
Mucoadhesive Buccal Films

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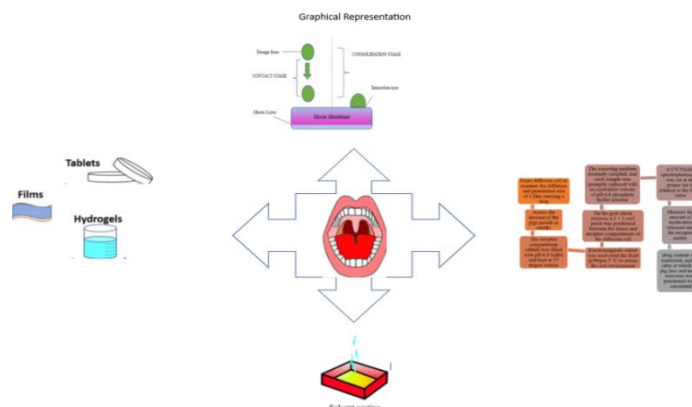
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Abstract: *Pharmaceutical formulations are experiencing a significant transformation as novel drug delivery techniques become increasingly available and effective. While there are many different types of medical dosage forms, each has its own limitations, such as tablet choking and painful parenteral dosages. Buccal drug delivery, which involves administering medication to the oral cavity, offers a convenient and easy-to-administer alternative. The oral route of medication administration has numerous benefits, including avoiding liver metabolism, enhancing drug bioavailability, and improving the onset of action. By directly entering the systemic circulation, active pharmaceutical ingredients can produce their therapeutic effects. As the buccal mucosa has a high degree of permeability and blood supply, it is a highly accessible drug delivery system. There are six theories that explain mucosal adhesion: electronics, wettability, adsorption, degradation, diffusion, and mechanics. Various in vitro and in vivo approaches have been used to study buccal drug delivery systems. This paper discusses the mechanisms of action, mucosal adhesion theories, and standard techniques for producing films. Key areas of study in buccal drug delivery systems include evaluating films for weight variation, thickness, folding endurance, surface pH, percentage of moisture absorption and loss, tensile strength, swelling index, content uniformity, and in vitro permeation studies.*

Keywords: *Buccal Films, Mechanism, Methods of Preparation, and Assessment, New Developments, Experimental Techniques.*

Graphical Representation



1. INTRODUCTION

The concept of buccal drug delivery can be traced back to ancient times when indigenous populations would chew on plant leaves or roots for their medicinal properties. The first recorded use of buccal administration for therapeutic purposes was in the 19th century when tobacco extract was applied to the oral mucosa for the treatment of migraine headaches. In the early 20th century, sublingual tablets were developed, and later in the 1960s, the first buccal adhesive tablet was introduced for systemic drug delivery. In order to enhance medication administration through the buccal mucosa, numerous buccal delivery systems, including films, gels, and patches, have been created and tested since then. Today, the buccal drug delivery system (BDDS) remains an active area of research and development in the pharmaceutical industry. The buccal drug delivery system is a method of delivering medications through the oral cavity's mucous membrane, specifically the buccal cheek area. This delivery method has a number of benefits, including quick drug absorption, avoiding first-pass metabolism, and better patient compliance because it is non-invasive. Buccal medication delivery can be utilised to treat oral disorders like mucositis or periodontitis locally as well as systemically. However, while designing buccal drug delivery systems, it's important to take into account the restricted space in the buccal region and the possibility of causing discomfort or harm to the oral mucosa.

