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Buccal Film - An Innovative Dosage Form

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ABSTRACT

To overcome the problems or deficiencies associated with another route of drug delivery like parental's, scientists and pharmaceutical researchers are exploring another route of drug delivery such as the transmucosal route. In the oral mucosal cavity, the buccal region offers greater advantages due to the high blood supply and relatively permeable mucosal region. Along with the route of drug delivery the drug delivery system is of utmost importance in terms of safety, efficacy, and patient compliance. One such drug delivery system i.e. The Buccal film is emerging as an advanced technology in comparison to convention drug delivery systems. The buccal film is an elegant, convenient and effective dosage form with improved bioavailability as it bypasses the hepatic first-pass metabolism and also protects the drug from GI degradation. It is also the most acceptable and palatable dosage form considering its small size, thickness, and small dosage in the film. The increased patient compliance is due to no need to swallow the formulation thus making it suitable for pediatric as well as geriatric patients. The present article provides insight on the benefits of buccal film, benefits of buccal film, method of preparation, and evaluation parameters.

INTRODUCTION:

Amongst other routes of drug delivery, oral is the most preferred route of drug administration and is also most preferred by patients over other routes of drug administration[4]. However, the Preoral route of drug administration offers certain disadvantages like GI degradation of drug, hepatic first-pass metabolism along with decreased compliance in the case of pediatric and geriatric patients. Consequently, other absorptive mucosae are considered as a potential route of drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery[2]. These advantages include bypassing hepatic first-pass metabolism, preventing the GI degradation of drugs, and faster drug absorption[2].

Buccal films are the most recently developed dosage form for buccal administration. They have gained importance as efficacious and novel drug delivery systems and are cost-effective with good patient compliance. As buccal films are implied for attachment to the buccal mucosa, they can be formulated to exhibit local as well as systemic action. The buccal film may be preferred over the buccal tablet, in terms of flexibility and comfort. Buccal films have direct access to the systemic circulation through the internal jugular vein, which bypasses the drug from the hepatic first-pass metabolism leading to high bioavailability. Further, these dosage forms are self-administrable, pharmacoeconomic, and have superior patient compliance. The film can be defined as a dosage form that employs water dissolving polymer, which allows the dosage form to quickly hydrate, adhere and dissolve when placed on the tongue, or in the oral cavity, which results in systemic drug delivery. The main property of the buccal film is that due to the large surface area of the film, it allows quick wetting of the film which accelerates absorption of the drug quickly when compared to tablets. The rich blood supply to the buccal region acts as a perfect and fast site of drug absorption. Mucoadhesive buccal films are also formulated for local treatment of fungal infection making the buccal film a favorable route of drug delivery for both local and systemic effects.

Benefits of Buccal Film:

- The larger surface area of buccal film leads to rapid disintegration and dissolution of the film which leads to faster release of API.
- No need to swallow[1].

- No need to chew[1]..
- Can be administered to unconscious patients.
- Increased bioavailability as it bypasses hepatic first-pass metabolism[1].
- API is protected from GI enzymes.
- Minimum side effects and faster onset of action.
- Self-administration is possible.
- Increased compliance in the case of pediatric and geriatric patients.
- Taste masking is also possible[1].
- Accurate dosing as compared to the liquid dosage form.
- Good mouthfeel and stability[1].

Anatomy of Oral Cavity:

The oro-mucosal region is adhesive and acts as a lubricant. There are 3 different categories of drug delivery in the oral cavity[3]:-

- Sublingual delivery: It is the systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.
- Buccal delivery: It is drug administration through the mucosal membranes lining the cheeks (buccal mucosa).
- Local delivery: It is drug delivery into the oral cavity.

The selection of the oral mucosa is based on the anatomical and permeability differences of the mucosal membranes. The mucosa of the buccal and sublingual region has only small amounts of ceramidem and is thus more permeable when compared to other regions of the oral cavity.

