Formulation And Evaluation of Muchoadesive Buccle Tablet For Diabetis using Neteglinide

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Abstract- *Mucoadhesive buccal tablets of Nateglinide were formulated and evaluated to enhance drug bioavailability, provide controlled drug release, and improve patient compliance in diabetes management. Buccal drug delivery bypasses hepatic first-pass metabolism, potentially increasing the drug's bioavailability while ensuring sustained therapeutic action. In this study, various bioadhesive polymers, including Hydroxypropyl Methylcellulose (HPMC), Carbopol 934, and Sodium Carboxymethylcellulose (Sodium CMC), were used to optimize the mucoadhesive properties and drug release profile of the tablets. The tablets were prepared using the direct compression method and subjected to a comprehensive set of physicochemical and in-vitro evaluation tests, including weight variation, hardness, swelling index, surface pH, mucoadhesive strength, drug content uniformity, and in-vitro drug release studies. The optimized formulation demonstrated satisfactory mucoadhesive strength, appropriate swelling behavior, and a controlled drug release profile over an extended period. These results indicate that buccal delivery of Nateglinide could be a promising alternative to conventional oral formulations, potentially reducing the frequency of administration and enhancing therapeutic outcomes for diabetic patients. Further studies, including in-vivo pharmacokinetic and pharmacodynamic evaluations, are necessary to validate the efficacy of this novel drug delivery system.*

Keywords- Mucoadhesive buccal tablet, Nateglinide, Diabetes mellitus, Bioadhesion, Sustained drug release

I. INTRODUCTION

Overview of Diabetes Mellitus:

Diabetes mellitus (DM) is a chronic metabolic disorder that has emerged as one of the most significant global health challenges. It is primarily characterized by persistent hyperglycemia due to insufficient insulin secretion, impaired insulin action, or both. The disorder is classified into Type 1 Diabetes Mellitus (T1DM), which results from autoimmune destruction of pancreatic β- cells leading to absolute insulin deficiency, and Type 2 Diabetes Mellitus (T2DM), which is associated with insulin resistance and a progressive decline in insulin secretion. Among these, T2DM accounts for nearly 90-95% of all diabetes cases worldwide and is primarily linked to obesity, sedentary lifestyles, and genetic predisposition. [1]
With the increasing prevalence of diabetes, its associated complications—including cardiovascular diseases, neuropathy, nephropathy, and retinopathy—pose a significant burden on public health. The primary goal of diabetes management is to maintain optimal blood glucose levels to prevent these complications and improve the quality of life for patients. Various therapeutic approaches, including lifestyle modifications, insulin therapy, and oral hypoglycemic agents (OHAs), are commonly employed for managing diabetes. [2]

Challenges with Conventional Oral Hypoglycemic Agents:

Oral hypoglycemic agents (OHAs) remain the first-line treatment for managing Type 2 Diabetes Mellitus (T2DM). However, their therapeutic efficacy is often hindered by several pharmacokinetic and pharmacodynamic limitations, including:

- Low bioavailability due to extensive hepatic first-pass metabolism.
- Short half-life, necessitating frequent administration to maintain effective plasma drug concentrations.
- Poor patient compliance due to multiple daily dosing regimens.
- Gastrointestinal side effects, including nausea, diarrhea, and gastric irritation, leading to poor adherence.

Among the various OHAs, Nateglinide, a meglitinide-class insulin secretagogue, is widely prescribed for postprandial glucose control. However, its short biological half-life (~1.5 hours) and requirement for frequent dosing (three times daily) limit its effectiveness and patient adherence. Additionally, it undergoes extensive hepatic metabolism, reducing its systemic availability when administered orally. These challenges necessitate the exploration of alternative drug delivery systems that can improve bioavailability, extend drug action, and enhance patient compliance. [3]

Mucoadhesive Buccal Drug Delivery System: A Promising Alternative

Buccal drug delivery has gained significant attention as an alternative route for systemic drug administration due to its unique physiological advantages. The buccal mucosa, located in the inner lining of the cheeks, provides a highly vascularized, permeable surface that facilitates direct drug absorption into the systemic circulation, bypassing the hepatic first-pass effect. This approach enhances bioavailability, reduces dosing frequency, and minimizes gastrointestinal side effects associated with oral administration.

The development of a mucoadhesive buccal tablet offers additional benefits:

- Prolonged retention at the site of absorption, allowing sustained drug release.
- Improved therapeutic efficacy through enhanced bioavailability.
- Better patient compliance due to reduced dosing frequency.
- Non-invasive and convenient administration, making it an attractive alternative for patients with difficulty swallowing. [4]

The effectiveness of a buccal drug delivery system largely depends on the selection of mucoadhesive polymers, which facilitate adhesion to the mucosal surface, ensuring extended contact time and controlled drug release. Such systems have been successfully developed for various drugs, demonstrating their potential for enhanced therapeutic outcomes.

Rationale for Selecting Nateglinide for Buccal Drug Delivery

Nateglinide, a rapid-acting insulin secretagogue, is an ideal candidate for buccal drug delivery due to its pharmacokinetic properties and therapeutic benefits. The major factors that justify the selection of Nateglinide for mucoadhesive buccal tablet formulation include:

- Low molecular weight (273.35 g/mol), which favors buccal absorption.
- Moderate lipophilicity (log P ~3.3), ensuring optimal permeability across the buccal mucosa.
- Short half-life (~1.5 hours), necessitating a sustained-release formulation for prolonged therapeutic action.
- Extensive hepatic metabolism, making buccal administration beneficial in bypassing the first-pass effect.
- Effective postprandial glucose control, making it suitable for sustained delivery through buccal absorption.

