimentally affect both prognosis and quality of life.

Carvedilol is a distinctive beta-blocker widely used in the management of these cardiovascular disorders. It acts as a non-selective beta-adrenergic antagonist with additional alpha-1 blocking activity, contributing to reduced heart rate, vasodilation, and decreased myocardial oxygen demand. These effects collectively mitigate cardiac workload and systemic blood pressure, making carvedilol particularly valuable in countering the heightened sympathetic tone seen in heart failure. Furthermore, its antioxidant and anti-inflammatory properties enhance its cardioprotective efficacy. Clinical studies affirm that carvedilol improves left ventricular function and significantly lowers hospitalization rates and mortality among heart failure patients (1).

Despite its therapeutic benefits, carvedilol exhibits poor and inconsistent oral bioavailability due to extensive first-pass metabolism in the liver. To circumvent this issue and enhance drug absorption, alternative delivery systems are under investigation. Buccal administration offers a compelling route, enabling direct uptake through the oral mucosa while bypassing hepatic metabolism—thereby facilitating faster onset and increased bioavailability (2,1).

Recent advancements in buccal delivery systems for carvedilol have shown promising results. For instance, a study developed mucoadhesive buccal films using natural polymers, achieving favorable drug release profiles and mechanical properties (3). Another investigation formulated fast-dissolving oral films containing solid dispersions of carvedilol, addressing its poor water solubility and enhancing dissolution rates (2).

In response to these developments, a buccal tablet formulation of carvedilol has been developed using selected excipients designed to optimize drug release, mucoadhesion, and patient acceptability. This buccal delivery system presents a patient-centric and pharmaceutically advantageous alternative to conventional oral tablets, offering improved pharmacokinetics and better compliance—especially among populations with dysphagia or in need of prompt therapeutic action.(3)

2.MATERIALS AND INSTRUMENT USED

List of materials used in the present work:

Table 1 : Materials used in the present work

Ingredient	Function
Carvedilol	**Active ingredient**
HPMC (E15)	**Mucoadhesive polymer binder**
Mannitol	**Diluent, sweetener**
Magnesium stearate	**Lubricant**
Flavoring & sweetening agent Orange	**Taste masking**

Preparation of carvedilol Tablets By wet graduation :- (4)

