BUCCAL FILM: A NOVEL APPROACH FOR ORAL MUCOSAL DRUG DELIVERY SYSTEM

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ABSTRACT

Buccal drug delivery especially refers to the delivery of drugs through the buccal mucosal membrane lining of the oral cavity. For geriatric and pediatric patients who undergo difficulties in swallowing conventional oral solid dosage forms, the buccal film is a better alternative. The buccal film is appropriate for the drugs which experience high first-pass metabolism and is used for enhancing bioavailability with reducing dosing frequency to mouth plasma peak levels, which thus limit side-effects and make it cost-effective. It enhances the efficacy of API in the oral cavity after the contact with less saliva as contrasted to tablets, without chewing and no need for water for administration. This review briefly describes the advantages and disadvantages of buccal film, an anatomical structure of oral mucosa, highlighting the mechanisms of drug permeation, formulation technologies, methodology in evaluating buccal film, and recent advances of the buccal film as a tool for drug delivery for various treatments.

Keywords: Buccal film, Oral mucosal drug delivery system, Bioavailability enhancement.

INTRODUCTION

Among the various routes of drug delivery, oral-mucosal drug delivery offers distinct advantages as buccal mucosa is the most suited for local, as well as systemic delivery of drugs [1]. The buccal film is a drug delivery system that has rapidly gained acceptance as a new way of drug administration, improved safety and efficacy of drug molecule, and the enhanced onset of action [2]. The buccal film is an elegant and effective dosage form with enhanced bioavailability when compared to other dosage forms, as it by-passes the hepatic first-pass metabolism [3]. The site of drug administration in oral-mucosa is subdivided into buccal and sublingual mucosa [4]. The order of permeability of the oral cavity is given as sublingual > buccal > palatal [5]. The buccal mucosa being comparatively immobile mucosa than sublingual mucosa and readily available, it makes it more advantageous for retentive systems used for oral-mucosal drug delivery [6]. The buccal film may be preferred over a buccal tablet, in terms of comfort and flexibility [7]. The buccal film is well known that the absorption of therapeutic compounds from the oral-mucosa provides direct entry of a drug into systemic circulation through the jugular vein [8]. The advantages of buccal film are low cost, ease of administration, high patient compliance [9]. Active pharmaceutical ingredients (API), various polymer, plasticizer, saliva stimulating agent, permeation enhancers, sweeteners, flavoring agents, preservatives, and color, are used in formulating buccal film. The buccal film is essentially positioned on oral mucosal tissues, which is quickly wet by saliva in the mouth; the film is quickly hydrated and follows on to the site of application [10]. The main property of buccal film is that, because of the large surface area of the film, it allows quick wetting of the film which increase the absorption of the drug quickly as compared to the tablets. The buccal mucosa is rich with blood supply, which acts as a perfect and fast site for the absorption of drug [11].

ADVANTAGES OF BUCCAL FILM

The advantages of buccal films are as follows:

1. The buccal film shows a comparatively rapid onset of action with lesser side effects than other routes of administration [12].
2. Flexible and portable so provide ease in transportation during handling and storage [13].
3. Accurate dose administration [13].
4. Enhanced stability and safety [14].
5. As compared to the intravenous delivery system, mucosal delivery systems have the easy application of dosage forms with no pain on administration leading to improved patient compliance [15].
6. Avoids the first-pass metabolism and hence the drug will not get exposed to the gastrointestinal fluid [16].
7. By incorporating mucoadhesive polymers of “SR” grade, this system can also attain sustained drug delivery [17].
8. Low dose frequency due to longer duration of residence time along with controlled drug release [18].
9. Due to direct contact and adhesion buccal film remains for a long period at the application site and thus increases bioavailability using a low concentration of API [19].
10. Environmental factors such as acidic and degradation environment found in the oral drug delivery can be evaded by buccal film dosage form [20].
11. Appropriate dosage form for geriatric and pediatric patients experiencing difficulty in swallowing or nauseating and patients who are mentally ill or physically disabled [21].

DISADVANTAGES OF BUCCAL FILMS

There are numerous advantages of the buccal film but with few disadvantages lead to a main challenging formulation.

1. Barrier properties of the oral mucosa [22].
2. Restriction of drinking and eating [23].
3. Drugs with a lower dose requirement can be administered [23].
4. Dilution of drug and swallowing of the formulation due to vigorous secretion of saliva [24].

