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Review Article

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MUCOADHESIVE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The main route of administration for drug products is the oral route, yet biologics are initially developed as injectables due to their limited stability through the gastrointestinal tract and solubility issues. In order to avoid injections, a myriad of investigations on alternative administration routes that can bypass enzymatic degradation and the first-pass effect are found in the literature. As an alternative site for biologics absorption, the buccal route presents with a number of advantages. The buccal mucosa is a barrier, providing protection to underlying tissue, but is more permeable than other alternative routes such as the skin. Buccal films are polymeric matrices designed to be mucoadhesive properties and usually formulated with permeability enhancers to improve bioavailability. Conventionally, buccal films for biologics are manufactured by solvent casting, yet recent developments have shown the potential of hot melt extrusion, and most recently ink jet printing as promising strategies. This review aims at depicting the field of biologics-loaded mucoadhesive films as buccal drug delivery systems. In light of the literature available, the buccal epithelium is a promising route for biologics administration, which is reflected in clinical trials currently in progress, looking forward to register and commercialize the first biologic product formulated as a buccal film.

KEYWORDS: Transmucosal drug delivery system; Solvent casting method; Hot melt extrusion technique.

1. INTRODUCTION

Among the various routes of drug delivery, transmucosal drugdelivery offer distinct advantages over peroral administration forsystemic effect. Among various transmucosal routes, buccal mucosa is the most suited for local, as well as systemic delivery of drugs. The unique physiological features make the buccal mucosa as an ideal route for mucoadhesive drug delivery system. These advantages include bypass of hepatic first-pass effect and avoidance of pre systemic elimination within the gastrointestinal tract.[1,2] The use of the oralcavity membranes as sites of drug administration has been the topic of increasing interest for the past decade. It is well known that the absorption of therapeutic compounds from the oral mucosa provides a direct entry of the drug into the systemic circulation, thereby avoiding first-pass hepatic metabolism and gastrointestinal drug degradation, both of which are associated with peroral administration.[3-5] Buccal films are the most recently developed dosage form for buccal administration. They have gained importance as efficacious in systemic drug delivery.[8] 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.[9] Buccal mucosa is rich with blood supply, which acts as a perfect and fast site for absorption of a drug.[10] Mucoadhesive buccal films have also been formulated to show the local action to treat fungal infections in the oral cavity.[11-15]

Potential Benefits of Buccal Films

- Buccal films provide large surface area that leads to rapid disintegration and dissolution in the oral cavity due to which it promotes the systemic absorption of Active pharmaceutical ingredient.
- No need of chewing and swallowing.
- No risk of chocking.
- The 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.
- Rapid onset of action and minimum side effects.
- Self administration is possible.
- Accurate dosing compared to liquid dosage forms.
- Taste masking is possible.
- Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- Ease of administration to pediatric, geriatric patients, and also to the patients who are mentally retarded, disabled or non-cooperative.
- Good mouth feel and good stability.

- Ease of transportation, storage and consumer handling.
- Requires less excipient.
- More economical.

However, the main limitation of the buccal films is that high doses cannot be incorporated.

2. Overview of the Oral Mucosa Structure

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer18, 19 can be seen in figure 1. The epithelium of the buccal mucosa is about 40- 50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The turnover time for the buccal epithelium has been estimated at 5-6 days20, and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 μm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized.[21] The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, nonkeratinized epithelia, such as the floor of the mouth and the buccal epithelia, do not contain acylceramides and only have small amounts of ceramide.[22-24] They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.

