

PROJECT WORK REPORT

TITLE: BUCCAL OF ANTI-DIABITIC(LINAGLIPTIN)

Submitted To Gujarat Technological University



IN

B. PHARMACY

SEMESTER-VIII

BY

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Declaration

We here by declare that thesis entitles **TO FORMULATION OF
BUCCAL FILM OF LINAGLIPTIN**

it is a bonafide and genuine carried out by our. The results or observational data presented in this report are original

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AIM: TO FORMULATION OF BUCCAL FILM OF LINAGLIPTIN

INTRODUCTION TO DISEASE:

noninsulin-insulin dependent diabetes mellitus type-2

- ❖ it usually begins as insulin resistance, a disorder in which the cells do not use insulin properly.
- ❖ As the need for insulin rises pancreas gradually loses its ability to produce insulin.
- ❖ Has a high degree of genetic predisposition; generally has a late onset.
- ❖ Over 90% cases of diabetes are type-2 DM
- ❖ CAUSE: reduced sensitivity of peripheral tissues to insulin.
- ❖ Type-2 diabetes is metabolic disorder which causes high blood sugar level or glucose level, which is referred as hyperglycaemia
- ❖ Hyperglycaemia takes place when the body cannot use natural insulin it produces.
- ❖ Type-2 diabetes also occurs when the body is unable to produce enough insulin.



causes of type-2 diabetes

High cholesterol
level

Smoking debits

High blood
pressure

overweight

Sedentary
lifestyle

- Type 2 diabetes is a disease that occurs when your blood glucose, also called blood sugar, is too high.
- Blood glucose is your main source of energy and comes mainly from the food you eat.
- Insulin, a hormone made by the pancreas, helps glucose get into your cells to be used for energy.
- In type 2 diabetes, your body doesn't make enough insulin or doesn't use insulin well.
- Too much glucose then stays in your blood, and not enough reaches your cells.

- type 2 diabetes occurs most often in middle-aged and older people.
- You are more likely to develop type 2 diabetes if you are age 45 or older, have a family history of diabetes, or are overweight or obese.
- Diabetes is more common in people who are African American, Hispanic/Latino, American Indian, Asian American, or Pacific Islander.

- Physical inactivity and certain health problems such as high blood pressure affect your chances of developing type 2 diabetes.

- You are also more likely to develop type 2 diabetes if you have prediabetes or had gestational diabetes when you were pregnant. Learn more about risk factors for type 2 diabetes.

- Type 2 diabetes occurs most often in middle-aged and older people.

symptoms of diabetes

- increased thirst and urination
- increased hunger
- feeling tired
- blurred vision
- numbness or tingling in the feet or hands
- sores that do not heal
- unexplained weight loss
 - Symptoms of type 2 diabetes often develop slowly—over the course of several years—and can be so mild that you might not even notice them.

- Many people have no symptoms. Some people do not find out they have the disease until they have diabetes-related health problems, such as blurred vision or heart disease.

Management of type-2 diabetes

- Managing your blood glucose, blood pressure, and cholesterol, and quitting smoking if you smoke, are important ways to manage your type 2 diabetes.
- Lifestyle changes that include planning healthy meals, limiting calories if you are overweight, and being physically active are also part of managing your diabetes. So is taking any prescribed medicines.
- Following your meal plan helps you manage your diabetes.

medicines need to treat my type 2 diabetes

- Along with following your diabetes care plan, you may need diabetes medicines, which may include pills or medicines you inject under your skin, such as insulin.
- Over time, you may need more than one diabetes medicine to manage your blood glucose.
- Even if you don't take insulin, you may need it at special times, such as during pregnancy or if you are in the hospital.
- You also may need medicines for high blood pressure, high cholesterol, or other conditions.