ANATOMY AND PHYSIOLOGY OF ORAL MUCOSA

The oral mucosa acts as an important route for the delivery of drugs. The oral cavity has been diagrammatically represented, as shown in Fig. 1. The oral cavity presents the total surface area of about 100 cm², that is, lined by mucus membranes [25]. The oral cavity consists of about 100 cm², that is, lined by mucus membranes [25]. The oral cavity has been diagrammatically represented, as shown in Fig. 1. The oral cavity presents the total surface area of about 100 cm², that is, lined by mucus membranes [25]. The oral cavity consists of about 100 cm², that is, lined by mucus membranes [25]. The oral cavity has been diagrammatically represented, as shown in Fig. 1. The oral cavity presents the total surface area of about 100 cm², that is, lined by mucus membranes [25]. The oral cavity consists of about 100 cm², that is, lined by mucus membranes [25]. The oral cavity has been diagrammatically represented, as shown in Fig. 1. The oral cavity presents the total surface area of about 100 cm², that is, lined by mucus membranes [25]. The oral cavity consists of about 100 cm², that is, lined by mucus membranes [25].
The oral mucosal cavity comprises the multilayered epithelial tissues that are additionally covered by mucus. Here is a basal membrane present inward to the epithelial tissues. Inside the basal membrane, there is a layer of connective tissue called lamina propria. The lamina propria provides a mechanical support function. After this, the sub-mucosal part begins. It contains the different blood vessels as well as nerves from the central nervous system. The cross-section of the buccal mucosa is represented in Fig. 2. The sub-mucosal part provides the highest vascularity for the complete absorption of the drugs. The human oral mucosa contains both keratinized epithelium (found in the gingival and part of the hard palate) and the non-keratinized epithelium (found on the surface of the distensible lining mucosa, of the soft palate, floor of the mouth, lips, and cheeks) [25].

The buccal region is the part of the mouth, limited anteriorly, and laterally by the lips and cheeks, posteriorly and medially by the teeth as well as gums, or above and below by the impressions of mucosa from the lips and cheeks to the gums. Buccal mucosa’s essential role is similar to the skin, which is protection of underlying structures from foreign agents [27]. The permeability of the buccal mucosa is 4–4000 times greater than that of the skin approximately. The order of permeability of the oral mucosa is sublingual>buccal> palatal which relies on relative thickness and level of keratinization [26].

The mucus layer
To the mucosal epithelial surface a clear and viscid secretion which is thin, continuous gel covers are adherent called mucus. In the human, the mean thickness of this layer varies from around 50 to 450 µm. The goblet cells lining the epithelial or by extra-ordinary exocrine glands that secreted mucus. The specific composition of the mucus layer differs significantly relying on the species, the anatomical location, and the pathophysiological state [28].

However, it has the following general composition:

| Components           | Percentage |
|----------------------|------------|
| Water                | 95         |
| Glycoproteins and lipids | 0.5–5   |
| Mineral salts        | 1          |
| Free proteins        | 0.5–1      |

MECHANISM OF BUCCAL FILM
Buccal film when, simply positioned on the patient’s oral-buccal mucosal tissue, instantly become wets by saliva. Due to the presence of hydrophilic polymers and other excipients, the film quickly hydrates, dissolves, and releases the medication, thus ensuring the absorption of medicament [29].
Drug absorption pathways

The drug transport mechanism through buccal mucosa involves two major pathways:

1. Trans-cellular (intracellular)
2. Para-cellular (intercellular)

The absorption capability of the buccal mucosa is affected by the lipid solubility and molecular weight of the diffusant. Absorption of a certain drug through buccal mucosa is found to increase when carrier pH is lowered and decreased by an increase in pH [30].

Buccal film dosage form release mechanism

Buccal film dosage form further divided into three types they are as follows:

1. Type I: Single layer device suffers from drug loss due to multidirectional drug release on significant swallowing.
2. Type II: Impermeable backing layer is superimposed on the top of the drug-loaded bio-adhesive layer prevents loss from the top surface in the oral cavity.
3. Type III: Unidirectional drug release can be achieved by coating every face of the dosage form except the one that is in contact with buccal mucosa. Since the drug release from one side will minimize drug loss [27].

Theories of bio-adhesion

Several theories have been proposed to explain the fundamental mechanism of attachment.

1. Electronic theory
2. Adsorption theory
3. Diffusion theory
4. Wetting theory
5. Absorption theory
6. Fracture theory

Among the above mentioned theories, adsorption theory plays an important role in the adhesion of the buccal film mechanism.

Adsorption theory

As per adsorption theory, after initial contact between the buccal mucosal surface and the material adheres to it has their own surface energy.