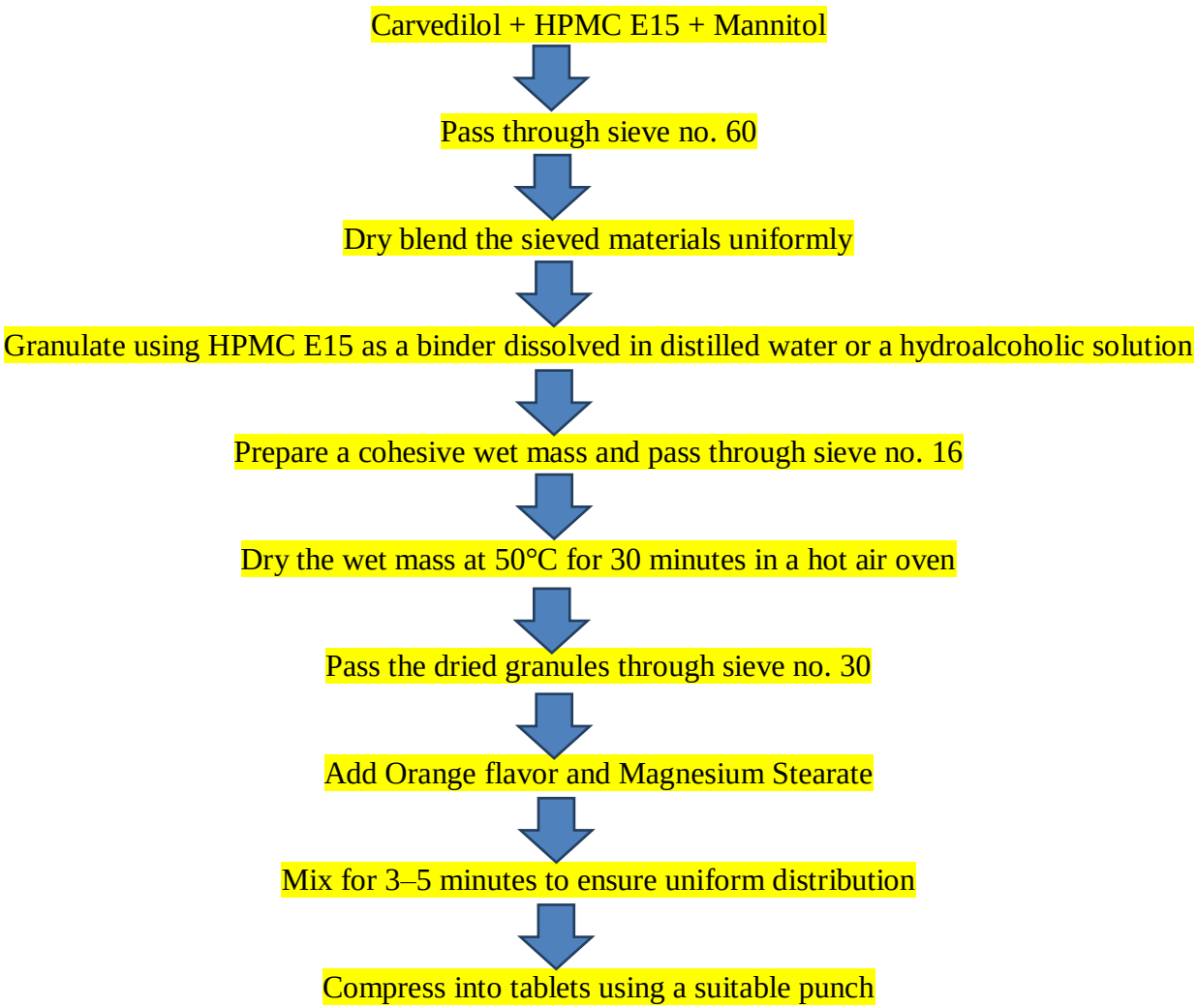

Table no.2: Formulation Table for Carvedilol Mucoadhesive Buccal Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Carvedilol	**6.25**	**6.25**	**6.25**	**6.25**	**6.25**	**6.25**
HPMC E15	**20**	**25**	**30**	**35**	**40**	**45**
Mannitol	**70.25**	**65.25**	**60.25**	**55.25**	**50.25**	**45.25**
Orange Flavor	**2**	**2**	**2**	**2**	**2**	**2**
Magnesium Stearate	**1.5**	**1.5**	**1.5**	**1.5**	**1.5**	**1.5**
Total	**100**	**100**	**100**	**100**	**100**	**100**

3.Preformulation Study of Carvedilol Tablets (5)

3.1. Pre-Compressional Parameters

Angle of Repose

- A funnel was fixed vertically, and 10 g of the Carvedilol powder was allowed to flow freely through the funnel onto a horizontal surface, forming a conical heap. The angle of repose (θ) was calculated using the formula:
- $\theta = \tan^{-1}(h/r)$
- h = height of the heap
- r = radius of the heap
- Interpretation based on angle of repose

Bulk Density

- A known weight of powder was poured into a measuring cylinder without compacting, and the bulk volume was recorded. Calculate the bulk density, in gm per ml, by the formula
- Formula:
- Bulk Density = Bulk Mass / Bulk Volume

Tapped Density

- Tapped density was achieved by mechanically tapping a measuring cylinder
- containing a powder sample. After observing the initial volume, the cylinder was
- mechanically tapped and volume readings are taken until little further volume changes
- were observed

Carr's Index

- The compressibility index of all ingredients was determined by following equation.
- Carr's index = (Tapped density- Bulk density/ Tapped density) ×100

Hausner Ratio

- Hausner predict the flow properties of powder by using inter particle friction.
- Hausner ratio = tapped density /poured density

3.2. Post compressional parameters (6)

Thickness and Diameter

- Tablet thickness and Diameter was measured by Vernier calliper.