Oral drug delivery is the preferred method of administering drugs due to its convenience, patient-friendliness, and cost-effectiveness. However, this route of drug administration has limitations that make it unsuitable for certain populations such as children, elderly and mentally ill patients who may have difficulty swallowing or absorbing the drugs. Some drugs may also be unstable and not survive the harsh conditions of the gastrointestinal tract or cause side effects such as nausea, vomiting, and irritation of the stomach wall. Additionally, the oral drug cannot be administered to patients who are comatose and has a slow beginning of effect and a foul taste. Despite these limitations, oral drug delivery remains advantageous as it allows for the avoidance of drug decomposition and is easily self-administered in case of

emergency. The medication can be quickly withdrawn from the oral cavity if a severe reaction takes place. [1]

Buccal Drug Delivery System (Bdds)

Oral medication delivery is a potential option as an alternative to other methods of drug administration due to its capacity to overcome certain limitations. When drugs are taken orally, issues like It is possible to prevent first-pass metabolism and medication degradation., particularly in cases of severe gastrointestinal conditions [2]. Furthermore, self-treatment via the oral cavity is simple and straightforward, and in case of poisoning, removing the medication from the oral cavity can be done quickly. Buccal administration is also a possible option for patients who are unable to take medications orally via the buccal route [3]. To put it differently, Since oral medication delivery avoids first-pass metabolism and drug breakdown, it is a desirable alternative to conventional drug administration techniques, as it is easy of self-treatment, and has the ability to administer drugs through the buccal route for patients who cannot take medications orally By retaining the dosage form close to the active ingredient for systemic administration or at the site of action, mucoadhesion has been a popular technique for increasing the efficacy of topical medications. This technique involves the dose form adhering to the biological membrane, which could be either epithelial tissue or a mucus layer covering the tissue. Oral medication administration frequently makes use of mucoadhesive polymers [4]. These polymers are made into broad sheets for oral films or strips, which are subsequently divided into individual dose units and packed for usage. [5] A buccal patch is a slow-release, insoluble drug delivery system that consists of one or more layers of polymer films or other excipients. The patch is made to stick to the gums, teeth, or lining of the mouth and deliver the medication gradually over time. In order to do this, mucoadhesive polymers can be used, which enables the drug to be released unidirectionally into the oral cavity, or both unidirectionally and bidirectionally. Once the patch has been used for a specific period of time, it can be removed and discarded. An ideal buccal patch should be flexible, resilient, soft, and firm enough to withstand oral pressure without tearing. To stay in the oral cavity for the necessary amount of time, it must also show good mucosal adherence. To assure the buccal patch's effectiveness, it is necessary to assess its mechanical, mucosal adhesion, and swelling properties. [6]

Advantages [7]



Fig 1: Advantages of Mucoadhesive Buccal Films

Limitations

Medications that cause irritation or have an unpleasant taste or smell are not suitable for administration through the buccal route. Additionally, drugs that are unstable under the conditions of the oral cavity, such as changes in pH, shouldn't be interpreted in this way, and only low doses can be administered through passive diffusion. Furthermore, intake and drinking may be restricted with oral dosage forms. However, buccal tablets can currently be swallowed by patients. Excessive hydration may cause the bioadhesive polymer to swell and affect the structural integrity of the composition by creating a smooth surface. [8]

Types:

Matrix Type

The matrix-type buccal patch is designed to release drugs and adhesives into the mucosa and oral cavity. It has a bi-directional configuration, allowing for drug delivery in both directions. The matrix design of the patch facilitates the controlled and sustained release of the drug through the buccal mucosa, providing an effective means of drug delivery for various medical conditions [9]

Reservoir Type

A type of oral patch known as a reservoir system has a hollow that is distinct from the adhesive layer and is used to store the medication and any additives. This design minimises distortion and deterioration of the buccal patch in the mouth cavity, prevents medication loss, and controls the direction of drug administration.[9]. By separating the drug from the adhesive layer, the reservoir system allows for better control over drug release and absorption, resulting in improved therapeutic efficacy for a variety of medical conditions.

Buccal films are thin, flexible, and adhesive films designed to adhere to the inner lining of the cheek (buccal mucosa) to deliver medication to the bloodstream. Here are some types of buccal films:

1. Mono-layered buccal films: These are single-layered films that contain a drug and a mucoadhesive polymer. They are typically used for delivering small-molecule drugs.
2. Bi-layered buccal films: These are two-layered films that contain a drug layer and a mucoadhesive layer. The drug layer contains the active ingredient, while the mucoadhesive layer helps the film adhere to the buccal mucosa.
3. Fast-dissolving buccal films: These are films that dissolve quickly in the mouth, allowing for rapid drug delivery. They are often used for emergency treatments or for patients who have difficulty swallowing pills.