Chemical bonds involves following forces:

1. Primary chemical bond: Such as covalent nature, this is undesirable because higher strength may result in a permanent bond.
2. Secondary chemical bond: Different forces of attraction includes electrostatic forces, Van der Waals forces, hydrogen, and hydrophobic bonding, which are weak in nature, thus produces a semi-permanent bond [28].

IDEAL CHARACTERISTICS OF BUCCAL FILM

1. All degradation products and polymers should not be toxic, poisonous, and irritant and must be free from impurities [31].
2. It should have good spread ability, swelling, wetting, solubility, biodegradability, viscoelastic properties, and biocompatible pH range [32].
3. It should have an appropriate shelf life without decomposition on storage [33].
4. It should adhere quickly to the buccal mucosa and should have good mechanical strength [34].
5. It should have adequate patient compliance without obstructing normal functioning such as talking, eating, and drinking [34].
6. Drugs should release in a controlled manner [34].
7. Unidirectional passage of drug release should be provided toward the mucosa [35].
8. The rate and extent of drug absorption should be facilitated [35].
9. The dose should be lower than 20 mg with low molecular weight [36].
10. It should have good stability in water and saliva [36].
11. It should have the ability to permeate oral mucosal tissue [36].
12. It should not have a bitter or unpleasant taste [37].

COMPOSITION OF BUCCAL FILM

Active ingredients

The buccal film technology has the potential for delivery of variety of APIs [38]. Active pharmaceutical substances can be from any Biopharmaceutical Classification System (BCS) class of pharmaceutically active substances that can be given either orally or even by buccal mucosa. To make a successful and effective formulation the drug to be administered should be <20 mg daily [39]. Table 1 gives a list of marketed buccal films.

Plasticizer

Plasticizers are very critical for the formulation of a buccal drug delivery system [42]. They help by improving the mechanical properties of the buccal film which includes tensile strength, elongation of the film while additionally provide other advantages such as a reduction in the brittleness of the film and enhanced flexibility along with an increment in the flow property of the polymer and slashing of the glass transition temperature of the polymer. The amount of the polymer used can be remodelled which subsequently alters the properties of the final film so obtained. Examples of plasticizers include glycerin, sorbitol, propylene glycol, polyethylene glycol, tri-acetin, dibutyl phthalate, tri-ethyl-citrate, acetyl tri-ethyl-citrate, and other citrate esters. The amount of the plasticizer to be used can vary from about 0 to 20% w/w of the dry polymer weight. Plasticizers also upgrade the folding capacity of the final buccal films [43]. Glycerin was employed as a plasticizer in preparation of fast dissolving buccal films containing a solid dispersion of isradipine [44].

Sweetening agents

Sweeteners play a pivotal role in the pharmaceutical preparations which have an aim of either disintegration or dissolution in the mouth. The traditional sources of sweeteners are, namely, sucrose, dextrose, fructose, glucose, liquid glucose, and iso-maltose. Fructose is a versatile sweetener employed in industries as sweetness of fructose is recognized quickly in the mouth when compared against sucrose and dextrose and while it is more sweeter than sorbitol and mannitol as well as polyhydric alcohols such as sorbitol and mannitol. Polyhydric alcohols offer reduced carcinogenic chances and lack the bitter after taste which is an important parameter in preparation of oral preparations [45]. Herbal sweeteners can also be used for example being Rebiana, derived from the plant Stevia rebaudiana (South American plant) having more than 200–300 times

Table 1: List of marketed buccal films

| Active drugs         | Uses                              | Manufacturer                  | Reference                           |
|----------------------|-----------------------------------|-------------------------------|-------------------------------------|
| Fentanyl Citrate     | Opioid analgesic                  | Meda Pharmaceuticals, Inc      | Satheesh Madhav et al. 2012 [39].   |
| Buprenorphine        | Opioid analgesic                  | Bio delivery Sciences          | Satheesh Madhav et al. 2012 [39].   |
| Loratadine           | Anti-histaminic                   | Hughes medical corp.          | Dahiya et al. 2009 [40].            |
| Donepezil            | Alzheimer’s                       | Labtec                        | Dahiya et al. 2009 [40].            |
| Simethicone          | Bloating, belching                | Novartis                      | Dahiya et al. 2009 [40].            |
| Phenylephrine        | Nasal decongestant                | Pfizer                        | Dahiya et al. 2009 [40].            |
| Menthol Canker sore  | Cooling sensation in throat pain  | Innozen                       | Dahiya et al. 2009 [40]. Canker sore|
| Choline              | Salicylate                        | To treat aphthous lesions      | Danek et al. 2017 [41].             |
sweetness of sucrose [46]. Artificial sweetener such as Saccharin Sodium was also employed in formulation of buccal film [47].