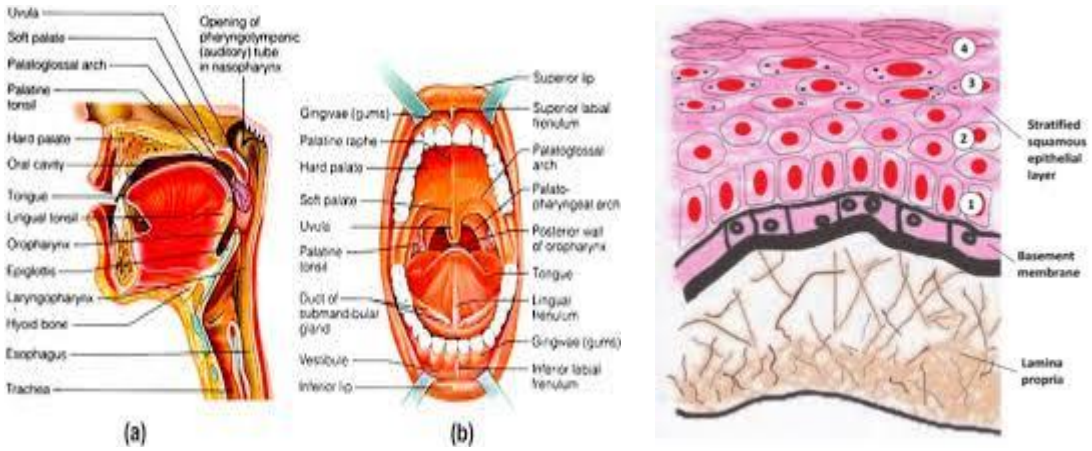

Figure 1: Anotomy of Oral Mucosa.

3. Biopharmaceutical aspects

MDFs disintegrate quickly in the mouth, facilitating the absorption of drug through the oral mucosa of mouth, pharynx and esophagus.[11] Absorption depends largely on factors like age, nature of the oral cavity and blood flow to oral cavity. Every drug has its own tissue permeability, perfusion rate, tissue binding, drug interaction profile and excretion rate so distribution and duration of action vary according to the drug. Any therapeutic agent can be incorporated to MDFs but those having lower doses and need a rapid onset of the action are preferred.

4. Characteristics of MDFs/importantfeatures

MDFs should have the properties like non-tacky like nature, convenience of dosing, easy to handle, suitable for labeling and packing, 1–10 mm in thickness, 1–20 cm2 in surface area, Rapid hydration and softening to release medicament, typical disintegration time in saliva 1–30 s, un obstructive, should not leave any residue in the mouth after disintegration and should provide a pleasant mouth feel.[12]

5. Ideal properties of candidate drugs

Different drugs are reported in the previous literature. Drugs showed have the pleasant taste, low doses, having smaller or moderate molecular weight, good stability in water as well as in saliva, should partially unionized at the pH of oral cavity, and should permeate oral mucosal tissues.[8]

6. Drugs that can be incorporated

Therapeutic categories that can be formulated in MDFsmay include cough/cold remedies (antitussives, expectorants), sore throat drugs, erectile dysfunction drugs, antihistamines, anti-asthmatics, drugs for gastrointestinal disorders, nausea, pain and CNS (e.g. anti-Parkinson's disease). Other applications may include caffeine strips, snoring aid, multivitamins, sleeping aid etc.[13]

7. Advantages of Buccal Drug Delivery System

Due to larger surface area rapid disintegrating and dissolution occurs in the oral cavity. MDFs are flexible and easily transported and handled, so they are superior to oral disintegrating tablets that are brittle and fragile and require special packaging for protection during storage and transportation. As compared to liquid oral formulations, dose is more précised in form of the strips. As no is required so these dosage forms are most friendly for dysphagic patients. They are rapidly wetted due to larger surface area and can be consumed anywhere as per suitability of the individual. Drugs can absorbed directly from the highly vascularized buccal mucosa and enter the systemic circulation bypassing first-pass hepatic metabolism. This helps improving the bioavailability of the drugs that undergo extensive first pass effect. Due to least hepatic metabolism, dose is reduced leading to decrease probability of dose related side effects. Mentally ill, disabled and uncooperative patients can be easily medicated. The product can be a substitute with more clinical advantage. The manufacturing of these MDFs is cost-effective with reasonably priced end-products. MDFs are alternative to ODTs as they have to face product identification for OTC drugs.[14]

8. Drawbacks/limitations

Different drawbacks like high dose, difficulty in dose uniformity, hygroscopic nature of drug, and requirement of special packaging for stability and safety of product are reported.

9. Formulation aspects of buccal films

9.1. Drugs

Various therapeutic substances can be delivered through buccal film but still there are few restrictions and limitation as drugs with high dosage and high molecular weights are difficult to be formulated as buccal film. Normally 5–30% (w/w) of drug can be used to formulate the buccal film. Hydrophilic drugs are in the form of dissolved material or in solid solution state while hydrophobic drugs are evenly dispersed in the buccal film.[15] Release of the drug can be modified and desired release profile can be achieved by using therapeutic moiety as milled, micronized or as nanoparticles. Consistency, dissolution profile and uniformity of the drug contents of buccal film can be enhanced and improved by using micronized particle of the drug. Cough, allergy, motion skinless, pain disorder and certain local oral disease condition can be best treated by using drug in the form of buccal film.