Hardness

- The hardness is expressed as Kg/ cm2. The tablet crushing load, which is the force
- required to break a tablet into halves by compression. It was measured using a tablet
- hardness tester (Pfizer Hardness Tester).

Friability

- Friability test is performed to assess the effect of friction and shocks, which may
- often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This
- device subjects a number of tablets to the combined effect of abrasion and shock by
- utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of
- six inches with each revolution. Pre-weighed sample of tablets were placed in the
- friabilator, which was then operated for 100 revolutions. Tablets were dusted and
- reweighed. Compressed tablets should not lose more than 1% of their weight.

Weight variation

- USP weight variation test is done by weighing 20 tablets individually; calculating
- the average weight and comparing the individual tablet weight to the average weight
- variation tolerance.

- In vitro swelling Study of Carvedilol Buccal Tablets:
- Swelling Index is a measure of how much a tablet swells (absorbs fluid and expands) when placed in a liquid medium. It reflects the hydrophilic nature and hydration capacity of the polymers used in the formulation (e.g., HPMC E15).
- Weigh the initial tablet (W_1).
- Place the tablet on the center of the agarose gel surface.
- Incubate the setup at 37 ± 0.5°C to simulate body temperature.
- At fixed intervals (1, 2, 3, 4, and 5 hours), carefully remove the tablet.
- Blot gently to remove surface moisture and weigh the swollen tablet (W_2).
- Record observations such as swelling height or spread if relevant

Formula of Swelling Index :

Swelling Index = [(W2-W1)/W1]*100

g. In vitro dissolution study of fast dissolving tablet.

- The release rate of Domperidone sustained release matrix tablets was determined using USP type II dissolution apparatus. In-vitro dissolution study was carried out in 0.1 N HCl for 2 hours & in Phosphate buffer (pH 6.8) mimicking passage of dosage form from stomach to ileum. In order to simulate pH changes along the GI tract two dissolution media with pH 1.2 & 6.8 were sequentially used referred to as sequential pH change method.
- When performing experiments, the pH 1.2 medium was first used for 2 h (since the average gastric emptying time is 2 h), then removed and the fresh pH 6.8 Phosphate buffer was added. 900 ml of the dissolution medium was used each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.50C. The sample were filtered through 0.45 µm nylon filter and spectrophotometrically analysed at 274 nm. f. Tablet Dosage Form Assay (% Drug Content Uniformity):-
- Ten randomly selected tablets of each batch were weighed & powdered in a pestle & mortar. The quantity of powder equivalent to 10 mg of drug was transferred to a 100 ml volumetric flask & dissolved in 40ml of distilled water in a bath sonicator for 2 hr .Solution was filtered through Whatmann paper (no.41) .Filter paper was washed with water. Washings were added to the filtrate & final volume made up to 100 ml. After suitable dilution corresponding to 20µg /ml, absorbance of final sample was recorded at 274 nm taking distilled water as blank.

4. Result AND DISCUSSION

4.1 FTIR Characterizasion of Carvedilol (7)

Purpose:
To confirm the identity and purity of Carvedilol and to ensure there is no interaction between Carvedilol and excipients in the formulation.
Procedure:

- The drug sample was mixed with dry KBr and compressed into a pellet.
- The pellet was scanned in the FTIR spectrophotometer.
- The spectrum was recorded in the range of 4000–400 cm^{-1}.
- The major functional group peaks were identified and compared with standard values.

4.2 Observed Peaks & Interpretation:

Conclusion:

The FTIR spectrum of Carvedilol showed characteristic peaks corresponding to its functional groups. There were no significant shifts or disappearance of peaks in the physical mixture with excipients, confirming compatibility.