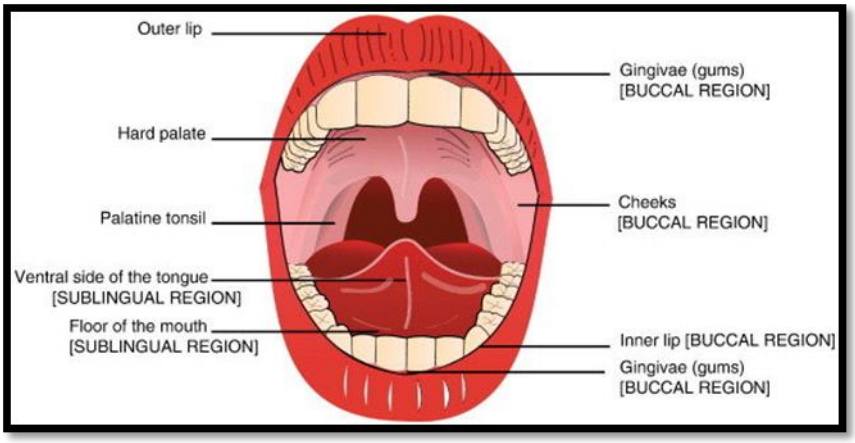

Fig. No. 1- Anatomy of the oral mucosa

The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailabilities of many drugs, and is convenient, accessible, and generally well accepted. The buccal mucosa is considerably less permeable than the sublingual area and is generally not able to provide the rapid absorption and good bioavailabilities seen with sublingual administration. Being more permeable than the buccal region the sublingual is usually not preferred due to lack of immobile mucosa, the sublingual region is continuously washed by a considerable amount of saliva which makes device placement difficult. Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action making it appropriate for drugs with short delivery period requirements with the infrequent dosing regimen. Due to two important differences between the sublingual mucosa and the buccal mucosa, the first difference is the lesser permeability of the buccal region than the sublingual route making it not so suitable for drugs that require rapid onset of action. While the second difference is the presence of immobilized mucosa making it a suitable region for retentive systems. Adhesion to the oral mucosa permits not only the intimacy of contact and the possibility of improved drug absorption but also the ability to achieve an optimum residence time at the site of administration. These characteristics make the buccal mucosa a more appropriate site for prolonged systemic delivery of drugs. Thus, the buccal region is suitable for drug molecules with less permeability or sustained-release formulations and perhaps peptide drugs.

FORMULATION ASPECTS OF BUCCAL FILM[5]:

Active pharmaceutical ingredient (API):

Generally, about 5-30% w/w of API can be loaded into the buccal film, depending on the solubility of the API it can be in a dissolved form in case the API is water-soluble it is in solution form. In the case of a water-insoluble drug, It is then uniformly dispersed into the film. As per the desired properties of the formulation, the API can be milled, micronized, nano-crystallized, or complexed with cyclodextrin or other suitable cpmplexind agents to increase its solubility which helps in the formulation of a film with smooth texture.

Mucoadhesive polymers:

Mucoadhesive polymers are classified into two main groups, such as hydrophilic polymers and hydrogels. The hydrophilic polymers most commonly used in buccal dry or partially hydrated dosage forms include polyvinyl alcohol [PVA], sodium carboxymethylcellulose [NaCMC], hydroxyl propyl methyl cellulose [HPMC], hydroxyl ethyl cellulose, and hydroxypropyl cellulose [HPC]. Hydrogels include anionic polymers like Carbopol, polyacrylates, cationic polymers like chitosan, and non-ionic polymers like eudragit analogs.

Plasticizers:

Plasticizers are added in a conc. Of about 0-20% depending on the desired characteristics of the film. Plasticizers give the film flexibility and tensile strength thus making plasticizers an important part of the formulation. Plasticizers are selected based on the type of solvent used and the compatibility of the plasticizer with the solvent. Plasticizers affect the mechanical properties of the film and thus should be selected carefully. The most commonly used plasticizers are Glycerine, Propylene glycol, PEG 400, Glycerol, etc.

Penetration enhancers:

The penetration enhancers are also important excipients added to the film and are required when the drug has to reach systemic circulation and also in the case of low permeability drugs. The penetration enhancer selected must be safe, non-irritant, and should have a reversible effect. It should not damage the epithelial layer permanently. The commonly used penetration enhancers are fatty acids, bile salts, surfactants, etc.

Taste masking agents:

Taste maskers are generally used in the case of APIs with bitter taste which makes the formulation unpalatable. Thus, before adding the API into the formulation the taste must be masked.

Sweeteners:

The sweeteners are generally used to improve the taste of the formulation and make the formulation much more palatable. Natural as well as artificial sweeteners are used in the formulation. The natural sweeteners include Glucose, dextrose, maltose, sucrose. Artificial sweeteners are used for diabetic patients like saccharine, aspartame, etc.

Saliva stimulating agents:

Generally, acids that are used in the preparation of food can be utilized as salivary stimulants. The purpose of using saliva stimulating agents is to increase the rate of production of saliva which would aid in the faster disintegration of the rapid dissolving film formulations. Citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them. These agents are used alone or in combination between 2 to 6% w/w of the weight of the film.