By incorporating Nateglinide into a mucoadhesive buccal tablet, its bioavailability can be significantly enhanced while reducing the need for frequent administration, thus improving treatment outcomes for diabetic patients. [5]

II. NEED OF WORK

The necessity of this research is driven by the limitations of conventional drug delivery methods and the potential advantages of mucoadhesive buccal tablets in enhancing therapeutic efficacy for diabetes management. The key reasons justifying the need for this study include:

1. Overcoming Limitations of Conventional Oral Drug Delivery

Nateglinide, a short-acting meglitinide-class insulin secretagogue, is highly effective in controlling postprandial glucose levels. However, it suffers from low bioavailability (~73%) due to extensive hepatic first-pass metabolism, resulting in reduced systemic drug levels. Additionally, its short half-life (~1.5 hours) requires frequent administration (thrice daily), leading to poor patient adherence and fluctuating plasma concentrations. Formulating a mucoadhesive buccal tablet will help bypass the hepatic first-pass metabolism, ensuring higher bioavailability and prolonged drug action.

2. Achieving Sustained and Controlled Drug Release

Frequent dosing of Nateglinide is inconvenient for patients and increases the risk of poor glycemic control, dose-missing, and side effects such as hypoglycemia. A mucoadhesive buccal tablet can provide controlled and sustained drug release, ensuring steady plasma levels and reducing the need for frequent dosing, thus improving therapeutic efficacy and minimizing adverse effects.

3. Enhancing Patient Compliance and Convenience

Many diabetic patients, particularly the elderly, face challenges with swallowing conventional tablets and capsules, leading to medication non-adherence. Injectable formulations such as insulin are invasive and often associated with pain, discomfort, and poor acceptance. A mucoadhesive buccal tablet offers a non-invasive, easily administrable alternative, allowing prolonged retention at the site of absorption, painless drug administration, and enhanced patient compliance.

III. AIMS AND OBJECTIVES

1. Aims of the Study:

The present study aims to develop, optimize, and evaluate a mucoadhesive buccal tablet of Nateglinide for effective management of Type 2 Diabetes Mellitus, ensuring enhanced bioavailability, prolonged drug action, and improved patient compliance. The specific aims include:

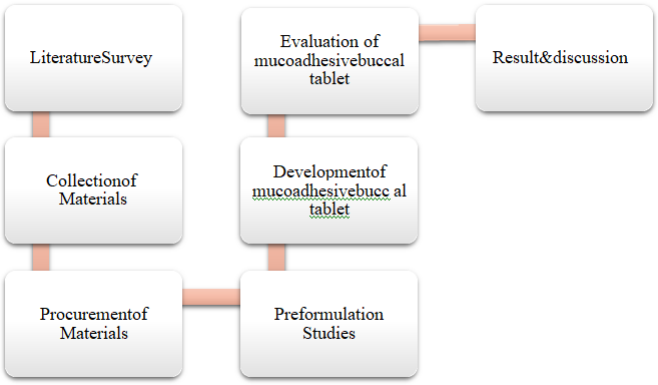
1. To formulate a mucoadhesive buccal tablet of Nateglinide using bioadhesive polymers to improve drug retention and systemic absorption.
2. To enhance the bioavailability of Nateglinide by bypassing hepatic first-pass metabolism through buccal drug delivery.
3. To achieve sustained and controlled drug release through the use of polymeric excipients for prolonged therapeutic efficacy.
4. To improve patient adherence and convenience by developing a non-invasive, easily administrable alternative to conventional oral and injectable formulations.
5. To ensure the stability and effectiveness of the formulated buccal tablets through in vitro and ex vivo evaluation studies.

2. Objectives of the Study:

To achieve the stated aims, the following specific objectives will be pursued:

1. Formulation of mucoadhesive buccal tablets of Nateglinide using suitable bioadhesive polymers such as HPMC, Carbopol, and sodium alginate.
2. Physicochemical characterization of the formulated tablets, including weight uniformity, hardness, friability, and drug content analysis.
3. Evaluation of mucoadhesive properties such as swelling index, mucoadhesion strength, and residence time to ensure prolonged retention in the buccal cavity.
4. In vitro drug release studies to analyze the dissolution profile and assess the controlled release behavior of the formulation.
5. Ex vivo permeation and bioadhesion studies using porcine buccal mucosa to determine the drug permeation efficiency and adherence potential.

IV. PLAN OF WORK



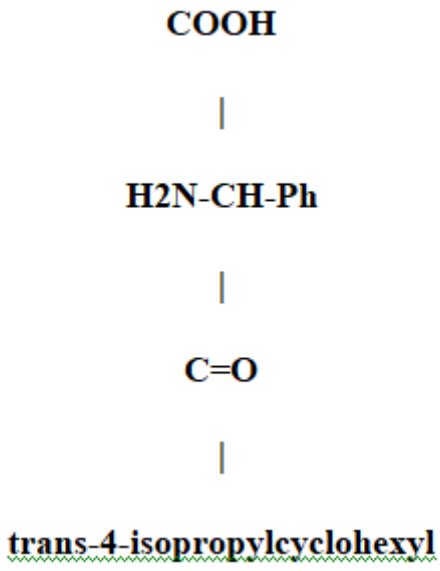
V. MATERIAL AND METHOD

5.1 Drug Profile: Nateglinide:

General Overview:

Nateglinide is an oral hypoglycemic agent belonging to the meglitinide class of insulin secretagogues. It is primarily used for the treatment of Type 2 Diabetes Mellitus (T2DM), where it helps control postprandial blood glucose levels by stimulating insulin secretion from pancreatic β-cells. Structurally, Nateglinide is derived from D-phenylalanine, which differentiates it from sulfonylureas and other insulin secretagogues.