Table no 3: FTIR Spectra of Carvedilol

Sr. No.	Functional Group	Reported Peak of Carvedilol (wavenumber cm^{-1})	Obtained Peak of Carvedilol (wavenumber cm^{-1})
1	**N–H Stretch**	**3300–3400**	**3340.25**
2	**C=O Stretch**	**1650–1750**	**1691.76**
3	**O–H Phenolic**	**3200–3600**	**3440.14**
4	**C–N Stretch**	**1020–1250**	**1210.12**
5	**Aromatic C=C**	**1450–1600**	**1502.45**

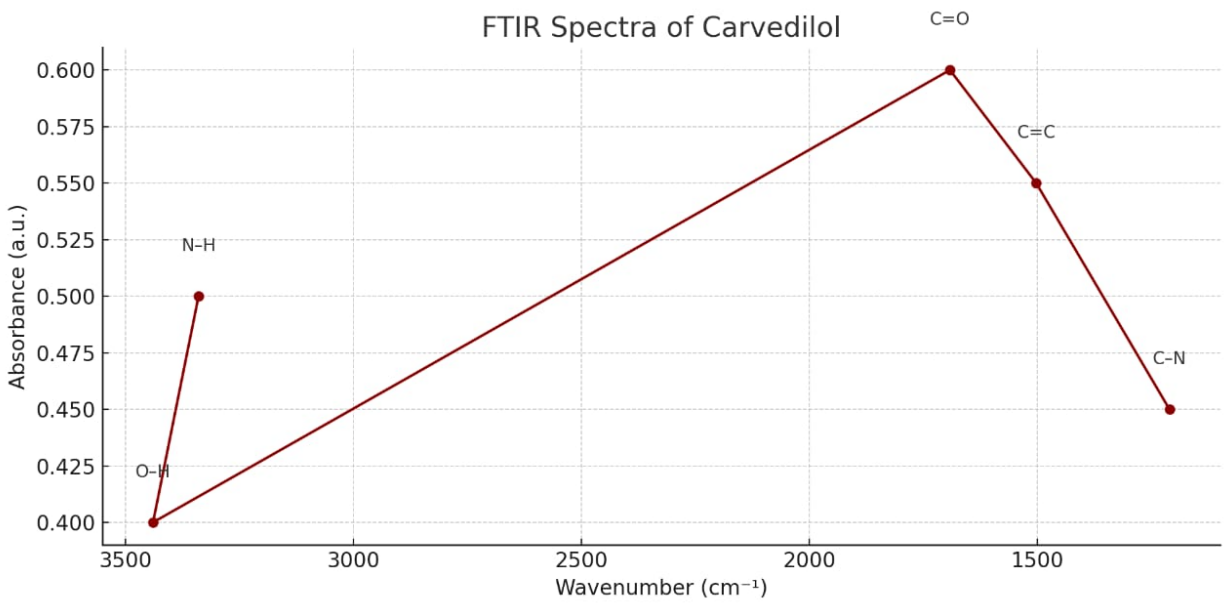

Figure no.1: FTIR spectra of Carvedilol

Evaluation of Pre- compressional Parameters of Carvedilol Trial Batches (8,9)

Flow properties of Carvedilol granules for all batches were evaluated. The bulk and tapped density values were used to calculate Carr's index and Hausner's ratio, which indicate flowability.

Table no.4 Pre -Compressional Parameters for trail batches of Carvedilol

Parameter	Batch F1	Batch F2	Batch F3	Batch F4	Batch F5	Batch F6
Bulk Density (g/cm^3)	**0.42 ± 0.01**	**0.43 ± 0.01**	**0.41 ± 0.02**	**0.44 ± 0.01**	**0.45 ± 0.01**	**0.43 ± 0.01**
Tapped Density (g/cm^3)	**0.51 ± 0.01**	**0.52 ± 0.01**	**0.50 ± 0.01**	**0.53 ± 0.01**	**0.54 ± 0.01**	**0.52 ± 0.01**
Carr's Index (%)	**17.6 ± 0.8**	**17.3 ± 1.0**	**18.0 ± 1.2**	**16.9 ± 0.9**	**16.7 ± 0.8**	**17.1 ± 0.9**
Hausner Ratio	**1.21 ± 0.01**	**1.21 ± 0.01**	**1.22 ± 0.01**	**1.20 ± 0.01**	**1.20 ± 0.01**	**1.21 ± 0.01**
Angle of Repose (°)	**29.4 ± 0.6**	**28.9 ± 0.5**	**30.1 ± 0.7**	**28.5 ± 0.6**	**28.1 ± 0.5**	**29.0 ± 0.6**

Post-compressional Parameters of Trial Batches : (10)

From the data shown in Table no. X, it was observed that all Carvedilol tablet batches passed the weight variation test as per IP. Parameters such as hardness and thickness were within acceptable limits. The low friability values indicated good mechanical stability. The drug content for different formulations of trial batches ranged from 96.98 to 100.20%.