health problems can may occurs with diabetes develop

- heart disease and stroke
- nerve damage

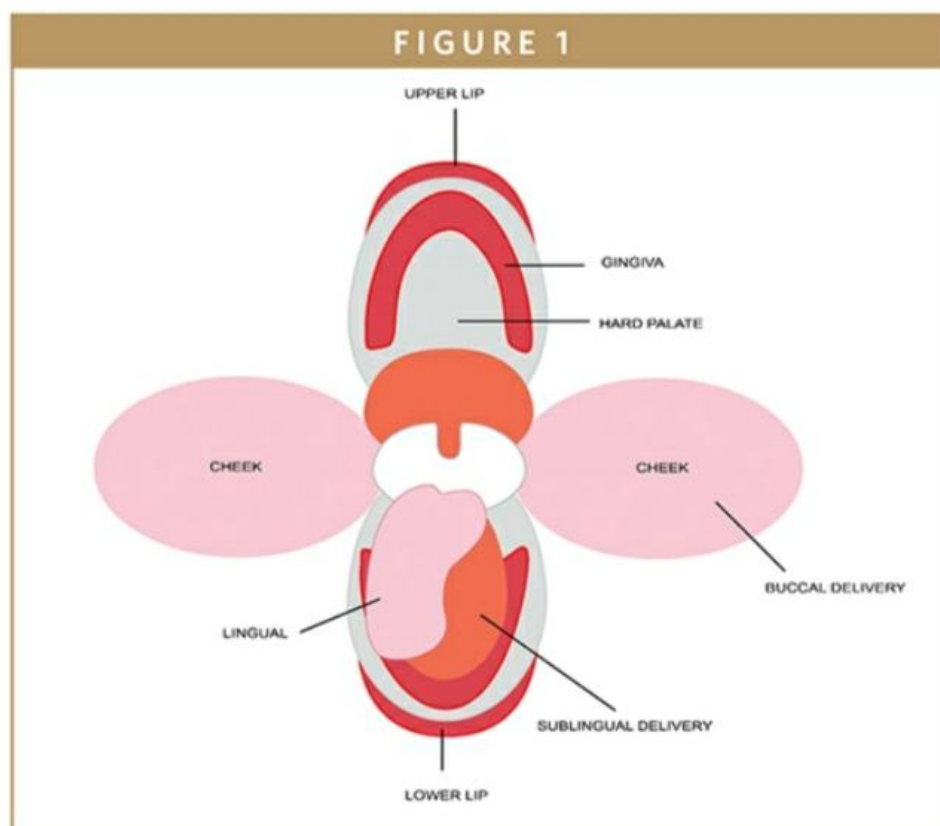
- kidney disease
- foot problems
- eye disease
- gum disease and other dental problems
- sexual and bladder problems
- non-alcoholic fatty liver disease (NAFLD).
- sleep, depression, some types of cancer.

INTRODUCTION OF BUCCAL FILM:

- Innovations in drug delivery hold the promise of minimizing dose-dependent side effects and maximizing biological activity while improving patient adherence.
- Peroral administration of drugs, the preferred route of drug administration in terms of patient experience, has several disadvantages, such as hepatic first-pass metabolism, longer onset of action, and enzymatic degradation of drugs within the gastrointestinal (GI) tract.
- When GI and hepatic degradation limit a drug's safety or efficacy, invasive injections are often the only viable mode of delivery – with the potential consequence of lower patient adherence.
- Buccal administration can achieve local and systemic effects and is attractive in that it overcomes the deficiencies of peroral administration.
- Indeed, substances absorbed through the buccal mucosa bypass gastrointestinal enzymatic degradation and the hepatic first-pass effect.
- Buccal administration further represents a better alternative to injections or tablets for those patients who have difficulty swallowing.