Buccal Mucosa

The buccal mucosa is a naturally adhesive and lubricated area inside the cheek, which allows for smooth movement between cells and reduces friction. Drug delivery can occur at four sites within a mouth's cavity, including the region of the tongue, the mouth's roof, and the gums, and the buccal area. Specifically, the buccal route refers to drug administration through the anatomical part located between the inner surface of the gums and cheek, which is also known as the buccal endometrium or mucosa. The inner, moist cheek lining known as the buccal mucosa is a component of the oral mucosa. Lamina propria, submucosa, and stratified squamous epithelium make up its structure. The buccal mucosa is a desirable location for medication administration because it has a healthy blood supply and a relatively porous epithelial layer. Buccal mucosa has the advantage of being easily accessible, non-invasive, and has a wide surface area for absorbing drugs. Buccal delivery bypasses the hepatic first-pass metabolism and allows for sustained drug delivery, which can improve therapeutic efficacy and patient compliance. The oral mucosa is commonly used for the delivery of drugs like nicotine, contraceptives, analgesics, and antiemetics. However, there are certain challenges associated with buccal drug delivery, including drug degradation in the oral cavity, poor adhesion to mucosal tissues, and variable absorption due to individual variations in oral physiology.[10]

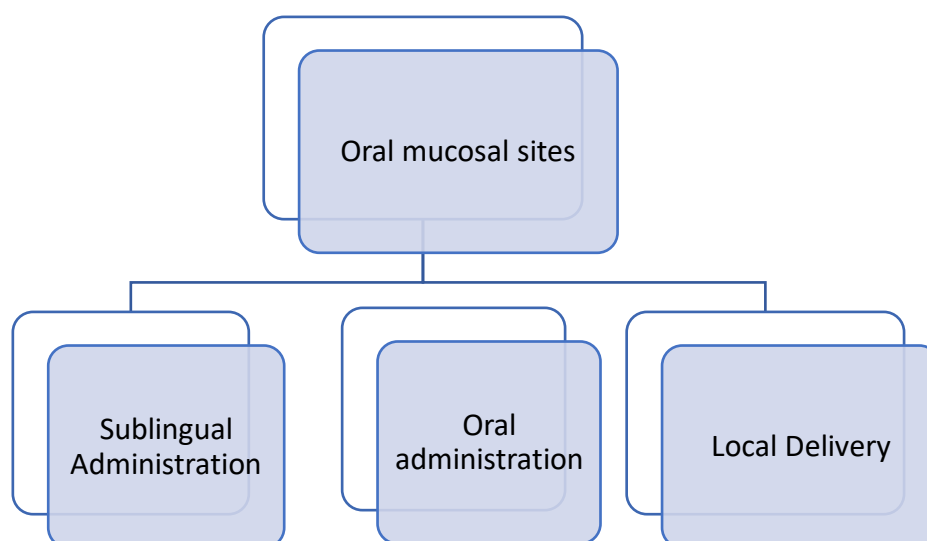


Fig 2: Oral Mucosal sites [11]

Mechanism of Mucoadhesion

Mucoadhesion refers to the ability of a drug and its carrier to attach to the mucosal layer, which is essential for the precise administration of medicinal agents. This process is multifaceted and involves several stages including adsorption and wetting, as well as the interpenetration of polymer chains. Through these mechanisms, the drug-carrier complex is able to cling to the mucous membrane and remain in place for an extended period, providing sustained release at the drug's intended target. Overall, the complex phenomenon of mucoadhesion is crucial for optimizing drug delivery and achieving therapeutic outcomes.[12]

1. The mucoadhesive delivery system is the immediate contact with the mucosal membrane through a wetting or swelling phenomenon.
2. Mucoadhesive delivery system penetration into a tissue or onto mucous membrane surface by interpenetration.[12]