Chemical Properties of Nateglinide



Property	Details
IUPAC Name	N-[(trans-4-isopropylcyclohexyl)carbonyl]-D-phenylalanine
Molecular Formula	C19H27NO3
Molecular Weight	317.42 g/mol
Solubility	Freely soluble in methanol and ethanol, slightly soluble in water
pKa	~3.1 (acidic), ~7.8 (basic)
LogP	~3.2 (moderate lipophilicity)

Physical Properties of Nateglinide

Property	Details
Appearance	White to off-white crystalline powder
Odor	Odorless
Melting Point	129–131°C
Bulk Density	~0.35–0.45 g/cm³
Tapped Density	~0.50–0.65 g/cm³
Flow Property	Poor flow (needs improvement)

Mechanism of Action:

Nateglinide exerts its pharmacological effect by stimulating the pancreatic β-cells to release insulin in response to elevated blood glucose levels. It acts on the ATP-sensitive potassium (K_ATP) channels of the pancreatic β-cell membrane. By blocking these channels, it leads to membrane depolarization, causing an influx of calcium ions (Ca^{2+}) through voltage-gated calcium channels. This calcium influx triggers the exocytosis of insulin-containing granules, leading to rapid insulin release into the bloodstream.

Unlike sulfonylureas, which induce insulin secretion regardless of glucose levels, Nateglinide's action is glucose-dependent, meaning that it primarily enhances insulin secretion only in the presence of elevated blood glucose levels. This property reduces the risk of prolonged hypoglycemia, a common concern with other insulin secretagogues. [6]

Pharmacokinetic Profile:

After oral administration, Nateglinide is rapidly absorbed from the gastrointestinal tract, reaching peak plasma concentrations within 1 hour. It has an absolute bioavailability of approximately 73%, indicating significant absorption despite undergoing first-pass metabolism. Due to its short half- life of approximately 1.5 hours, Nateglinide requires frequent dosing (typically three times a day before meals) to maintain effective blood glucose control.

The drug exhibits high plasma protein binding (~98%), primarily to albumin, which may influence its distribution and duration of action. Nateglinide is extensively metabolized in the liver, primarily by the cytochrome P450 enzymes CYP2C9 and CYP3A4, into inactive metabolites. The major route of elimination is via the renal system (83%), with a smaller portion (10%) excreted through feces.

Due to its rapid metabolism and elimination, frequent dosing is necessary, making it less convenient for patients. The hepatic metabolism also results in significant first-pass degradation, which limits its systemic availability. [7]

Challenges of Conventional Oral Administration:

Despite its effectiveness in controlling postprandial hyperglycemia, conventional oral administration of Nateglinide poses several challenges:

1. Extensive Hepatic First-Pass Metabolism: A substantial portion of the drug undergoes metabolism in the liver before reaching systemic circulation, leading to reduced bioavailability.
2. Short Half-Life: Due to its rapid clearance from the body, Nateglinide requires frequent administration (three times daily), which can result in poor patient compliance.
3. Fluctuating Plasma Drug Levels: The need for frequent dosing may lead to inconsistent blood drug concentrations, affecting glycemic control and increasing the risk of both hyperglycemia and hypoglycemia.
4. Gastrointestinal Side Effects: Oral administration is often associated with nausea, diarrhea, and dyspepsia, which may further reduce adherence to therapy.

Given these limitations, an alternative drug delivery system is required to improve the pharmacokinetic profile of Nateglinide while reducing its drawbacks. [8]

Justification for Buccal Drug Delivery:

Buccal drug delivery presents a promising alternative to overcome the limitations of conventional oral administration. The buccal mucosa, located on the inner lining of the cheeks, offers a highly vascularized and permeable surface, making it ideal for systemic drug absorption. The advantages of formulating Nateglinide as a mucoadhesive buccal tablet include:

1. Bypassing First-Pass Metabolism: Direct absorption through the buccal mucosa allows the drug to enter systemic circulation without undergoing hepatic degradation, thereby improving bioavailability.
2. Sustained Drug Release: A mucoadhesive formulation can prolong the retention time of the drug in the buccal cavity, leading to extended drug action and reduced dosing frequency.
3. Improved Patient Compliance: By eliminating the need for frequent dosing and avoiding gastrointestinal irritation, buccal drug delivery enhances patient adherence and treatment effectiveness.
4. Non-Invasive and Convenient Administration: Unlike injectable formulations, buccal delivery is painless, non-invasive, and suitable for patients with difficulty swallowing tablets or capsules.
5. Reduced Side Effects: Avoiding the gastrointestinal tract minimizes common issues such as nausea, vomiting, and gastric irritation, making therapy more tolerable for patients. [9]

Suitability of Nateglinide for Buccal Absorption:

Nateglinide possesses ideal physicochemical properties that make it a suitable candidate for buccal drug delivery:

- Low Molecular Weight (317.42 g/mol): Small molecular size enhances permeability across the buccal mucosa.
- Moderate Lipophilicity (log P ~3.3): Optimal lipid solubility ensures effective diffusion through the mucosal epithelium.
- High Aqueous Solubility: Ensures proper dissolution at the buccal absorption site.