Details of Buccal Site:

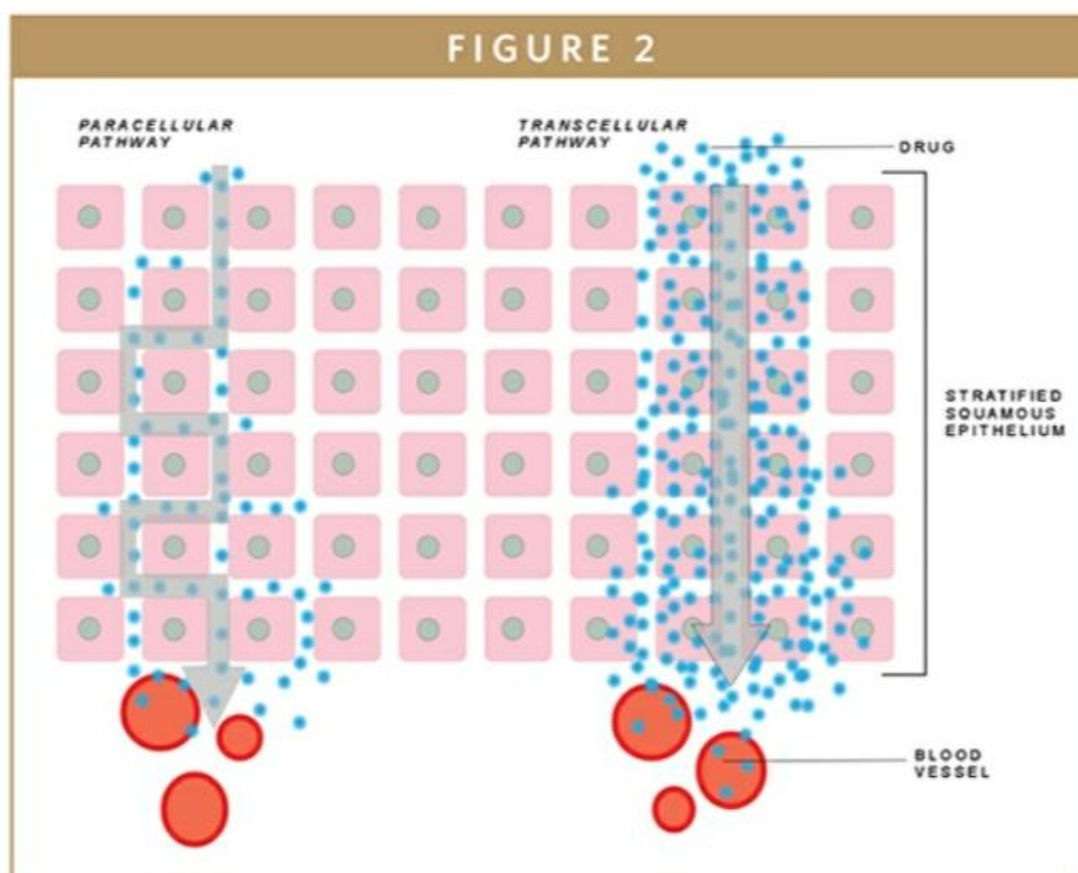
- The buccal area is the inner lining of the cheek and lip, representing about one third of the surface area of the oral cavity.
- The buccal mucosa consists of a surface layer of stratified squamous epithelium linked to the underlying connective tissue by a basal lamina.



- A network of blood capillaries is present in the connective tissue where drugs that have permeated through the epithelium can enter the systemic circulation via the internal jugular vein.
- The buccal epithelium acts as a barrier to hydrophilic drug permeation, while the connective tissue, which is more

hydrophilic in nature, appears to affect the diffusional lag time of lipophilic compounds.

- Drug transport across the mucosa can be trans- or paracellular with most hydrophilic drugs and macromolecules permeating through passive paracellular diffusion and lipophilic compounds and small hydrophobic molecules predominantly passing through by paracellular transport.



- As such, the cell membrane acts as the major transport barrier for hydrophilic compounds, and the intercellular spaces pose as the major barrier to permeation of lipophilic compounds.

The Importance of Mucoadhesion:

Mucoadhesion is when two surfaces, one of which is a mucous membrane, adhere to each other. It is a critical parameter for buccal

administration and formulation materials with optimal adhesive properties to be selected.