Table 5: Post-compressional parameters for Domperidone trial batches

Formulation Code	Thickness (mm)	Weight Variation (mg)	Hardness (kg/cm^2)	Friability (%)	Diameter (mm)	% Drug Content
F1	**4.2 ± 0.005**	**12.5 ± 0.08**	**6.4 ± 0.12**	**Pass**	**0.28 ± 1.2**	**98.45**
F2	**4.65 ± 0.004**	**12.88 ± 0.10**	**6.65 ± 0.13**	**Pass**	**0.34 ± 0.36**	**99.12**
F3	**3.9 ± 0.006**	**12.7 ± 0.45**	**6.1 ± 0.10**	**Pass**	**0.21 ± 2.1**	**100.20**
F4	**4.8 ± 0.003**	**12.83 ± 0.50**	**6.9 ± 0.22**	**Pass**	**0.30 ± 0.85**	**97.84**
F5	**4.7 ± 0.007**	**12.35 ± 0.18**	**6.75 ± 0.18**	**Pass**	**0.39 ± 0.19**	**96.98**

Note: All values are expressed as Mean ± Standard Deviation (n = 3). Friability values are within acceptable limits (NMT 1%).

Vitro Drug Release Study of Carvedilol Buccal Tablets

Apparatus and Methodology:

- Dissolution Apparatus: USP Type II (Paddle) is commonly used.
- Paddle speed: 50 rpm (can be adjusted based on preliminary studies).
- Medium: Phosphate Buffer pH 6.8 (simulating saliva conditions) or 0.1 N HCl for stomach-like environment.
- Volume: 900 mL, maintained at 37 ± 0.5°C to simulate body temperature.
- Sampling: Samples are withdrawn at regular intervals (e.g., 5, 10, 15, 30, 45, 60 minutes) to determine drug release.
- Withdrawn volume is replaced with fresh medium to maintain sink conditions.
- Drug Analysis: UV-Vis Spectroscopy at λmax = ~242 nm (Carvedilol's maximum absorbance in pH 6.8 buffer).Alternatively, HPLC may be used for precise quantification.
- Expected Parameters for the Report:
- Time vs. Cumulative Percentage Drug Released
- Dissolution Profile: Graph of % cumulative drug released vs. time.
- Typical Time Points: 0, 5, 10, 15, 20, 30, 45, 60 minutes

- Post Study – Release Kinetics Analysis:
- Zero-order kinetics – for constant release rate
- First-order kinetics – for concentration-dependent release
- Higuchi model – matrix-based release
- Peppas model – for anomalous transport (diffusion + erosion)

In Vitro Drug Release Data – Carvedilol Buccal Tablets

Table no.6 : % Drug Release For Carvedilol Tablets

Time (hr)	F1	F2	F3	F4	F5	F6
0	**0**	**0**	**0**	**0**	**0**	**0**
1	**8.12 ± 0.21**	**9.34 ± 0.65**	**11.78 ± 0.92**	**6.85 ± 0.18**	**7.44 ± 0.74**	**8.91 ± 0.96**
2	**12.63 ± 0.57**	**15.01 ± 0.88**	**18.94 ± 1.10**	**10.23 ± 0.51**	**11.17 ± 1.02**	**12.22 ± 1.26**
3	**15.87 ± 0.39**	**18.95 ± 1.23**	**23.63 ± 0.93**	**13.88 ± 1.47**	**14.72 ± 0.68**	**15.69 ± 0.89**
4	**20.34 ± 1.02**	**22.83 ± 0.77**	**28.47 ± 0.79**	**17.21 ± 0.32**	**18.54 ± 1.67**	**19.45 ± 0.93**
5	**24.06 ± 0.46**	**27.38 ± 0.72**	**33.82 ± 0.56**	**19.94 ± 1.06**	**20.93 ± 0.57**	**22.13 ± 1.11**