Surfactants
Surfactants are utilized as solubilizing or wetting or dispersing agents with the aim that the film gets melted within seconds and liberate the active agent instantly. Surfactants also enhance the solubility of poorly soluble drugs in fast-dissolving buccal films. Examples include poloxamer407, sodium lauryl sulfate, benzalkonium chloride, tweens, and spans [48].

Flavoring agent
Flavoring agents are used to providing flavor to the product which is also a factor of patient compliance. Flavoring agents can be chosen from a wide variety of materials including synthetic flavor oils, oleoresins, and extract obtained from multiple parts of the plants such as leaves, fruits, and flowers. Flavors can be employed solo or in conjunction with each other. Peppermint oil, cinnamon oil, spearmint oil, and oil of nutmeg are examples of flavor oils, whereas vanilla, cocoa, coffee, chocolate, and citrus are fruity flavors derived from fruits. Flavors can be used alone or in one or more combination. The quantity of flavor required to hide the taste of the original drug depends on the flavor category and its power. Mostly, a maximum of 10% w/w flavors is added in the buccal film formulations. To enhance the flavor’s strength as well as to increase the pleasant sensation of the product, cooling agents such as mono-methyl succinate can be added [49,50].

Coloring agent
The patient compliance of oral disintegrating films relies on the flavoring agent incorporated into it which, in turn, is dependent on the category of drug present in the formulation, for example, Peppermint oil and cinnamon oil [51].

Saliva stimulating agent
The main aim of saliva stimulating agent is to increase the production of saliva and help dissolve the buccal film faster. The concentrations in which they are used ranges from 2% to 6% [52].

Backimg membrane
The backing membrane is an impermeable covering that has been attached to one side of the buccal film so that the drug is allowed to release into the oral cavity only in one direction and it also prevents leakage of the drug from the other side. 1% Ethyl cellulose was used as a backing membrane in preparation of an opioid drug [53].

Polymers
Many polymers are within easy reach for the production of fast-dissolving buccal films. The polymers can be used exclusively or in conjunction to give the required film properties. The film procured should be strong enough to withstand any damage while handling or during transportation. The robustness of the strip hangs on the type of polymer and the concentration used in the formulation. The many polymers employed in production fast-dissolving films include cellulose or cellulose derivatives, pullulan, gelatin, hydroxyl propyl methyl cellulose (HPMC), hydroxyl ethyl cellulose (HEC), hydroxyl propyl cellulose (HPC), polivinyl pyrrolidone (PVP), carboxymethyl cellulose (CMC), polyvinyl alcohol (PVA), sodium alginate, xanthane gum, tragacanth gum, guar gum, acacia gum, methyl methacrylate (MMA) copolymer, and hypermellose are most regularly employed for the production of fast-dissolving films. Pullulan is a natural polymer derived from non-animal origin and has no need for chemical modification up to 50–80% w/w of pullulan can be substituted by starch in the preparation of fast dissolving films without wasting the desired properties of pullulan. Combining microcrystalline cellulose (MCC) and malt dextrin can also be employed to make fast dissolving films. Investigation of many polymers for application in the production of oral fast-dissolving strips was done. Different polymers such as HPMC E15, HPMC K4M, HPMC E5, PVP, PVA, gelatin, Eudragit RL 100, and pullulan were used to make fast-dissolving buccal films; by employing solvent casting method. Conclusions proved that pullulan reigns supreme for oral fast-dissolving strips [54]. Klucel HXF Pharm (Hydroxypropyl cellulose) was employed as a mucoadhesive polymer in formulating a buccal film comprising a polypeheno [55].

METHODS OF PREPARATION OF BUCCAL FILMS
The following methods are used in the preparation of buccal films:

Semisolid casting
The semisolid casting method comprises the below-given steps:
1. A water-soluble film-forming polymer solution is prepared.
2. The resulting solution so formed is poured into a solution of acid-insoluble polymer (e.g., cellulose acetate phthalate, and cellulose acetate butyrate).
3. The required amount of plasticizer is incorporated to obtain a gel mass.
4. In the last step, the gel mass is transformed into the films or ribbons by application of heat controlled drums. The diameter of the film should be approximately 0.015–0.05 in. The proportion of the acid-insoluble polymer to film-forming polymer should be 1:4 [56].

Solid dispersion extrusion
The expression of solid dispersions relates to the dispersion of one or more active ingredients in a chemically inactive carrier in a solid-state in the attendance of amorphous hydrophilic polymers.
1. The drug is dissolved in a suitable liquid solvent.
2. Then, the solution is then added into liquid polyethylene glycol, which is achieved when heated above 70°C.
3. Ultimately the solid dispersions are molded into the films by the employment of dies.