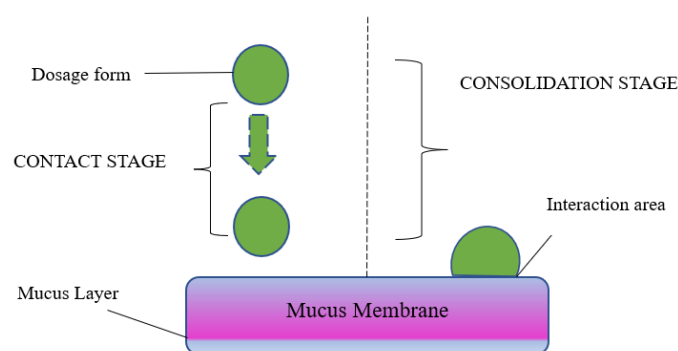


Fig 3: Mechanism of Mucoadhesion

Theories of Mucoadhesion

1. The electronic theory
 2. The adsorption theory
 3. The diffusion theory
 4. The mechanical interlocking theory
 5. The wetting theory
1. **Electronic theory:** According to this theory, mucoadhesion is primarily driven by electrostatic interactions between charged groups on the mucoadhesive and mucus surfaces. This theory assumes that the mucus layer contains charged groups, such as carboxyl, sulfhydryl, and amino groups, and that mucoadhesives with opposite charges can adhere to the mucus layer through electrostatic attraction.
 2. **Adsorption theory:** This theory proposes that mucoadhesion is a result of the adsorption of mucoadhesive molecules onto the mucus layer. The van der Waals forces, hydrogen bonds, and other intermolecular forces between the mucoadhesive and mucus molecules cause the adhesion to occur.

3. **Diffusion theory:** This theory suggests that mucoadhesion occurs through the diffusion of mucoadhesive molecules into the mucus layer, followed by an entanglement of polymer chains. This leads to the formation of a polymer network within the mucus layer, which enhances adhesion and prolongs drug release.
4. **Mechanical Interlocking Theory:** This theory proposes that mucoadhesion occurs due to the physical interlocking of mucoadhesive molecules with the mucus layer. This occurs when the mucoadhesive material penetrates the mucus layer and becomes entangled with the mucus strands. Overall, the mechanism of mucoadhesion is complex and involves multiple factors. The different theories provide insights into the various mechanisms that contribute to mucoadhesion and are used to design effective mucoadhesive delivery systems. [13]
5. **Wetting Theory:** According to this theory, a liquid's affinity for adhesion increases as its contact angle with the substrate surface decreases. The degree of wetting is determined by the contact angle that exists between a liquid and a substrate surface. A smaller contact angle means that the liquid will spread and stick to the substrate surface more readily because of its increased affinity for that surface. This is because a smaller contact angle implies that the cohesive forces within the liquid are weaker than the adhesive forces between the liquid and the substrate surface.

Design of Buccal Mucoadhesive Dosage Forms

Buccal Tablets: A type of oral medication known as a buccal tablet is intended to be inserted between the cheek and gum, allowing the drug to be absorbed into the bloodstream through the mouth's mucous membranes. Compared to conventional oral pills, this delivery strategy may result in faster and more effective absorption. [14]

Buccal Films: The buccal membrane, which is more flexible, capable of precisely calculating the medication dosage, and can extend the residence period, and for the patient's comfort, mucosal sheets and tablets are preferable over gels and ointments. [14]. By securing the wound's surface, the oral membrane can also lessen pain, enhancing the effectiveness of the treatment.

Buccal Gels and Ointments: Semisolid dosage forms are advantageous because they can be easily absorbed by the oral mucosa. However, the difficulty of insufficient gel retention at the application site can be addressed by using bioadhesive preparations. Bioadhesive polymers, such as sodium carboxymethyl cellulose, have the ability to transition from a liquid to a semi-solid state. This adjustment in state improves the viscosity of the formulation, resulting in a delayed or controlled release of the medication. This enhanced viscosity also allows the bioadhesive preparation to adhere to the mucosa for an extended period of time, increasing the effectiveness of the medication. [15]

Formulation Aspects of Buccal Films

- Active pharmaceutical ingredient
- Polymers: HEC, HPC, polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), Carbopol, and other mucoadhesive polymers.

