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REVIEW ARTICLE **OPEN ACCESS**

A Review on Novel Approaches of Mucoadhesive Oral Film Manufacturing Aspects

Achala A. Mulay, Smita D. More, Nilesh S. Kulkarni
P. E. Society's, Modern college of Pharmacy (For Ladies), Moshi, Pune 412105 , Maharashtra, India.
Savitribai Phule Pune University, Pune, Maharashtra, India.
Email: mulayachala@gmail.com

ABSTRACT
Oral route are most commonly preferred route for delivering drug. The aim of the present study was to gives an overview about the principles of creation of mucoadhesive bonds & about novel dosage form. Mucoadhesive film in terms of their composition, preparation & practical usage. It may be preferred over adhesive tablet in terms of flexibility and comfort. This study focused on development of a mucoadhesive buccal delivery system with a twofold objective of offering a rapid as well as a prolonged delivery with enhanced therapeutic efficacy.
Keywords: *Oral mucosa,Mucoadhesive polymer, Buccal film, Dosage form.*

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INTRODUCTION

In recent years, significant interest has been shown in the development of controlled drug delivery to, or via mucous membrane by the use of bio adhesive or mucoadhesive polymers [1-3]. These dosage form can be administer by different routes, including ocular, nasal, rectal and vaginal, for local and systemic delivery.

Among the various drug delivery system is found to be the most promising because, buccal mucosa, itself provides a protective covering for the underlying tissues, acting as a physical barriers against Toxin & microorganism [7].

The use of the oral cavity membranes as sites of drug 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 GI drug degradation, both of which are associated with perioral administration [6].

Mucoadhesion is a state in which two materials, one of which is mucous or a mucous membrane is held together for an extended period of time. Various mucoadhesive polymer have been investigated &identified generally hydrophilic macromolecules that contain numerous hydrogen bond forming groups and will hydrate & swell when placed in contact with an aqueous solution [4].

Buccalfilms 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 a 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. Buccal films may be preferred over buccal tablet, in terms of flexibility and comfort.

Buccal films have direct access to the systemic circulation through the internal jugular vein, which bypass the drug form the hepatic first pass metabolism leading to high bioavailability. Further, these dosage forms are self-administrable, pharmocoeconomic and have superior patient compliance.

The film can be defines as a dosage form that employs a 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.

Buccal mucosa is rich with blood supply, which acts as a perfect and fast site for absorption of the drug, it also have good accessibility as well as quick & easy removal of dosage form in case of need. The development of novel delivery system for existing drug molecules not only improves the drugs performance in terms of efficacy and safety but also improves the patient compliance & overall therapeutic benefits to a significant extent [5].
Mucoadhesive buccal films have also been formulated to show the local action to treat fungal infections in the oral cavity.

POTENTIAL BENEFITS OF BUCCAL FILMS

- Buccal films provides large surface area that leads to rapid disintegration and dissolution in the oral cavity due to which it promotes the systemic absorption of active p'ceutical ingredient.
- No need of chewing and swallowing
- No risk of chocking,
- The film increases the systemic bioavailability of the drugs, as it bypass 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.
- Good mouth feel and good stability.
- Requires less excipient.
- More economical.

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

ANATOMY AND PHYSIOLOGY OF ORAL MUCOSA [11, 13]

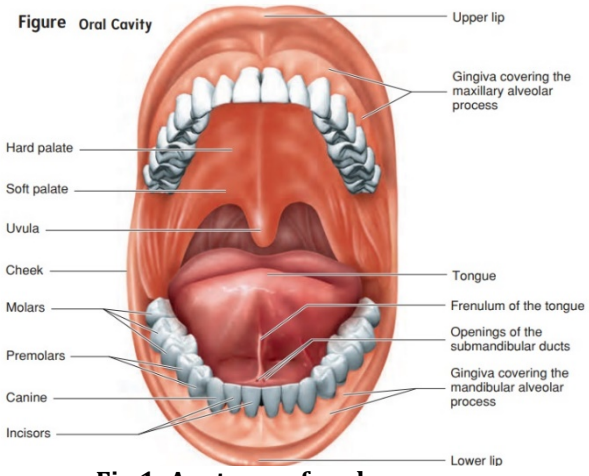

Fig.1: Anatomy of oral mucosa.