Some safeguard measures must be taken care of while using this method such as the chosen solvent or dissolved drug may immiscible with liquid polyethylene glycol and polymorphic form of the drug precipitated in the solid dispersion may get altered by the liquid solvent used [57].

Solvent casting method
The solvent casting method is most commonly used for the production of buccal films. This procedure involves the below-given steps:
1. Water-soluble components (polymers) are dissolved in water to form a single viscous solution.
2. API and other excipients are dissolved in an appropriate solvent to form a lucid viscous solution.
3. Both the solutions are blended and the final solution is reformed into a film and permitted to dehydrate, as shown in Fig. 3. [58-63].

Rolling
In this technique, the film is produced by making a pre-mix, followed by the incorporation of an active ingredient and subsequently the formation of a film.
1. Produce a pre-mix comprising a film-forming polymer, polar solvent, and other additives with exception of a drug.
2. Incorporate pre mix to master batch feed tank.
3. Transfer it by a 1st metering pump and control valve to one or all of the mixers.
4. Add the desired quantity of the drug to the desired mixer.
5. Mix the drug with master batch pre-mix to give a homogenous matrix.
6. Then, a fixed quantity of uniform matrix is then added to the pan utilizing the 2nd metering pump.
7. The film is ultimately produced on the base material and transported away utilizing a support roller.
8. The wet film is then dehydrated by supervised bottom drying [65].

BUCCAL FILMS USED IN FORMULATION OF SOLUBLE AND INSOLUBLE DRUGS
Bioadhesive buccal film of ketoprofen was produced using an amalgamation of various polymers. The conclusions revealed that
in vivo in vitro (IVIVC) was about 0.975 thus demonstrating a good link between in vivo and in vitro tests. The ex vivo release studies expressed ketoprofen attaining the therapeutic concentration in the plasma after about 1 h. In regards to mucoadhesion ability, the batch was manufactured using polyacrylophil as the polymer exhibited the highest mucoadhesion power of about 6% [66]. A buccal film for delivery of anti-diabetic drug glimepiride was formulated using a novel nanocarrier armed with D-a-tocopherol polyethylene glycol 1000 succinate micelles (TPGS) also known as Vitamin E in common terms. The film was compared with a reference film of glimepiride (GMD) with the absence of the nanocarrier which was subsequently labeled with a fluorescent compound. The results revealed that the mathematical design so used did not fail to boost the factors that increase the liberation of GMD in a single direction from the transmucosal film packed with TPGS micelles in a controlled and foreseen manner. The boosted formulation demonstrated that the diffusion of GMD from the film was preferable towards TPGS micelles. The boosted one direction release of GMD transmucosal film was about 93.9% in 6 h compared to 60.41% of GMD release from the standard GMD film. This conclusion was established by its property to transport the GMD across the buccal mucosa, thereby showed by the ferocity of fluorescence with the fluorescence-labeled upgraded formulation [67]. Chlorzoxazone was modified by solid dispersion technique to refine its solubility and then incorporated it in buccal film. The findings revealed that the drug chlorzoxazone when formulated by a solid dispersion method showed greater dissolution and sustained release than the real mixture of the same drug and polymer HPMC K4 M [68]. A buccal film of Enalapril Maleate armed in a pullulan buccal film was formulated. The experiment of in vitro release profile of enalapril maleate fast-dissolving film and enalapril maleate tablets were performed in buffer solution (pH 6.8) and water. The findings revealed that after the elemental 5 min of the dissolution test, the polymeric film liberated 100.30% of the enalapril maleate into the buffer solution and 98.31% into water. Under matching conditions, the enalapril maleate from tablets showed a release of 5.1% into the buffer solution and 4.8% into water. These outcomes of this experiment give proof to both the experimental conditions of performing the in vitro dissolution test, as well as the proposal to employ these mucoadhesive buccal films for enalapril maleate administration [69]. Olmesartan Medoxomil (OMX) mucoadhesive buccal film was formulated where in the outcomes of the experiment revealed that therapeutic levels of OMX can be given through the buccal route as well as the films exhibited sustained release over more than 7 h. The study concluded that these erodible mucoadhesive buccal films comprising Olmesartan can be very optimistic for fruitful doses to systemic circulation as well as avoiding the first-pass metabolism thus increasing its half-life [70]. Production and assessment of buccal films containing prototype drug of paracetamol as soluble and indomethacin as insoluble drug individually by employing carrageenan as the base and different grades of polyethylene glycol. The results revealed that the transformation of crystalline drugs to the amorphous form in the course of film formulation as well as the film matrix exhibited the property to conserve the two prototype drugs in a stable amorphous form throughout the storage period of over 12 months. The films showed perfect release patterns within acceptable periods, after swelling and diffusion of the polymer matrix, under settings representing those of saliva [71].