9.2. Excipients

The contact between buccal mucosa and the film is very important to deliver the drug efficiently and this is the reason due to which the main focus is to the mucoadhesive polymers in the formulation of buccal drug delivery system especially buccal film.[18,19]

9.3. Penetration enhancers

Substances that are used to enhance the penetration of the active moiety are called penetration enhancers. They should not produce irritation and have reversible effect. One of the simple examples of penetration enhancer is the use of water. When the skin gets hydrated it gradually increases the permeability as water cause the opening of the compact structure[24,25] of needle base. There are various chemical that has the ability to enhance the penetration that includes surfactants (such as Tween) fatty acids (such as oleic acid), terpenes (like eucalyptus) and solvents (like ethanol).[26] Others are bile salts, azone, currently chitosan, its derivatives, and polymers with the property of mucoadhesion also have the potential of being penetration enhancer.

9.4. Taste masking and Sweetening agents

To enhance the patient compliance it is important to mask the bitter taste of drugs. Taste masking agents are certain methods can be used to mask the bitter taste like formation of complex or technology for salting out etc. (buccal film). Sweetening agent is the important component in orodispersble formulation especially formulations designs for peads. Both natural 9and artificial sweeteners are included in the formulations. Sucrose, dextrose, fructose, glucose, liquid glucose and maltose are the examples of natural sweeteners while saccharin, aspartum, sucralose, all-time, neotameacesulame-K etc. are the examples of artificial sweeteners.[15] Different active pharmaceutical ingredients, their dose, and therapeutic uses are listed in Table 2.

9.5. Saliva stimulating agent

These agents are used to enhance the production of saliva which assists in the disintegration of the buccal film. Saliva stimulating agents include acids like citric acid, tartaric acid, ascorbic acid and malic acid. These acids can be used alone as well as in combinations. Few sweetening agents like glucose, fructose, xylose, maltose, lactose etc.[15]

9.6. Flavoring agents

Orodispersable system can includes another substance known as flavoring agent. Palatability and acceptance of an orodispersable dosage form like buccal film depends initial flavor quality, observe within few seconds after administration of the drug. Flavoring agents include various agents and few of them are Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg, vanilla, cocoa, coffee, chocolate, citrus, apple, raspberry, cherry and pineapple etc.[15,26]

9.7. Coloring agents

Coloring agents are use to improve the appearance of buccal film. There are different FD&C approved coloring agents.[15,29]

10. Manufacturing Methods

The buccal film manufacturing process includes the following techniques.

1. Solvent casting technique
2. Hot melt extrusion technique

10.1 Film 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.[30,31]

- Prepare casting solution
- Deaerate the solution
- Pour the solution into a mold
- Dry the casting solution
- Cut the final dosage form containing desired amount of drug
- Packing

10.2. Hot melt extrusion technique

In this method mixture of pharmaceutical ingredients is melted. In order to achieve homogeneous mixture in various dosage form like tablets, granules, pallets or film, the melted material is pushed to pass through a small opening (orifice of a die).[32–34] Although this method is rarely used for the manufacture of film but there are certain evidence in the literature that this method can beuse for film preparations.[29,31,35]

Finnaly the melt is sharped in to the film by the dies. There are certain benifits of hot melt extrusion.

- Fewer operation unit
- Better content uniformity
- An anhydrous process

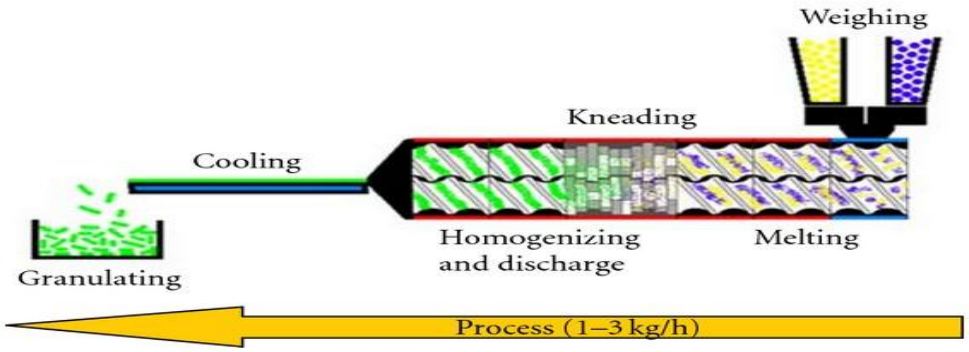

Figure 2: Schematic diagram of the HME process.