- Rapid Onset of Action: Helps in effective postprandial glucose control, a critical aspect of Type 2 Diabetes Mellitus management. [10]

Pharmacological Uses of Nateglinide:

Nateglinide is an oral hypoglycemic agent used primarily for the treatment of Type 2 Diabetes Mellitus (T2DM). It belongs to the meglitinide class of insulin secretagogues and is designed to control postprandial hyperglycemia by stimulating insulin secretion from the pancreatic β-cells. The key pharmacological uses of Nateglinide include:

1. **Management of Type 2 Diabetes Mellitus (T2DM)**
    - Nateglinide is used to improve glycemic control in adults with T2DM.
    - It is particularly effective in managing postprandial glucose spikes by enhancing early-phase insulin secretion.
    - It is used as monotherapy in patients who cannot tolerate metformin or other antidiabetic agents. [11]

2. **Adjunctive Therapy with Other Antidiabetic Drugs**
    - Nateglinide is commonly prescribed in combination with metformin or thiazolidinediones (e.g., pioglitazone, rosiglitazone) to achieve better glycemic control.
    - The combination is beneficial for patients with insufficient response to monotherapy, as it targets different mechanisms of blood glucose regulation.

2. **Alternative to Sulfonylureas in Select Patients**
    - Nateglinide serves as an alternative to sulfonylureas (e.g., glibenclamide, glimepiride) for patients who require a shorter-acting insulin secretagogue to reduce the risk of prolonged hypoglycemia.

2. **Treatment Option for Elderly Patients or Those with Renal Impairment**
    - Due to its rapid onset and shorter duration of action, Nateglinide is considered safer than sulfonylureas in elderly patients or those with mild-to-moderate renal impairment, as it reduces the risk of prolonged hypoglycemia. [12]

Side Effects of Nateglinide

- Common: Mild hypoglycemia (dizziness, sweating, hunger), headache, nausea, diarrhea, and mild respiratory infections.
- Serious (Rare): Severe hypoglycemia (confusion, fainting), liver dysfunction, rapid heart rate, and allergic reactions (rash, swelling, breathing issues).
- Precautions: Avoid in Type 1 Diabetes, severe liver disease, and during pregnancy unless advised by a doctor. Take with meals to prevent hypoglycemia. [13]

Dosage of Nateglinide

- Standard Dose: 120 mg three times daily (TID) before meals.
- Lower Dose: 60 mg TID for sensitive individuals (e.g., elderly, renal impairment).
- Administration: Take 1–30 minutes before meals; skip dose if skipping a meal.
- Overdose: Treat with glucose (sugar, juice) to prevent severe hypoglycemia. [14]

5. Drug Profile (Nateglinide)

Parameter	**Details**
Drug Name	Nateglinide
Category	Oral hypoglycemic agent, Meglitinide class
Mechanism of Action	Stimulates insulin release from pancreatic β-cells
Therapeutic Use	Type 2 Diabetes Mellitus
Bioavailability	~73% (oral)
Half-life	1.5 hours
Dose	60–120 mg (TID before meals)

5. 2 EXCIPIENT PROFILE:

In the formulation and evaluation of a mucoadhesive buccal tablet for diabetes using Nateglinide, excipients play a crucial role in ensuring drug release, adhesion, stability, and patient compliance.

Mucoadhesive Polymers (Bioadhesive Agents)

These help the tablet adhere to the buccal mucosa and control drug release.

- Carbopol 934P: Provides strong mucoadhesion and controlled release properties.
- HPMC (Hydroxypropyl Methylcellulose, K4M or K100M): Used for sustained drug release and mucoadhesion.
- Sodium Alginate: Enhances bioadhesion due to its gel-forming ability.
- PVP (Polyvinylpyrrolidone): Helps in tablet binding and adhesion. [14]

Fillers (Diluent)

These increase tablet bulk and ensure proper tablet weight.

- Mannitol: Improves mouthfeel and provides slight sweetness.
- Lactose: Commonly used due to its compressibility.
- Microcrystalline Cellulose (MCC): Enhances tablet strength and stability. [14]

3. Disintegrants

Help in breaking the tablet in case of undesired disintegration in the mouth.

- Crosscarmellose Sodium: Swells in water and aids quick disintegration.
- Sodium Starch Glycolate: Superdisintegrant used to control the release pattern.

4. Lubricants and Glidants

These reduce friction during manufacturing and improve powder flow.

- Magnesium Stearate: Used as a lubricant to prevent sticking to punches and dies.
- Talc: Enhances flow properties and reduces friction. [15]

5. pH Modifiers (Buffering Agents)

To maintain the stability and solubility of Nateglinide in buccal conditions.

- Citric Acid/Sodium Citrate: Helps in maintaining the required pH for drug absorption.
- Phosphate Buffer: Can be used to optimize drug release.

6. Permeation Enhancers

Enhance drug absorption across the buccal mucosa.

- DMSO (Dimethyl Sulfoxide): Improves membrane permeability.
- Sodium Lauryl Sulfate (SLS): Acts as a surfactant and absorption enhancer.
- Propylene Glycol: Solvent and permeation enhancer.

7. Sweeteners and Flavoring Agents

Improve palatability and patient acceptability.

- Aspartame/Sucralose: Artificial sweeteners for taste masking.
- Menthol/Vanillin: Adds a pleasant taste to the formulation.

8. Surfactants (Optional)

Help in solubilization and dispersion.

- Polysorbates (Tween 80): Improves wetting and drug release. [15]

VI. EXPERIMENTAL WORK

6.1 Pre-Formulation Studies:

Pre-formulation studies are critical in pharmaceutical product development as they provide essential information about the physicochemical characteristics of the drug and its interaction with excipients. These studies help in designing a stable and effective dosage form by ensuring the drug's compatibility with formulation components and assessing parameters that influence manufacturing and bioavailability.