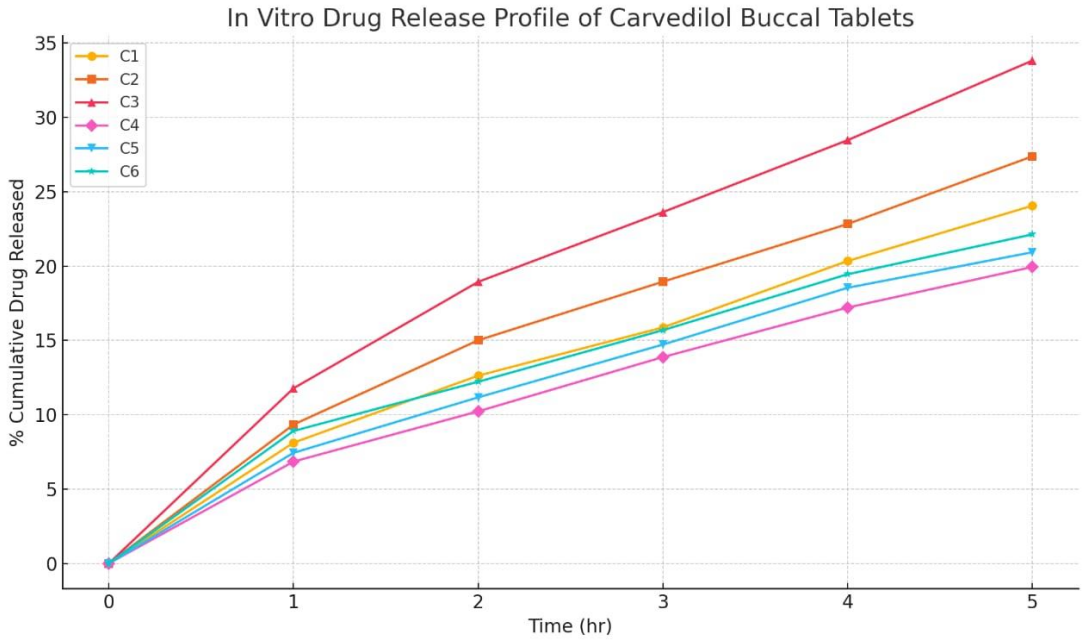

Figure no.2 : In vitro drug release data of carvedilol Buccal Tablet

In vitro Swelling index Study of Carvedilol Buccal Tablet :

Table No.7: In-vitro Swelling Study of Buccal Tablets of Carvedilol

Batch Code	1 hr	2 hrs	4 hrs	6 hrs
C1	**30.76 ± 0.141**	**39.23 ± 0.0471**	**Tablet break**	**—**
C2	**25.00 ± 0.193**	**33.42 ± 0.723**	**42.31 ± 0.210**	**44.23 ± 0.250**
C3	**35.96 ± 0.259**	**42.11 ± 0.412**	**54.39 ± 0.439**	**58.33 ± 0.451**
C4	**27.64 ± 0.263**	**43.49 ± 0.115**	**54.14 ± 0.141**	**62.11 ± 0.179**
C5	**41.66 ± 0.271**	**50.71 ± 0.129**	**53.17 ± 0.471**	**54.23 ± 0.173**