- Plasticizers: Propylene glycol, PEG-100, PEG-400, etc
- Backing Layer: Ethyl cellulose
- Penetration enhancer: Unsaturated cyclic ureas (non-surfactants), methyl oleate, phosphatidylcholine (a fatty acid), oleic acid, capric acid, lauric acid, lauric acid/propylene glycol, and cyclodextrins (Inclusion complexes). [16]

Method of Preparation of Buccal Films [17]

❖ Drying and Casting

- ✓ vapor casting
- ✓ Sem solid casting

❖ Extrusion

- ✓ Extrusion of hot melt
- ✓ Extrusion with solid dispersion

❖ Rolling approach

1] **Solvent casting:** When creating a buccal film for drug delivery, solvent casting is a standard approach. In this method, the polymer is dissolved in a suitable solvent to create a polymer solution. After completely blending the solution, the API is added. After that, the resulting mixture is poured onto a flat surface and let to dry. The drug molecules and polymer combine to produce a thin film when the solvent evaporates. The buccal film may be made to stick to the buccal mucosa and release the medication gradually over a prolonged period of time. The solvent casting technique allows for the precise control of the film thickness and drug release kinetics.[18]

2] **Semi-solid casting:** Semi-solid casting is a technique used to prepare buccal films, which are thin films or strips placed inside the mouth to deliver drugs locally or systemically. In this method, a semi-solid mixture of polymers, plasticizers, and drug is poured onto a mold and then allowed to solidify. The film is then peeled off and cut into desired sizes. Semi-solid casting offers several advantages over other methods of buccal film preparation, such as easy handling, reproducibility, and uniform drug distribution.

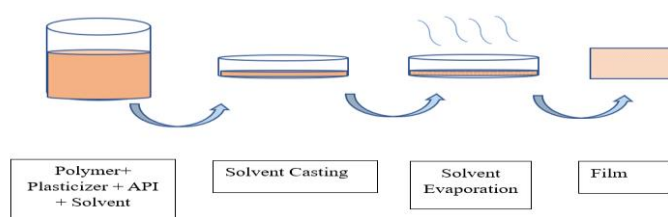


Fig4: Solvent Casting Technique

3] **Extrusion of Hot Melt:** Hot melt extrusion (HME) is a widely used tactic in the preparation of buccal films. In the preparation of buccal films, the HME process involves the melting and mixing of a polymer, a plasticizer, and the active pharmaceutical ingredient (API) at a controlled temperature and pressure. The molten mixture is then extruded through a die and cast onto a substrate, such as a release liner or a backing film, to form a thin film.

The choice of polymer and plasticizer in the HME process is critical to the properties of the final buccal film. Commonly used polymers include polyvinyl alcohol, polyethylene oxide, and hydroxypropyl methylcellulose, while plasticizers such as glycerol, polyethylene glycol, and propylene glycol are used to increase the film's flexibility and stickiness.[19]

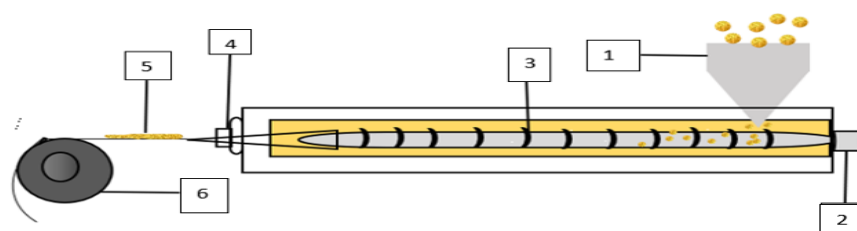


Fig5: Hot melt Extrusion- Labelling 1. Hopper, 2. Motor, 3. Extruder screw, 4. Film die, 5. Film, 6. Roller.