11. Characterizations

11.1. Chemical stabilities studies

Chemical compatibility studies are performed to identify any possible interaction between the ingredients. Fourier transformer infra-red spectrum, differential scanning calorimetery and X-ray diffraction are the techniques usually used to conduct the compatibility studies.[36]

11.2. Thickness measurements

Electronic digital micrometer, digital vernier caliper or micro screw gauge can be used to measure the thickness of the patch. Thickness of the different location (corners and the center) is measured to assess the average thickness of the film.[31,32]

11.3. Swelling study

Swellability of the film is measured by placing the sample film continuing agar plate in an incubator kept at 37 + 2 °C. Increase in diameter of the film and weight gain by the film is calculated is calculated at different time intervals (1–5 h). Swellabilityis calculated as.[37]

$\%S = (X_t - X_o / X_o)\ 100$

Where X_o = original weight or diameter of the film and X_t = weight or diameter at time *t*.

11.4. Surface pH

It is important to measure the surface pH of the films to assess the any side effect that may be produce inside the body. Acidic or basic pH can be the cause of irritation to mucosal. Initially the film is placed in 1.0 ml distilled water having pH 6.5–0.05 for 2 h. Specially designed glass tube is used for this purpose. To measure the surface pH combined glass electrode -is brought near the surface for a time interval of 1 min.[38]

11.5. Folding endurance

Folding endurance is used to observe the flexibility of the film which is an important physical property of a buccal film. It is measured by folding the selected sample of the film at an angle of 180 and observes when it breaks. Another way to measure the flexibility of the film is to fold the film 300 times without breaking. Value of folding endurance is calculated in terms of numbers of fold without breaking the film.[39]

11.6. Moisture content

Moisture contents of the film are calculated by finding the difference between the weights measured initially prior to the placement of film in the desiccators and after specific time interval. Calcium chloride is placed in the desiccators and the whole apparatus is kept for 24 h. Following equation is used to measure the %

% moisture content = initial weight - final weight / Initial weight x 100

11.7. Moisture uptake

Sample film is taken and weighed and then keep it in desiccators at room temperature. After 24 h film is taken

out and expose to 84% relative humidity. Saturated solution of potassium chloride is used in desiccators till a constant weight is obtained. Following formula is used for the calculation of % moisture uptake.[41]

Moisture uptake = Final weight - Initial weight / Final weight x 100

11.8. Surface morphology

Various techniques are used to observe the surface morphology. It includes SEM (scanning electron microscopy), electron microscopy and scanning tunneling microscopy. SEM is most widely used. Shape, size and number of pores present on the surface of the film are observed by SEM.[36]

11.9. *In-vitro* dissolution studies

In-vitro drug release is calculated for given formulation using USP dissolution apparatus. Temperature is kept at 37 ± 0.5 °C and the rotation speed is adjusted at 50 revolutions per min and dissolution media of 900 ml is used. Samples are drawn at different time intervals. Sample is replaced with same volume of fresh medium. % drug release is observed by analyzing the sample using spectrophotometer at specified wave length.[32]

12. Organoleptic evaluation

Organoleptic evaluation is done to observe and check sweetness and flavor, whether they are acceptable or not. An electronic tongue measurement is design having test sensors to observe the taste *in vitro.*[42]

12.1. *Ex–vivo* Permeation Studies

Ex-vivo studies are performed using modified Franz diffusion. There are two compartments one of them is donor while other is receptor compartment that has the capacity of 18 ml with 0.785 cm^2 area for diffusion. 37 °C temperature is maintained with the help of water jacket. Artificial mucosal membrane or mucosal membrane of animal (rabbit) is used for permeation studies. Membrane is mounted between two chambers. Phosphate buffer of pH 7.4 is used to fill the receptor compartment. Membrane is stabilize in an hour. Once the membrane is stabilized the film is placed and samples are taken. The taken volume is replaced with fresh media. [43]

Name of the commercially available buccal film.

CONCLUSION

Due to success, advantages and ease of access of drug delivery through oral mucosal tissue the buccal and sublingual routes have favourable opportunities and many formulation approaches; although the current commercially available formulation are mostly limited to tablets and films. The buccal mucosa offers several advantages for controlled drug delivery for long period of time and also favourable area for systemic delivery of orally unsatisfactory drugs and attractive alternative for non-offensive delivery of potent peptide and protein drug molecule. There is renewed interest and active product development activity for following generation of oral mucosal delivery system. Oral mucoadhesive dosage forms will continue be an exciting research focus for improving drug absorption especially for the new generation.

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