Flavoring agents:

It is an important excipient mainly in the case of orally disintegrating films. The flavoring agents help to improve patient compliance mostly in pediatric patients. Various oils like peppermint oil and fruit flavors like apple, mango, strawberry, etc. can be added to improve patient compliance and eliminate the unpleasant drug after taste.

Colouring agents:

To improve the elegant appearance of films, coloring agents are incorporated in the formulation. FD&C-approved coloring agents are used.

METHOD OF PREPARATION:

The buccal film manufacturing process includes the following techniques.

- Solvent casting technique

- Hot-melt extrusion technique

1. Solvent casting technique:

It is a widely used method of preparation of the buccal film. The steps involved are:

- Water-soluble polymers are dissolved in water to form a viscous solution.
- API and other excipients are dissolved in a suitable solvent medium.
- Both solutions are mixed to form a homogenous solution.
- The solution formed is then cast and allowed to dry.

2. Hot-melt extrusion technique:

A hot-melt extruder is used in this process. This technique involves shaping a polymer into a film via the heating process. A blend of pharmaceutical ingredients including API in the dry state is filled in the hopper, conveyed, mixed, and subjected to the heating process, and then extruded out in molten state melted by the extruder. The molten mass thus formed is used to cast the film. A critical step is the casting and drying process. This technique has many advantages, such as this process involves lower temperature and shorter residence times of the drug carrier mix, absences of organic solvents, continuous operation possibilities, minimum product wastage, good control of operating parameters, and possibilities to scale up.

EVALUATION OF BUCCAL FILM:

Weight and thickness:-

Three films of each formulation are taken and weighted. The average weight of the film is then calculated. For the thickness of the film, three films of each formulation are taken and their thickness is measured at three different places using a micrometer screw gauge of vernier caliper. The mean value is then calculated.

Drug content uniformity:-

5 films of the final formulation weighted previously are dissolved in 100ml of isotonic buffer pf pH 6.8. this solution is then filtered using Whatman filter paper and after suitable dilution, the drug was analyzed using a spectrophotometer.

Surface pH of the film:-

The film was allowed to swell on the surface of the agar plate for 2h. The pH of the swollen film was then determined using a pH paper. A mean of three readings is to be recorded.

Swelling index [5]:-

The weight and diameter of the original film samples are measured, the samples are then allowed to swell on the surface of the agar plate kept in an incubator maintained at 37 ± 0.2ºC. The weight of the films (n=3) is determined at different time intervals (1-5 h). The percent swelling, % S is to be calculated using the following equation:

$$\text{Percent swelling } [\%\ S] = [Xt - Xo / Xo] \times 100,$$

Where, Xt =The weight of the swollen film after time t, x

Xo =The initial film weight at zero time.

Folding endurance:-

The films sample is folded repeatedly in the same place till it breaks. The no. Of times a film can be folded without breaking is known as its folding endurance. A mean of three films is taken.

Morphological Characteristics:-

The morphological characteristic is determined with help of Scanning Electron Microscopy (SEM).

Tensile strength:-

The property of film that requires load causing deformation and finally failure of a film is called tensile strength. Two clamps spaced at equidistance are positioned in such a way that film strips are placed in between them. By applying load at rupture and knowing the cross-sectional area of fractured film, a tensile film can be calculated by the following equation:

Tensile strength (N/mm2) = Breaking force (N)/Cross-sectional area of sample (mm2).

Percent Moisture loss:-

Three films are placed in a desiccator with anhydrous calcium chloride, the films are taken out after 3 days and then weighed. The percentage moisture loss was calculated by the formula:

Percentage Moisture Loss= [(Initial weight – Final weight) / Initial weight] × 100

Percent Moisture Absorption:-

The films are kept in a desiccator at room temp for 24hrs with saturated potassium chloride solution at 84% RH. The films are weighted after 24hrs. The percent moisture uptake is calculated by the formula:-

Percentage moisture uptake = [(Final weight – Initial weight) / Initial weight] × 100.

***In-Vitro* dissolution Study[5]:-**

USP type II apparatus (Basket type apparatus) was used for dissolution studies with pH 6.8 buffer (50 ml) as a dissolution medium at 37°C temperature and speed at 50 rpm. 1ml of sample solution was withdrawn and equilibrated with a fresh dissolution medium. Whatman filter paper of 0.45 μm was used to filter the buccal films and API was analyzed spectrophotometrically at λmax.