4] Extrusion with Solid Dispersion: This method involves dissolving the medication in a suitable solvent, then adding the resultant solution to molten polyethylene glycol (PEG) at a temperature below 70°C. The solvent used should be miscible with the drug but immiscible with the molten PEG to allow for complete solvent evaporation. As the solution is added to the molten PEG, the drug begins to precipitate out of the solution and forms a solid dispersion with the PEG matrix. The solvent that is utilized can have an impact on the drug's polymorphism in the solid dispersion. Solvents that promote the formation of a specific polymorphic form of the drug can be chosen to ensure consistency in the final product.[20]

5] Rolling Method: Well with the rolling method, a premix is prepared, active chemicals are added, and then a film is formed. Polar solvents, film-forming polymers, and other components are included in the premix (except API). The master batch feed tank has been filled with API. The charge is supplied by the first metering pump and control valve. The mixer is filled with the required amount of medication and swirled for a sufficient amount of time to produce a homogenous matrix. Using platen rollers, medium, and substrate.[21]

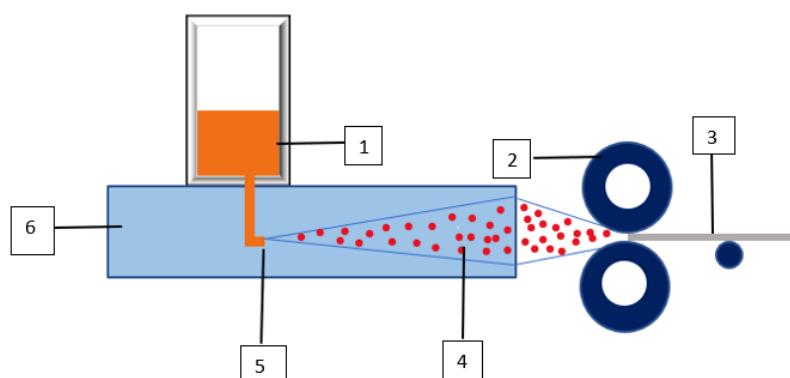


Fig6: Rolling Method- Labelling- 1. Liquid metal, 2. Consolidation rolls, 3. Spray rolled strip, 4. Atomized spray, 5. Atomizer nozzle, 6. Inlet gas.

Evaluation

- 1] **Weight variation:** To measure thickness, each patch's thickness can be measured using a thickness gauge, or an ordinary screw gauge at various points on the patch. The thickness average is then determined. The patch is then divided into pieces measuring $(1 \times 1 \text{ cm}^2)$ or 10 mm, and the piece's individual weight is measured to detect any weight anomalies. [22]
- 2] **Thickness:** With the help of a calibrated micrometre screw gauge, the buccal film thickness is determined. Five separate locations on the film are used to assess the thickness, and the mean value is computed. This is done to guarantee the consistency of the film's thickness due to the direct correlation with regard to the film's dosage accuracy that supports the reproducibility of the formulation procedure.[22]
- 3] **Folding Endurance:** Folding endurance is evaluated by folding the film continuously until it breaks in the same place. How many times the film could be folded in the same position without breaking determines the value of folding endurance.[23]
- 4] **% Moisture absorption:** In general, buccal films are designed to be stable and maintain their shape and properties when exposed to saliva and other fluids in the mouth. They typically contain hydrophilic polymers, which can absorb moisture and help to keep the film in place against the mucosal surface. The percentage moisture absorption of buccal films can be determined using the same formula as for other materials-
$$\text{Percentage moisture absorption} = ((\text{Wet weight} - \text{Dry weight}) / \text{Dry weight}) \times 100\%$$
- 5] **% Moisture loss:** A piece of the film is cut out and weighed. After that, the sample is put in a desiccator with fused anhydrous calcium chloride. For 72 hours, the desiccator is maintained shut so that any moisture in the sample can be absorbed by the calcium chloride. After 72 hours, the sample is removed from the desiccator and reweighed. The following formula is used to compute the average % moisture loss:
formula:
$$\% \text{ Moisture Loss} = ((\text{Initial Weight} - \text{Final Weight}) / \text{Initial Weight}) \times 100$$
 where Initial Weight is the weight of the sample before it was placed in the desiccator, and final Weight is the sample's weight following which was removed from the desiccator.[24]
- 6] **Tensile strength:** A film's tensile strength is a measurement of the amount of load required to cause deformation failure of the film. This property is determined by performing a tensile test on a film strip of specific dimensions. The test involves holding the film strip between two clips positioned at a specific distance and applying a load until the film ruptures. The film's tensile strength is then calculated using the following equation:
$$\text{Tensile Strength} = \text{Load at Rupture} / \text{Cross-sectional Area of Fractured Film}$$
 In this equation, the load at rupture is the amount of force required to break the film, and the area of the cross-section of the fractured film is the area of the film that has been