Mucoadhesion happens in two stages – the contact stage followed by the consolidation stage when adhesive interactions are established. There are likely multiple mechanisms at play causing adhesion. Importantly, adhesive joint failure will occur as a result of overhydration of a dosage form, or as a result of epithelia or mucus turnover. The turnover time for the buccal epithelium has been estimated to be 3 to 8 days compared to about 30 days for the skin.⁴

Site Advantages:

- In addition to the major benefit of systemic delivery that bypasses liver and gut degradation for greater bioavailability and lesser side effects, the mouth has a relatively large area for drug application and good accessibility compared to the nose, rectum, and vagina.
- the rapid cell turnover in the buccal mucosa reduces the risk of tissue damage or irritation.⁶ While the sublingual mucosa is more permeable, vascularized and thinner than the buccal mucosa, the surface of this mucosa is smaller, constantly washed by the saliva, and the shear exerted by the tongue makes it difficult to maintain the dosage form in contact with the sublingual mucosa.
- For all of these reasons, the cheek mucosa is a preferred site within the oral cavity for the administration of controlled-release systems that need to adhere for an extended period of time.

Buccal Dosage Forms:

- the buccal mucosa is only now being extensively studied as a novel drug delivery route, its potential for drug delivery has been known to mankind for centuries.
- Native Americans introduced chewing tobacco to European settlers in the 1500s, and coca leaves were chewed 8,000 years ago by Peruvian foragers.
- The buccal mucosa has been targeted using conventional dosage forms, such as tablets, troches and lozenges, and mouth washes and sprays, with several such products currently on the market.
- The challenge is in holding these dosage forms at the site of absorption, dosing precision (liquids) and discomfort (tablets). Tablets have the potential to separate from the mucosa, be swallowed, and then adhere to the wall of the esophagus causing a choking hazard, especially for children and the elderly.

More advanced drug delivery systems include films, patches, bilayer tablets, hydrogels, and tapes along with the use of micro- and nano-particulates are being developed to overcome the limitations of conventional dosage forms.

FILMS FOR BUCCAL DELIVER:

- Mucoadhesive films are a preferred dosage form for buccal mucosa administration given their flexibility, comfort, palatability, and adjustable size.
- They have demonstrated improved patient compliance compared to adhesive tablets.

- In contrast to liquid, gel, and ointment formulations, mucoadhesive films stay in contact with the mucosa longer, cover a larger surface area, and therefore provide more accurate drug dosing.
- Indeed, mucoadhesive films can be designed through careful material selection to maintain extensive adhesive contact with the mucosal membrane, prolonging the retention time of the delivery system for increased total drug absorption.
- Film compositions are designed to achieve the following physical properties: bioadhesive strength, tensile strength, pliability, flexibility, and extended disintegration.
- These properties are critical to achieve the target drug-release profile, patient acceptability, and compatibility with commercial manufacturing processes.
- Achieving the target specifications of buccal polymeric films is highly dependent on the type and concentration of the selected polymers and the dose of active ingredients being delivered.

Benefits of buccal film:

- Dose accuracy and comparatively better stability than other buccal drug delivery systems such as gel, cream or ointment.
- Fast absorption of drugs through rich vasculature of buccal region,
- Flexibility in drug release towards buccal mucosa,
- Easy termination in emergency cases,
- No need of chewing and swallowing.
- Film increases the systemic bioavailability of the drugs, as it bypasses the hepatic first pass metabolism.

- Drug can be protected from degradation by GI enzymes and the acidic environment.
- Minimum side effects.
- Self-administration is possible.
- Accurate dosing compared to liquid dosage forms.
- Taste masking is possible.
- Prolongs residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- Ease of administration to paediatrics, geriatric patients, and also to the patients who are mentally retarded, disabled or non-cooperative.
- Good mouth feel as compared to buccal tablet.