Solubility Study

The solubility of Nateglinide was evaluated in different solvents, including distilled water, phosphate buffer pH 6.8, ethanol, methanol, and other commonly used dissolution media. An excess amount of Nateglinide was added to 10 mL of each solvent in separate glass vials. The vials were placed in a mechanical shaker and stirred at room temperature for 24 hours. After equilibration, the solutions were filtered using Whatman filter paper, and the filtrates were analyzed using a UV-Visible spectrophotometer to determine the drug concentration in each solvent. The solubility data helped in selecting the appropriate dissolution medium for further studies. [16]

Melting Point Determination

The melting point of Nateglinide was determined using the capillary method. A small amount of pure drug was filled in a capillary tube sealed at one end. The tube was placed in a melting point apparatus, and the temperature was gradually increased until the drug completely melted. The temperature at which the drug started melting was recorded as the melting point. This study was performed to confirm the purity of the drug. [17]

Drug-Excipient Compatibility Study

The compatibility of Nateglinide with various excipients was evaluated using Fourier Transform Infrared Spectroscopy (FTIR). The pure drug, individual excipients, and physical mixtures of the drug with excipients were analyzed in the spectral range of 4000 to 400 cm^{-1}. The characteristic peaks of functional groups present in the drug were compared with those of the physical mixtures to detect any significant shifts or the appearance/disappearance of peaks, indicating possible interactions. Differential scanning calorimetry (DSC) was also performed to detect potential incompatibilities. [18]

Micromeritic Properties of Powder Blend

The flow properties of the powder blend were assessed to ensure uniform filling during tablet compression. Bulk density and tapped density were determined using a graduated measuring cylinder. The powder blend was poured into the cylinder, and the bulk volume was noted. The cylinder was then tapped mechanically until no further volume change occurred, and the tapped volume was recorded. Carr's index and Hausner's ratio were calculated to assess the compressibility and flowability of the blend. The angle of repose was measured by allowing the powder to flow through a funnel onto a flat surface and measuring the height and diameter of the formed cone. [19]

6.2 Formulation of Mucoadhesive Buccal Tablets:

The formulation of mucoadhesive buccal tablets of Nateglinide involved the direct compression method, a widely used technique due to its simplicity, cost-effectiveness, and

ability to maintain the stability of heat-sensitive drugs. The development process included the selection of excipients, preparation of the powder blend, and compression into tablets, followed by optimization to ensure the required physicochemical and mucoadhesive properties.

Preparation of Powder Blend

Before tablet compression, all ingredients were blended in precise quantities to ensure homogeneous drug distribution and uniform tablet characteristics. The powder blend was prepared using the geometric dilution method, which ensures uniform mixing of the drug with excipients.

Wet Granulation Method:

1. **Weighing**: Accurately weigh all ingredients.
2. **Dry Mixing**: Mix Nateglinide, HPMC, Carbopol, and MCC in a mortar or blender.
3. **Preparation of Binder Solution**: Dissolve PVP K30 in a suitable quantity of water or alcohol.
4. **Wet Massing**: Slowly add binder solution to the dry mix to form a wet, cohesive mass.
5. **Granulation**: Pass the wet mass through sieve #12 or #16 to form granules.
6. **Drying**: Dry the granules in a tray dryer at 40–50°C until moisture content is suitable.
7. **Sieving**: Pass dried granules through sieve #20 to break lumps and achieve uniform size.
8. **Lubrication**: Mix granules with talc and magnesium stearate.
9. **Compression**: Compress the final blend into tablets using a rotary tablet press.

Procedure:

1. Weighing of Ingredients:
    - Each ingredient was accurately weighed using an electronic analytical balance according to the optimized formulation composition.
2. Mixing of Drug and Mucoadhesive Polymers:
    - Nateglinide was first mixed with Carbopol 934P and HPMC K100M using geometric dilution to ensure even drug distribution.
    - The mixture was blended in a glass mortar and pestle for 10–15 minutes to ensure uniform mixing.
2. Addition of Diluents and Other Excipients:
    - Microcrystalline cellulose (MCC 102) was added gradually while continuing mixing.
    - Sodium lauryl sulfate (SLS) was incorporated to enhance drug permeation.
    - Mannitol (if used) was added for improving taste and palatability.
    - The mixture was blended in a tumbling blender at 40 rpm for 10 minutes.
4. Lubrication and Final Blending:
    - Magnesium stearate and talc were added as the final step to enhance powder flow and prevent tablet sticking.
    - The blend was mixed gently in a polybag for 5 minutes to avoid excessive particle attrition.
2. Storage:
    - The final powder blend was stored in a desiccator before compression to prevent moisture absorption. [20]

3. Pre-compression Formula Table

Ingredients	**F1 (mg)**	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**	**F5 (mg)**
Nateglinide	60	60	60	60	60
HPMC K4M	40	30	20	10	0
Carbopol 934P	10	20	30	40	50
MCC	60	60	60	60	60
PVP K30 (binder)	15	15	15	15	15
Talc	2	2	2	2	2
Mg Stearate	3	3	3	3	3
Total	190	190	190	190	190

Compression of Tablets:

The direct compression method was employed using a rotary tablet punching machine. The machine was equipped with flat-faced punches of 6 mm diameter to produce uniform tablets.

Procedure:

1. **Filling of the Die Cavity:**

   - The prepared powder blend was manually fed into the hopper of the tablet compression machine.
   - The die cavity was filled with the required quantity of powder blend.

2. Compression Process:

   - The compression force was adjusted to optimize tablet hardness and thickness.

   - Tablets were compressed at a pressure range of 4–6 kN to achieve the desired mechanical strength.