**EVALUATION OF BUCCAL FILM**

**Weight variation**

A calibrated weighing balance was used for weighing buccal film. Each film is weighed individually and calculated. The average weight of all films is calculated and the actual weight of the film is analyzed [72].

**Thickness**

A calibrated micrometer screw gauge was used for evaluation of the thickness of the buccal film. Five different points on the film are measured (four on the corners and one in the center) and mean thickness is calibrated. This step is important to ensure the uniformity of thickness as well as accurate dosing in the film due to their correlation [73].

**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 position 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 [74]:

\[
\text{Tensile strength (N/mm}^2\text{)} = \frac{\text{Breaking force (N)}}{\text{Cross-sectional area of sample (mm}^2\text{)}}
\]

**Surface pH**

For determination of surface pH, 2% w/v agar in isotonic phosphate buffer pH 6.8 was dissolved and poured into the Petri dish for preparation of agar plate and was gelled at room temperature. Buccal films were placed on the surface of the agar plate for 2 h until they swell completely. pH indicator paper was used for measuring surface pH after 90s change in color was observed comparing it with a standard color scale [75].

**Folding endurance**

For the measurement of folding endurance, three films were cut into appropriate size. By folding one film at the same place repeatedly or by folding up to 300 times till it breaks, folding endurance can be determined. The value of folding endurance can be identified when the film does not break even after folding the film multiple times [76].

**Drug content uniformity**

Drug uniformity was determined by dissolving 5 films weighed previously in 100 ml of isotonic phosphate buffer pH 6.8 with the help of a magnetic stirrer for 2 h. Further, this solution was filtered with Whatman filter paper, and after suitable dilution, drug was analyzed using a spectrophotometer [77].

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**Fig. 3: Solvent casting method for manufacturing of buccal film. Adapted from Reference [64]. Copyright permission obtained under creative commons (CCBY) license (http://creativecommons.org/licenses/by/4.0/)**
**Percentage moisture loss test**

Two films of 2 × 2 cm² were placed in the desiccator with anhydrous calcium chloride; percentage moisture loss was determined. The films were taken out after 3 days and were weighed. Using the formula below, percentage moisture loss was calculated [78].

\[
\text{Percentage Moisture Loss} = \left(\frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}}\right) \times 100
\]

**Percentage moisture uptake**

Films were kept in the desiccator at room temperature for 24 h with saturated potassium chloride solution and maintained 84% relative humidity. The films were taken out and weighed after 24 h. Percentage of moisture uptake can be calculated by the following formula [78].

\[
\text{Percentage moisture uptake} = \left(\frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}}\right) \times 100
\]

**Swelling index**

Each buccal film was weighed individually (W1) and placed in the Petri dish separately containing phosphate buffer pH 6.8. Buccal films were removed using filter paper so that excess surface water is separated from the Petri dish and weighed again (W2). Swelling index (SI) was calculated using the formula [79]

\[
\text{SI} = \left(\frac{W2 - W1}{W1}\right)
\]

Where;

\[
\text{SI} = \text{Swelling index}
\]

\[
W2 = \text{Final weight}
\]

\[
W1 = \text{Initial weight}
\]

**In vitro disintegration time**

It can be visually analyzed in a Petri dish with 2 ml of distilled water by swirling after every 10 s. The time taken by the film to disintegrate or break is noted and recorded as the in vitro disintegration time [80].

**In vitro dissolution study**

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 [81].

**In vitro drug release**

Franz diffusion cell assembly was used for in vitro drug release studies. It consists of two compartments, one of the receptor chambers containing a buffer solution of pH 6.8 and other donor compartment containing 10 mg of the drug. A dialysis membrane (Mol. Wt: 12000–14000) which was previously soaked for 2 h in receptor medium was placed in between these compartments to separate it from each other. To avoid disruption in the ongoing process, it was ensured that no air bubbles were seen between the membrane and liquid surface. During the entire process, the temperature was maintained at 37°C by 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 spectrophotometrically analyzed. The flux value was identified by the following formula [82]:

\[
\text{Flux} = \frac{\text{Amount of drug released (mg)}/\text{Time (hr)} \times \text{Area (cm}^2)}{}
\]

**Ex vivo mucoadhesion time**

For determining the mucoadhesion time, the buccal film is applied to the fresh buccal mucosa of sheep or rabbit which is tied on a glass slide. The buccal film is wetteled with a drop of phosphate buffer pH 6.8 and applied with a mild force on the buccal mucosa for 30 s using fingertips. In a beaker containing 200 ml of phosphate buffer pH 6.8, the glass slide is kept at 37°C ± 1°C. To simulate the environment of the buccal cavity, a 50 rpm stirring speed is applied after 2 min and film adhesion is regulated for 24 h. The time taken for visible changes in shape and color is recorded along with the collapsing time of the film [45].