Oral mucosal region is adhesive in nature and acts as a lubricant, allowing the cells to move relative to one another with less friction. Four sites namely buccal cavity, the lingual area, the palate and gingival region have been used for drug administration. The most commonly use site for drug administration of the four sites mentioned above is the buccal route. The anatomic site for drug administration between the check and gingival is known as the buccal mucosa.
The oral mucosa is composed of three layers. The first layer is the stratified squamous epithelium, underneath this later lays teeh basement membrane. The basement membrane overlies of the lamina propria and sub mucosa. The constitution of the epithelium within the different sites of the oral cavity shows dissimilarity. The epithelium is the soft palate, buccal and sublingual area is not keratinized, therefore not containing ceremides and acylceramidesm which are associated with providing a barrier function [18].
The mucosa of the buccal and sublingual region have only small amounts of Ceram idem and is thus more permeable when compared to other regions of the oral cavity.

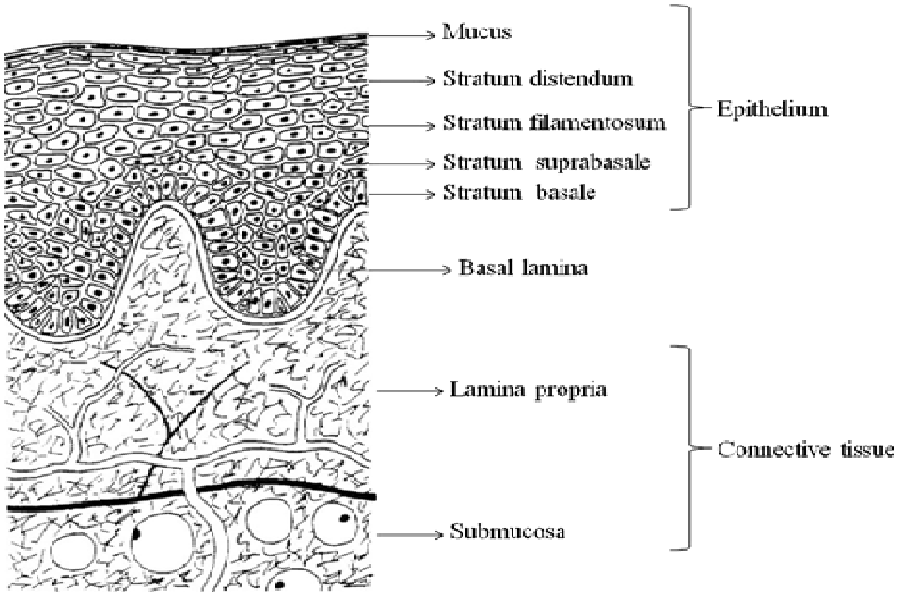

Fig.2: Histology of oral mucosa

A layer of mucus is present on the surface of the epithelial layer of cells. This plays a major role in the cell-to-cell adhesion, oral lubrication, as well as mucoadhesion of mucoadhesive drug delivery systems. The buccal are has an expanse of smooth andrelatively immobile surface, which is suitable for placement of a retentive system. For buccal drug delivery, 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.

In humans, the approximate surface area of the oral mucosa is 100 cm^2. The oral mucosa can be differentiate as the masticatory mucosa which is 25% of total oral mucosa having a thickness of 100- 200 µm. the lining mucosa covers 60% of total area & has a thickness of 500-800μm. It is present in lips, cheeks, oral cavity floor, etc. [13].

These characteristics make the buccal mucosa as a more appropriate site for prolonged systemic delivery of drugs.

MECHANISM OF MUCOADHESION

Transportation of drug involves mainly 2 basic routes: Trans cellular or intracellular which demands to cross the cellular membrane with lipid & polar domain, but paracellular or intracellular transport is accomplished through passive diffusion through extracellular lipid domain [21].