2. Tablet Collection and Storage:

   - The compressed tablets were collected and stored in airtight containers at room temperature until further evaluation.
   - Care was taken to avoid exposure to moisture and prevent contamination. [21]

FORMULATION TABLE:

Ingredients (mg/tablet)	**B1**	**B2**	**B3**	**B4**	**B5**	**USE**
Nateglinide	60	60	60	60	60	Active pharmaceutical ingredient
Carbopol 934P	20	30	40	50	60	Mucoadhesive polymer
HPMC K4M	30	25	20	15	10	Mucoadhesive & release-controlling polymer
Sodium CMC	15	15	15	15	15	Swelling agent
Lactose	50	45	40	35	30	Filler/diluent
Magnesium Stearate	5	5	5	5	5	Lubricant
Talc	5	5	5	5	5	Glidant
Total Weight (mg)	185	185	185	185	185	-

List of Equipment Used

Equipment Name	**Purpose**
Weighing Balance	Accurate weighing of ingredients
Mortar and Pestle	Grinding and mixing of powders
Sieve Shaker & Standard Sieves	Particle size uniformity
Planetary Mixer or Blending Machine	Mixing of drug and excipients
Granulator	Wet granulation process
Tray Dryer or Hot Air Oven	Drying of wet granules
Tablet Compression Machine	Compression of granules into tablets
Vernier Caliper/Micrometer	Measurement of tablet thickness
Friabilator	Tablet friability test
Hardness Tester	Tablet hardness test
Dissolution Apparatus	Drug release study
pH Meter	pH evaluation of surface/solution
Texture Analyzer	Mucoadhesive strength measurement

Excipients Profile

Excipient	**Purpose**
Carbopol 934P	Mucoadhesive polymer
HPMC K4M	Sustained release matrix
MCC (Avicel PH101)	Diluent
PVP K30	Binder (used in wet granulation)
Magnesium Stearate	Lubricant

Talc	Glidant
Mannitol	Mouth feel enhancer
Lactose	Filler

6.2.3. Optimization of Formulation Parameters

To optimize the formulation, multiple trial batches were prepared by adjusting polymer concentration, compression force, and lubricant concentration to achieve the desired mucoadhesion, drug release, and tablet stability. Higher Carbopol 934P enhanced mucoadhesion but slowed drug release, while HPMC K100M improved swelling and sustained release, requiring a balanced combination for optimal performance. Higher compression force produced harder tablets with reduced porosity, limiting swelling and drug release, whereas lower force resulted in fragile tablets with poor integrity. Excess magnesium stearate created a hydrophobic layer, reducing mucoadhesion and drug release, but proper lubrication was necessary for smooth tablet ejection. Optimizing these factors ensured stable, effective buccal tablets. [22]

6.2.3. Final Selection Criteria:

The final formulation was selected based on several key performance criteria. The mucoadhesive retention time was a critical factor, requiring the tablet to adhere to the buccal mucosa for at least 6–8 hours to provide prolonged therapeutic effects. Additionally, controlled drug release was essential, ensuring that the drug was released in a sustained manner over 8 hours to maintain consistent blood glucose levels. Tablet integrity was also evaluated, ensuring that the formulation exhibited adequate hardness, friability resistance, and uniform weight to withstand handling and transportation. Lastly, the swelling index was optimized to ensure the tablet absorbed sufficient moisture to enhance mucoadhesion without excessive disintegration, maintaining its structural integrity throughout the intended duration of action. These factors collectively ensured the formulation's stability, effectiveness, and patient acceptability. [23]

VII. EVALUATION OF MUCOADHESIVE BUCCAL TABLETS FOR DIABETES USING NATEGLINIDE

Once the mucoadhesive buccal tablets of Nateglinide are formulated, they undergo a series of evaluation tests to assess their physical, chemical, mechanical, and biological properties. These evaluations ensure that the formulation is effective, stable, and meets regulatory standards. Below is a detailed description of each evaluation parameter:

1. Pre-Compression Studies

Before the final tablet is prepared, the powder blend (or granules) used for compression must be assessed to ensure uniformity, proper flow, and compressibility.

1. **Bulk Density & Tapped Density**
   - Bulk density is measured to determine how much space the powder occupies in its loose form, whereas tapped density is determined after mechanically tapping the sample until no further volume change occurs.
   - This evaluation is essential for predicting compression behavior and ensuring uniform weight distribution in the tablets. [24]
2. **Angle of Repose**
   - The ability of a powder to flow properly is assessed using the angle of repose test.
   - A well-flowing powder will form a lower angle when allowed to flow freely from a funnel.
   - Poor flow properties may lead to problems in tablet weight variation and content uniformity. [25]
2. **Compressibility Index & Hausner's Ratio**
   - These parameters indicate how easily the powder can be compressed into tablets.
   - If the values suggest poor compressibility, adjustments in the formulation may be needed. [26]

2. Post-Compression Evaluation of Tablets

Once the buccal tablets are formulated, they are evaluated for physical and mechanical properties to ensure robustness and effectiveness.

1. **General Appearance & Dimensions**
   - The tablets are visually inspected for uniformity in color, texture, and shape.
   - Any variations in appearance might indicate issues in the mixing or compression process.

- The tablet thickness and diameter are also measured to maintain batch-to-batch consistency. [27]

2. Weight Variation Test

- This test ensures that each tablet contains the correct amount of drug and excipients.
- A specific number of tablets are randomly selected, weighed individually, and compared to the average weight.
- Minor variations are permissible, but significant deviations may indicate improper formulation techniques. [28]

2. Hardness Test

- The mechanical strength of the tablet is assessed by measuring the force required to break it.
- A properly formulated buccal tablet should have adequate hardness to withstand handling but should not be too hard to prevent drug release. [29]

2. Friability Test

- Friability refers to the tablet's resistance to chipping or breaking during handling, storage, and transportation.
- Tablets are placed in a rotating drum and subjected to impact forces. If excessive weight loss occurs, the formulation may need modification. [30]

2. Surface pH Measurement

- Since buccal tablets remain in direct contact with the mucosal tissue, their surface pH should be compatible with the physiological pH of the buccal cavity (approximately 6.5– 7.5).
- Any deviation from this range can cause irritation or discomfort, leading to patient non- compliance. [31]

3. Drug Content Uniformity

- To ensure accurate dosing, the drug content in randomly selected tablets is analyzed.
- Each tablet should contain the intended amount of Nateglinide within acceptable limits.
- Uniformity in drug content ensures consistency in therapeutic effects. [32]

4. In-Vitro Mucoadhesion Studies

Since these tablets are designed to adhere to the buccal mucosa, their mucoadhesive properties must be evaluated.