DETAILS OF DRUG AND OTHER EXCIPIENTS:

1) Linagliptin

- Linagliptin is used along with diet and exercise and sometimes with other medications to lower blood sugar levels in patients with type 2 diabetes (condition in which blood sugar is too high because the body does not produce or use insulin normally). Linagliptin is in a class of medications called dipeptidyl peptidase-4 (DPP-4) inhibitors.
- It works by increasing the amounts of certain natural substances that lower blood sugar when it is high.
- Linagliptin is not used to treat type 1 diabetes (condition in which the body does not produce insulin and, therefore, cannot control the amount of sugar in the blood) or diabetic ketoacidosis (a serious condition that may develop if high blood sugar is not treated).
- Linagliptin used in combination with insulin to treat diabetes has not been studied to date.

- Over time, people who have diabetes and high blood sugar can develop serious or life-threatening complications, including heart disease, stroke, kidney problems, nerve damage, and eye problems.
- Taking medication(s), making lifestyle changes (e.g., diet, exercise, quitting smoking), and regularly checking your blood sugar may help to manage your diabetes and improve your health.
- This therapy may also decrease your chances of having a heart attack, stroke, or other diabetes-related complications such as kidney failure, nerve damage (numb, cold legs or feet; decreased sexual ability in men and women), eye problems, including changes or loss of vision, or gum disease. Your doctor and other healthcare providers will talk to you about the best way to manage your diabetes.

Other excipients:

1)Eudragit RSPO

Chemical name: poly (ethyl acrylate, methyl methacrylate, trimethyl ammonium ethyl methacrylate chloride)

Formula:C₁₉H₃₄CLNO₆

Physical form: white powder

Mo. Weight:407.9 g/mol

2)HPMC K4M

Chemical name: hydroxy propyl methyl cellulose

Formula:C₅₆H₁₀₈O₃₀

Melting point:>145c

Application: controlled release agent; extended release agents; modified-release agent

Viscosity:4000Cst for 2%w/v

Solubility: soluble in cold water

3)HPMC E15

Chemical name: methanol E15 premium LV

Mo. Weight:10k-15k g/mol

PH:5-8.2%w/v

Application: film forming agents; release modifying agent

Viscosity: 15cst for 2%w/v

Density: 0.341g/mol

Solubility: soluble in cold water

Storage: well close container, in cool and dry place

4)PEG 400

Chemical name: polyethylene glycol 400

Physical state: liquid

Colour: slight yellow viscous liquid and bitter in test

Formula: HOCH₂(CH₂OCH₂)

PH: 4-7 for 5% solution at 25c

Application: plasticizer and penetration enhancer

Viscosity:90cst at 25c

Density: 1.128g/mol

5)Carbopol 940

Chemical name: carboxy poly methylene

PH: 2.5-3.0

Glass transition temp.:100-105c

Application: tablet binder; viscosity increasing agent

Viscosity: carbomers disperse in water to form acidic colloidal solution of low viscosity which when neutralized produce highly viscous gels

Density: 1.76-2.08 g/mol

Solubility: soluble in water and after neutralization soluble in ethanol and glycerine

Storage: storage in airtight; corrosion resistant container in cool, dry place. the use of glass, plastic or resin-linked container is recommended for the storage condition.

Method of preparing a buccal film:

1. Solvent Casting Technique

Solvent casting method is one of the most widely used methods for the manufacturing of buccal film. It has advantages of easy preparation, being cheap and can easily be adopted at lab scale. It involves following steps.

- (1) Prepare casting solution.
- (2) De-aerate the solution.
- (3) Pour the solution into a mould.
- (4) Dry the casting solution by evaporation.

(5) Cut the final dosage form containing desired amount of drug.

(6) Packing

- **2. Hot melt extrusion technique**
- In this method mixture of polymers and active pharmaceutical ingredients is melted.
- In order to achieve homogeneous mixture in various dosage form like tablets, granules, pellets or film, the melted material is pushed to pass through a small opening (orifice of a die).
- It produces thin film which further gets dried and packed.

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