broken. The units of tensile strength are typically expressed in force per unit area, such as Pounds per square inch (PSI) or Newtons per square metre (N/m²). [25]

- 7] **Swelling Index:** A swelling index study is carried out to evaluate and compare the hydration characteristics of film polymers. Separate membranes (w₁) must be weighed before being put in a petri dish with a phosphate buffer solution that has a pH of 6.8. After that, samples are obtained periodically from the Petri plate, and any extra water is delicately wiped away using filter paper. The inflated film is then weighed once again (w₂). To calculate the swelling index of each system, the following formula is used:

Swelling Index = $(w_2 - w_1) / w_1 * 100$ In this equation, The weight of the film before swelling is w₁, while the weight of the film after swelling is w₂, and the result is expressed as a percentage. The swelling index provides an indication of the degree to which the film polymer absorbs water and swells under the given conditions.[26]

- 8] **Surface pH:** The films are allowed to swell by being in contact with 1 ml of distilled water for 2 hours at room temperature. By bringing the electrode into direct contact with the film's surface and allowing it to acclimate for one minute, the pH is determined. [27]

- 9] **Drug Content uniformity:** Buccal film is individually dissolved in 100 ml of pH 6.8 buffer before being added to the mixture and diluted as needed. The amount of medication in the film is determined using a spectrophotometric absorbance measurement at 242 nm. The average drug content is estimated.[28]

- 10] **In-vitro Release studies:** Using a few drops of phosphate buffer solution, a 2×2 cm² sample was put onto a microscope slide to examine the release rate of active components (pH 6.8). The slide was then positioned at a 45° angle in a 250 ml beaker with 100 ml of pH 6.8 phosphate buffer solution and kept in a water bath with circulating water that was held at 37°C. A suitable system was chosen to take out turbulence's impact on the discharge rate in order to assure stability. Regular samples were taken every 10 minutes for 90 minutes, starting from the time the slide was placed in the beaker. Prior to each sample collection, the slide was quickly removed and the buffer solution was mixed using a glass rod. A graduated pipette was used to extract 5 ml of the material and immediately passed through a fiberglass tube (such as a filter) to eliminate any solid particles. The slide was then quickly returned to the beaker, and the buffer solution was instantly altered. To stop the liquid from evaporating, a petri dish was placed on top of the beaker. The collected samples were examined using a UV-visible spectrophotometer at wavelengths of 235.5 nm and 264.5 nm, with the required dilution, to ascertain the number of active components. The spectrophotometer was used to calculate the samples' optical densities.[29]

- 11] **In-vitro diffusion study:** Using a modified Franz diffusion cell with a cellophane membrane, an in vitro diffusion investigation was conducted. Phosphate buffered saline (PBS), which has a pH of 6.8, served as the diffusion study's medium. The membrane, which was subsequently positioned between the donor and recipient Franz compartments,

was patched with a 1*1 cm² patch. The cellophane membrane was brought into contact with PBS pH 6 in the receptor compartment while being stirred with a magnetic bead stirrer at a speed of 50 rpm at 37 degrees Celsius. Regular 1 ml samples of the appropriate range were retrieved from the receiving chamber and replaced by new PBS that had a pH of 6.8. An ultraviolet-visible spectrophotometer was used at the appropriate wavelength and dilution to measure the drug concentration in the tests. The amount of drug released into the receptor media was calculated using the sample's optical density.[31]

12] Kinetic analysis: This is accomplished by selecting the formulations' best-fitting mathematical model. The dissolving data are entered into the appropriate mathematical models to get the R and k values. The model that fits the formulation in question the best is the one for which the R-value is the highest. The formulation's fickian or non-fickian diffusion pattern is determined using the n value for the best-fit model, which is kept on file. [32]