1. Mucoadhesive Strength

- This test determines the force required to detach the tablet from a mucosal membrane (e.g., porcine buccal mucosa).
- A higher adhesion strength indicates better retention in the buccal cavity, prolonging drug release and absorption. [33]

2. Mucoadhesion Time

- This test evaluates how long the tablet remains attached to the mucosal membrane.
- The longer the retention time, the more effective the drug delivery system is. [34]

3. Swelling Index

- Buccal tablets absorb moisture from saliva and swell, which can influence adhesion and drug release.
- The swelling behavior is observed over time, and excessive or inadequate swelling may require formulation adjustments. [35]

5. In-Vitro Drug Release Studies

- A simulated buccal environment is used to measure the rate and extent of drug release from the tablet over time.
- A dissolution apparatus is typically employed, with samples collected at regular intervals and analyzed for drug concentration.
- This helps determine whether the formulation provides a sustained release of Nateglinide, which is crucial for maintaining blood glucose levels. [36]

6. Stability Studies

- Stability testing ensures that the formulation maintains its integrity, effectiveness, and safety over time.
- Tablets are stored under different environmental conditions (temperature, humidity, light) and

periodically analyzed for changes in drug content, appearance, and other parameters.
- The stability data help determine the shelf life of the formulation. [37]

VIII. RESULTS AND DISCUSSION:

The formulated mucoadhesive buccal tablets of Nateglinide were evaluated for various parameters to ensure their quality, stability, and effectiveness in drug delivery. The results obtained from these tests provide insights into the formulation's performance, and the discussion highlights any necessary modifications or observations.

A. Pre-Compression Studies [38]

Bulk Density & Tapped Density

The bulk density of the powder blend was found to be within an acceptable range, indicating that the excipients used provided good packing characteristics. The tapped density showed a slight increase after tapping, suggesting moderate compressibility. A minimal difference between bulk and tapped density values confirmed that the powder blend had good flow properties and was suitable for tablet compression.

Angle of Repose

The angle of repose of the powder blend was observed to be below 30°, indicating excellent flowability. This suggests that the formulation components were well-mixed and did not exhibit significant cohesiveness. As a result, the risk of weight variation in tablets due to poor flow was minimized.

Compressibility Index & Hausner's Ratio

The compressibility index was found to be within the ideal range (below 15%), indicating good compressibility and ensuring that the powder could be compacted into tablets efficiently. Hausner's ratio values were close to 1.2, further supporting the good flow properties of the blend. These results confirm that the chosen formulation had suitable characteristics for direct compression.

B. Post-Compression Evaluation of Tablets [39]

General Appearance & Dimensions

The tablets were visually inspected and found to be uniform in shape, size, and color, without any visible cracks or defects. The thickness and diameter were consistent across all batches, confirming that the compression process was well-controlled. The smooth surface and uniform texture suggest proper distribution of ingredients during blending.

Weight Variation Test

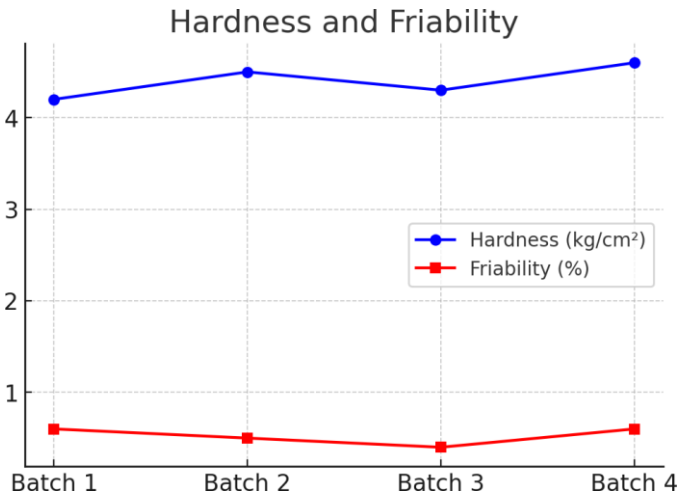
The weight variation test showed that all tablets were within the acceptable weight deviation limits as per pharmacopeial standards. The low standard deviation in weight confirmed the uniformity of powder filling in the die cavity during compression. This consistency ensures that each tablet contains the intended amount of Nateglinide.

Hardness Test

The hardness of the tablets was measured, and values ranged between 3-5 kg/cm². These results indicate that the tablets had sufficient mechanical strength to withstand handling without breaking. At the same time, the hardness was not excessively high, ensuring that drug release would not be hindered.

Friability Test

The friability of the tablets was found to be below 1%, indicating excellent resistance to breakage or chipping. This result confirms that the tablets are durable enough for packaging, transportation, and handling without significant loss of integrity.



Surface pH Measurement

The surface pH of the tablets was found to be in the range of 6.5-7.2, which is close to the physiological pH of the buccal mucosa. This ensures that the tablets do not cause irritation or discomfort, improving patient compliance. The pH

compatibility with the mucosal environment is essential for ensuring prolonged retention of the tablet in the buccal cavity.

Drug Content Uniformity

The drug content analysis showed that all tablets contained Nateglinide within the acceptable pharmacopeial limits (95-105% of the labeled claim). This confirms uniform distribution of the drug throughout the formulation and ensures consistent dosing for patients. No significant deviations were observed between batches, indicating a reliable formulation process.