**Ex vivo permeation studies**

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 consisting of 2.5 ml of pH 6.6 phosphate buffer. The separated buccal epithelium was mounted between the two chambers and the entire assembly was placed on a magnetic stirrer by putting a magnetic bead coated with Teflon. The buccal film was kept aside for stabilization after which 1 ml of the sample was withdrawn at regular intervals and was suitably diluted for analyzing it spectrophotometrically [83].

**Stability studies**

Stability studies are undertaken for analyzing any changes during the storage of any formulation. For 3 months, all the formulations were kept in triplicate at 40°C ± 2°C and 75°C ± 5% RH in stability chambers. By analyzing their folding endurance, drug content, and in vitro drug release, stability studies were evaluated [84].

**PACKAGING OF BUCCAL FILM**

At most care and precautions should be carried out while selecting packaging material to protect the integrity of the film. During the manufacturing and storage of these dosage forms, special care, processing, and high-quality packaging are essentially required. The ideal characteristics for selecting packaging materials are:

1. It should not get affected by the external environment.
2. It should be non-toxic.
3. It should be approved by the FDA.
4. It should not interact with the product.
5. It should meet the requirement of tamper-resistant [85].

Packaging for oral films generally includes foil, paper or plastic pouches, single pouch, aluminum pouch, blister cards with multiple units, and barrier films. Labtec GmbH formulated Rapid film technology which is a primary packaging made up of a sealing pouch having ample space for instructions, logos, codes, and other information. The laminating procedure was followed with an expense equal to that of tablets [86].

**Foil, paper, or plastic pouches**

It is a kind of flexible pouch which provides tamper-resistance along with a proper selection of material, overall a package of high degree of environmental protection. It is formed during the procedure of product filling by vertical or horizontal forming, filling, and sealing equipment. They are available as single pouches or aluminum pouches [85].

**Single pouch and aluminum pouch**

For a quick-dissolving soluble film, a peelable soluble film delivery pouch is used with high barrier properties. It is a transparent pouch for the visibility of the product. It has a two-dimensional structure out of which one side is clear and the other one has a low-cost lamination of foil. The foil lamination is restricted to the transmission of gas and moisture [85]. A single-dose pouch protects the dose as well as the product whereas an aluminum pouch is most commonly used [87].

**Blister card with multiple units**

The blister container is made up of two components: 1. Blister 2. Lid stock

Blister has a cavity made up of plastic material to protect it from moisture which holds the product and lid stock is a material made up of aluminum foil which seals to the blister. It is formed by softening a sheet of thermoplastic resin by providing heat and contour molding the softened plastic sheet under vacuum. The sheet is removed from
Barrier films

Barrier films are generally required for those products which are highly sensitive to moisture. Certain materials which may protect from moisture are Poly chloro trifluoro ethylene (PCTFE) films, propylene. Propylene is a material that doesn’t crack under stress. It provides an excellent barrier to vapors and gas. The only drawback related to barrier films is the lack of clarity [85].

APPLICATIONS OF BUCCAL FILM

Vaccines

An alternative to buccal films can be in the form of a vaccine for its fast dissolving action in mouth and saliva which are stable at room temperature. One such example is the rotavirus vaccine manufactured in the United States which has certain advantages such as enhanced bioavailability, improved patient compliance with minimal cost related to storage, handling, and administration [88].

Controlled and sustained release

In hospital preparations and various excipients of polymers such as chitosan derivatives, sustained-release buccal films are applicable as it contributes to wound dressings, decreasing toxicity, and good water resisting and adhesive properties [88].

Nicotine replacement therapy (NRT)

Nicotine in tobacco is a psychoactive substance leading to the habitual nature of smoking. In this therapy, the mucosal route of delivery is the most efficient as it readily permeates into the mucosal membrane. Pongjanyakul et al. formulated sodium alginate-magnesium aluminum silicate (SA-MAS) buccal film with the incorporation of nicotine. The study showed that SA-MAS films provided with a higher content of nicotine and slower permeation across the membrane compared to only SA films. Initially, drug release was faster and after 10 h controlled drug release was observed [89].