***In-Vitro* Drug release[5]:-**

Franz diffusion assembly is used to determine the *in-vitro* drug release. The assembly contains two compartments, the receptor compartment and the donor compartment. The receptor compartment contains a buffer solution of pH 6.8 and the donor compartment contains 10mg of the drug. A dialysis membrane was soaked in a receptor medium for 24hrs and then placed between the compartments. During the entire process, the temperature was maintained at 37°C by a circulating water bath. At a specific time interval, till 8 h 0.5 ml of the sample was withdrawn from the receptor chamber and filled with fresh buffer. Suitable dilution was carried out and the amount of drug release was spectroscopically analyzed. The flux value was identified by the following formula:

Flux = Amount of drug released (mg)/Time (hr) × Area (cm^2)

***Ex-Vivo* permeability study[5]:-**

For performing permeation studies modified Franz diffusion cell was utilized. Two compartments, one of the donor compartments and other receptor compartments were seen of 25 ml capacity. To maintain the temperature at 37°C, the receptor compartment was enclosed with a water jacket. The receptor chamber consist of about 22-23 ml of pH 6.6 phosphate buffer. The separated buccal epithelium was then mounted between the two chambers and the entire assembly was placed on a magnetic stirrer by putting a magnetic bead. It was kept aside for stabilization after which 1 ml of the sample was withdrawn at regular intervals and was suitably diluted for analyzing its spectrophotometrically.

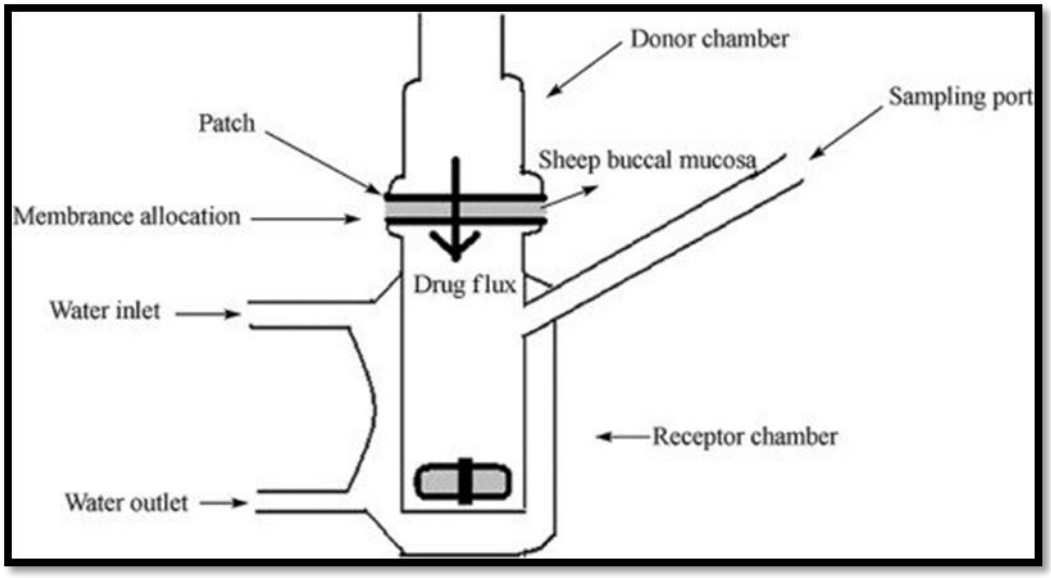

Fig. No. 2- *Ex- Vivo* Permeability study assembly In Franz diffusion cell

Stability studies:-

Stability studies were performed to analyze the change in the formulation during storage. The formulations are kept in triplicate for 3 months at 40ºC ± 2ºC and 75± 5% RH in the stability chamber. The films are analyzed after 3 months for folding endurance, drug content, and *in-vitro* release.

APPLICATION:

- Multilayer drug film construction is possible, which is an emerging area for immediate application. Two or more drugs could be combined into one format and the layers may be formulated to have the same or various dissolution rates.

- The films can be formulated in such a way that the dissolution rates of the drugs can range from minutes to hours.

- Films act as gastro retentive dosage forms, in which the dissolution of the films could be triggered by the pH or enzyme secretions of the gastrointestinal tract, and could be potentially used to treat gastrointestinal disorders.

CONCLUSION:

The present review concludes that the buccal film is an accurate and acceptable dosage form with good patient compliance and convenience which protects the drug from hepatic first-pass metabolism and GI degradation and shows good bioavailability of the API. It is the most promising and innovative dosage form for both pediatric and geriatric patients and also for patients with mental illness and swallowing difficulties. The buccal film has the potential to replace the conventional dosage form due to its advantages over the conventional dosage forms and can be manufactured at low costs. This technology provides a good tool for the maintenance of drug therapeutic value, as well as pharmacoeconomic value.

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