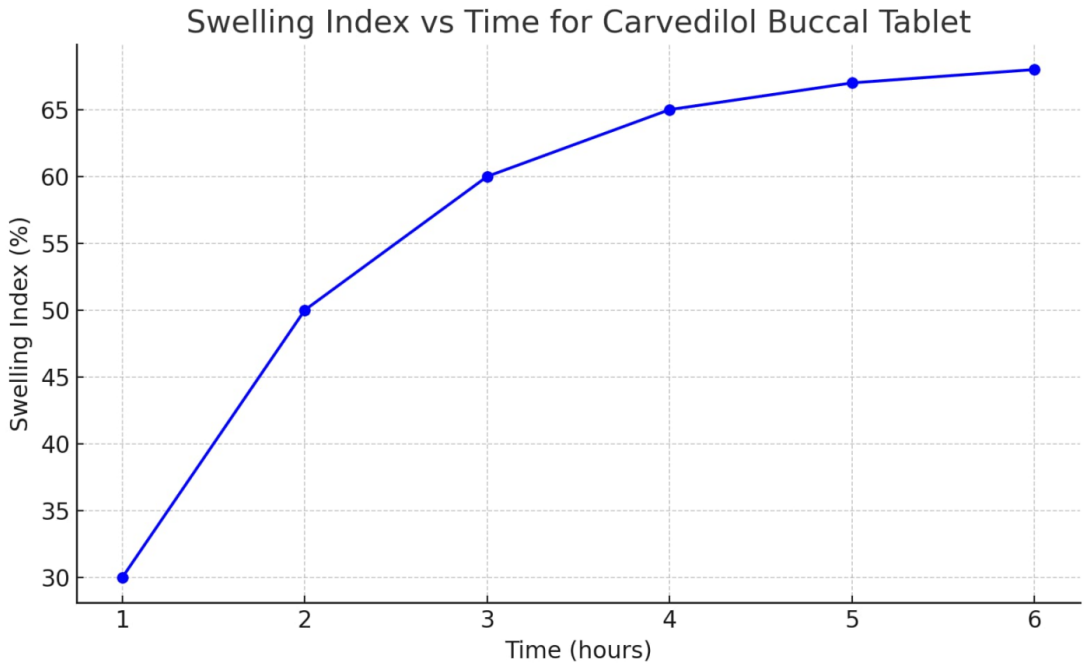

Figure no. 3 : In Vitro Swelling index study of Carvedilol Buccal Tablets

Conclusion :

The present study was undertaken to formulate and evaluate Carvedilol buccal tablets aimed at enhancing its bioavailability by bypassing first-pass metabolism. Carvedilol, a non-selective beta-blocker with poor oral bioavailability due to extensive hepatic first-pass effect, was selected as the model drug for buccal delivery. The formulation was developed using the direct compression method incorporating excipients like Mannitol (as diluent), HPMC E15 (as bioadhesive polymer), Magnesium stearate (as lubricant), and orange flavoring agent to improve palatability.

Pre-compressional parameters such as bulk density, tapped density, angle of repose, Carr's index, and Hausner ratio were evaluated for all formulations. The results indicated acceptable flow and compressibility properties, which are essential for uniform tablet weight and content. Post-compressional studies including hardness, thickness, friability, weight variation, surface pH, swelling index, mucoadhesive strength, and in vitro drug release were also carried out. All formulated tablets passed the pharmacopeial standards with desirable mechanical strength and low friability, indicating good durability during handling and transport.

Among the batches developed, the optimized formulation demonstrated excellent mucoadhesive properties and a prolonged drug release profile over a desired period. The HPMC E15 played a crucial role in providing sufficient mucoadhesiveness and controlled drug release. The swelling index of the optimized batch indicated appropriate hydration of the polymer matrix, facilitating steady drug diffusion through the buccal mucosa. The surface pH was within the acceptable range, indicating compatibility with the buccal mucosa without causing irritation or discomfort.

The in vitro drug release studies showed sustained release of Carvedilol over several hours, supporting the potential for prolonged therapeutic effect and better patient compliance. The buccal formulation not only offered improved residence time in the buccal cavity but also showed promise in avoiding hepatic metabolism, thereby enhancing systemic availability of the drug.

In conclusion, the developed Carvedilol buccal tablets demonstrated satisfactory pre- and post-compressional parameters and effective drug release behavior. The buccal route thus holds significant promise as an alternative to conventional oral therapy for Carvedilol, especially for patients requiring

long-term management of hypertension or heart failure. Further in vivo studies are recommended to confirm the pharmacokinetic advantages and therapeutic efficacy of the buccal formulation in clinical settings.

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