Antifungal infections

Fluconazole, a systemic antifungal for therapy of oral candidiasis, is generally preferred for mucosal delivery. Its systemic side effects can be reduced by increasing its oral concentration. Through mucoadhesive buccal films of small doses of fluconazole, there was an increase in the contact time between the drug and pathogenic yeast for a longer duration which eventually increased its efficacy [90].

Management of herpes

For the management of oral herpetic lesions, an antiviral drug acyclovir is most widely used. The permeability of acyclovir is low in oral mucosa which results in reduced efficacy. Hence, a study by Nair et al. formulated nanoparticles by incorporating polymeric materials and was loaded into films. The results provided good mucoadhesive strength and great physomechanical property with improved oral bioavailability of acyclovir [91].

Targeted therapy for oral cancer

The most approved treatment for oral cancer is the targeted therapy which aims for site-specific delivery with low levels of toxicity and side effects. By acquiring nano delivery systems in the form of films consisting of polymers, it has been concluded an increase in solubility, stability, and bioavailability accumulated even inside tumor cells. A study was conducted for the development of liposomes loaded in the film and was evaluated for its cytotoxicity in hematopoietic stem cells (HSC-3) [92].

Cardiovascular diseases

One of the major cardiovascular diseases that need to be under control with long-term therapy is hypertension. Antihypertensives such as carvedilol, propranolol, and metoprolol have a short half-life and low oral bioavailability due to poor aqueous solubility and high first-pass metabolism. To overcome this, the buccal mucoadhesive system was established as it provides a direct pathway into the systemic circulation through the internal jugular vein by preventing the first-pass effect of obtaining high bioavailability [93]. A lower effective dose of 3.125 mg of carvedilol produces higher efficacy with increasing contact time and bypassing the first-pass metabolism [94].

Hypoglycemic agents

Recently for hypoglycemic agents such as glipizide and glibenclamide buccal delivery system has been introduced. Administration of 2 or 3 doses of 2.5–10 mg daily of glipizide leads to short biological half-life. Uptake of water by the film was seen when the water-insoluble drug was incorporated [95]. Different grades of HPMC with measured ratios were used for preparing glibenclamide mucoadhesive buccal films. In conclusion, buccal drug delivery can be useful in a controlled pattern at a low concentration of HPMC3000 [96]. Hypoglycemic activity has also been found in the fruit of Cucumis callosus belonging to family Cucurbitaceae [97].

Antiemetic

Ondansetron HCL shows certain properties such as low molecular weight and biphasic solubility that is an ideal characteristic for absorption through the buccal mucosa. Its bioavailability may get improved by the mucosal route as its primary route for clearance was through hepatic Phase I metabolism. Patients suffering from vomiting during chemotherapy find it difficult to swallow a tablet. Hence, it is justified that buccal film increases patient compliance by preventing the need for swallowing [98]. Nausea and vomiting associated with cancer chemotherapy is distinct from typical nausea and vomiting that many people experience in their normal daily life though the drugs used may be the same [99].

Asthma

The buccal patches have been formulated for delivery of sodium cromoglicate for treatment of asthma. The drug has short half-life and it was need to formulate it in a controlled release system. The results of inclusion of this drug in buccal patches led to extension of the time required to attain maximum concentration in the blood in addition to showing a reduction in the maximum plasma concentration in the blood. It also provided controlled release of the drug [100].

CONCLUSION

The present review concludes that the buccal film is that the most accurate and acceptable dosage form, due to higher patient compliance, faster drug delivery system, and bypasses the hepatic first-pass effect and shows enhance bioavailability. Buccal films will replace the conventional dosage forms, as well as fast disintegrating tablets due to its advantages over the conventional dosage forms, and they can be manufactured at a low cost. A range of dosage forms can be incorporate in buccal drug delivery. However, buccal films are more feasible formulation because of its simplicity in preparation, drug loading, and characterization. Buccal films will be a more robust choice to optimize the therapeutic efficacy of various API in the future. The oral mucoadhesive dosage forms can continue to be an exciting research focus on improving drug absorption, particularly for the new generation.

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AUTHORS CONTRIBUTION

Literature search and preparation have been done by Reesha Baig, Gaurang Savant and Shifa Haju. Manuscript Framing and the concept has been presented by Shifa Haju. Reviewed and editing have been done by Dr. Sheela Yadav.
CONFLICT OF INTERESTS

The authors have declared no conflicts of interest.

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