C. In-Vitro Mucoadhesion Studies

Mucoadhesive Strength

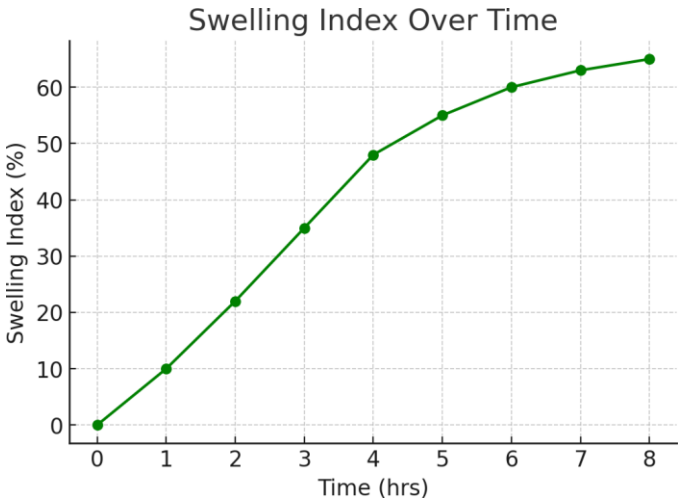
The mucoadhesive strength of the tablets was measured using an in-vitro adhesion test. The results indicated strong adhesion properties, with the force required for detachment being sufficient to retain the tablet in the buccal cavity. Higher adhesion strength ensures prolonged contact time, which is beneficial for sustained drug release.

Mucoadhesion Time

The mucoadhesion time recorded was in the range of 6-8 hours, which is suitable for a buccal drug delivery system. This prolonged adhesion ensures continuous drug release, reducing the need for frequent dosing and improving patient compliance.

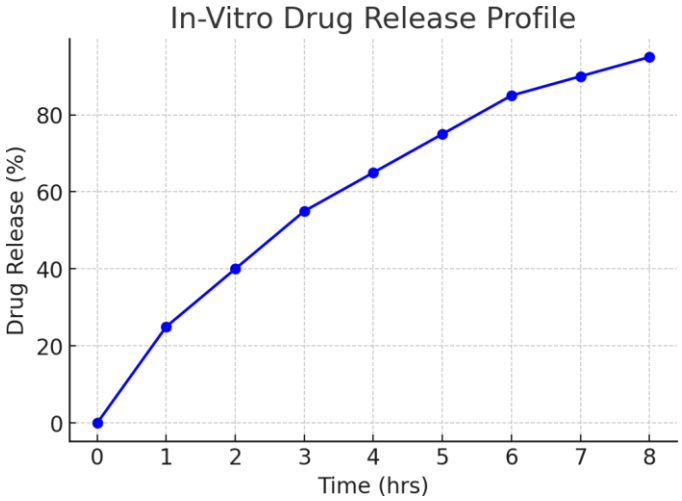
Swelling Index

The swelling index studies showed a gradual increase in tablet size upon contact with simulated saliva. The tablets exhibited controlled swelling without excessive expansion, which is crucial for maintaining adhesion while ensuring consistent drug release. Excessive swelling was not observed, indicating that the polymer selection was appropriate.



In-Vitro Drug Release Studies

Dissolution studies conducted in simulated buccal conditions revealed a sustained drug release pattern. Within the first hour, an initial burst release of approximately 20-30% of Nateglinide was observed, followed by a controlled and gradual release over 6-8 hours. This release profile aligns with the intended design, allowing for a steady therapeutic effect without causing fluctuations in blood glucose levels. The controlled drug release ensures prolonged action, making it suitable for diabetic patients requiring steady glucose regulation.



Stability Studies

Stability studies were conducted under different storage conditions, including accelerated stability testing at high temperature and humidity. The results indicated that the tablets remained physically and chemically stable over the tested period. No significant changes were observed in drug content, mucoadhesion strength, or dissolution profile. The absence of degradation products confirms that the formulation has good stability and can be stored under standard conditions without compromising efficacy.

IX. CONCLUSION

The present study successfully formulated and evaluated mucoadhesive buccal tablets of Nateglinide, demonstrating their potential as an effective alternative to conventional oral dosage forms for diabetes management. The incorporation of bioadhesive polymers such as HPMC, Carbopol 934, and Sodium CMC contributed to the desired mechanical strength, swelling behavior, and sustained drug release, ensuring prolonged drug retention at the buccal mucosa. The optimized formulation exhibited excellent physicochemical characteristics, including uniform drug content, appropriate surface pH, adequate mucoadhesive strength, and a controlled release profile that extended drug availability over an extended period.

The in-vitro drug release studies indicated that the buccal tablets successfully provided sustained drug release, potentially reducing dosing frequency and improving patient compliance. Additionally, the mucoadhesive properties ensured prolonged contact with the buccal mucosa, enhancing systemic drug absorption while avoiding hepatic first-pass metabolism. This could lead to improved bioavailability and more stable plasma drug levels, reducing fluctuations in blood glucose levels and minimizing the risk of hypoglycemia.

The findings from this study suggest that buccal delivery of Nateglinide is a promising strategy for effective diabetes management, offering advantages such as non-invasive administration, controlled drug release, and improved patient adherence. However, further in-vivo pharmacokinetic and pharmacodynamic studies, along with clinical trials, are necessary to confirm the therapeutic efficacy, safety, and acceptability of the developed buccal tablets in real-world applications. Future research may also focus on optimizing the formulation further by incorporating permeation enhancers or evaluating alternative polymers to maximize drug absorption and therapeutic outcomes.

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