13] Ex- Vivo permeability study: [30]

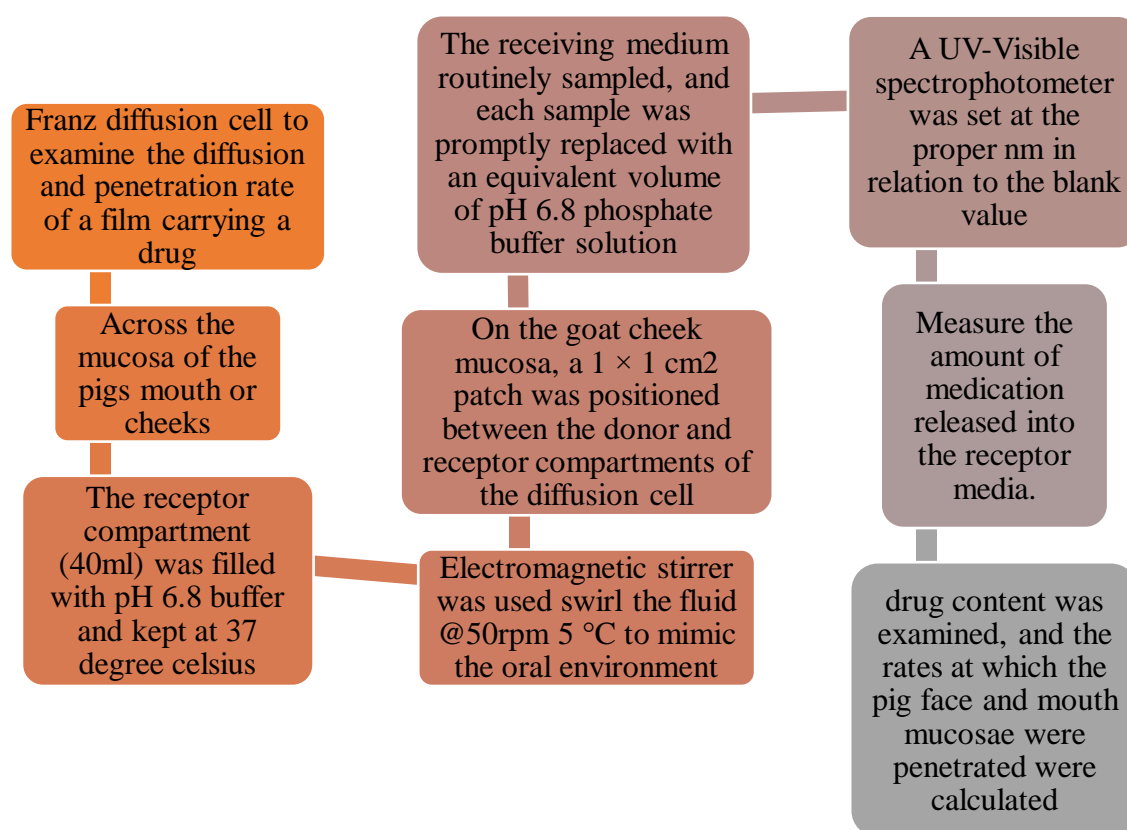


Fig7: Ex-vivo permeability study [30]

2. CONCLUSION

Recent innovations and research in buccal films have focused on improving drug delivery through the buccal mucosa. New Technology has been created to improve the permeation of drugs, such as using iontophoresis, ultrasound, and microemulsions. Researchers have also investigated the use of chitosan and alginate as examples of natural polymers, in buccal films to improve their mucoadhesive properties and prolong the drug release. Other approaches include the use of nano-sized methods for delivering medication, like liposomes and solid lipid nanoparticles, which can increase drug absorption and bioavailability. Overall, these recent innovations and research in buccal films have shown promising results in improving drug delivery through the buccal mucosa, which has the potential to offer many advantages over traditional drug delivery methods, such as improved patient compliance, reduced side effects, and faster onset of action.

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