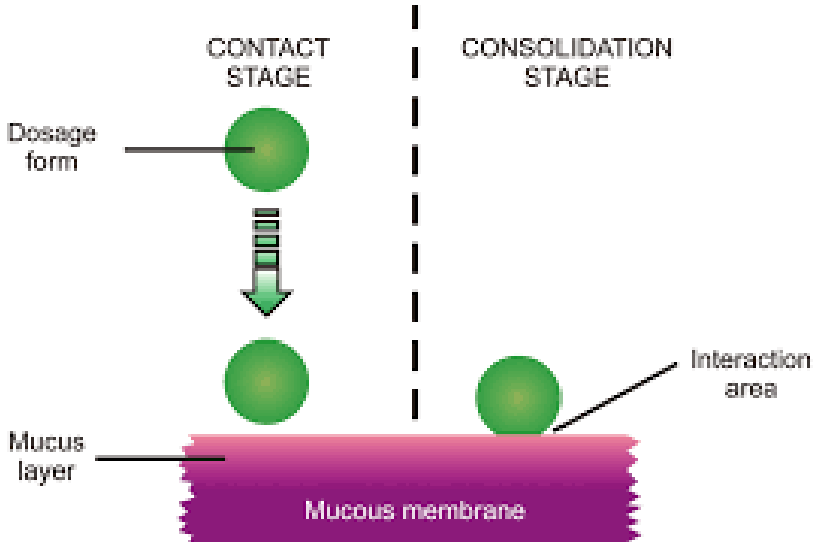

Fig.3: Mechanism of Mucoadhesion

Mucoadhesion can be classified into broadly into 3 categories:

1. Mucoadhesion includes aggregation of platelets & healing of the wound
2. It involves the biological phase and simulated substrate
3. Adhesion of an artificial material to a substrate of biological nature.

Basic mechanism that is involved in mucoadhesion is generally divided into 2 steps–

- Contact stage- which explains the contact between the mucoadhesive polymer & mucous membrane with spreading & smelling of the formulation.
- Consolidation stage- here mucoadhesive materials are activated by presence of moisture, plasticizers, the system allowed the mucoadhesive molecule to break free & further bonded by weak Vander Waals & hydrogen bonds.

To explain the mechanism of mucoadhesion, multiple theories has been proposed-

- Electronic theory
- Adsorption theory
- Diffusion theory
- Wetting theory
- Fracture theory
- Mechanical theory
- Cohesive theory.

Electronic theory: This theory explains the adhesion take place by means of electron transfer between the mucous& the mucoadhesive system arising through differences in their electronic structures. This results in the formation of electrical double layer of charges at the mucous and mucoadhesive interface. Electrostatic forces are an important cause of bond adhesion rather than merely a result of high joint strength [22].

Adsorption theory: This theory explains intermolecular force (hydrogen bonding) and Vander Waals forces, results in adhesive interaction amongst the substrate surface [13].

Diffusion theory: The theory explains the inter penetration of both polymer &mucin chains to a sufficient depth to create a semi-permanent adhesive bond. The adhesion force increases with the degree of penetration of the polymer chains. This penetration rate depends on diffusion coefficient, flexibility, and nature of the mucodhesive chains, mobility and contact time. The interpenetration required to produce an efficient bioadhesive bond lies in the range 0.2 -0.5µm. the depth of the penetration of polymer &mucin chain can be estimated by following equation:

$$l = (tDb)^{1/2}$$

Where t is the contact time & Db is the diffusion coefficient of the mucoadhesive material in the mucous.

Wetting theory: The theory explains surface spreading property of liquid systems measured by contact angle [25].

Fracture theory: According to this theory, the adhesive bond between system is related to the the force required to separate both surfaces from one another. "Fracture theory" relates the force for polymer detachment from the mucus to the strength of their adhesive bond [23].

Mechanical theory: It explains the diffusion of the liquid adhesive in to the micro cracks and irregularities present on the substrate surface there by forming an interlocked structure which gives rise to adhesion [25].

Cohesive theory: the phenomena of bioadhesionr are mainly due to intermolecular interactions amongst like molecules [26].

FORMULATION ASPECTS OF BUCCAL FILMS:

Table: Generalized details of different ingredients of fast dissolving oral films [10]

Sr. No.	Ingredients	Amount
1	Drug (API)	5-30%
2	Water soluble polymer	40-50%
3	Plasticizers	0-10%
4	Saliva stimulating agent	2-6%
5	Sweetening agent	3-6%
6	Surfactant	Q.S
7	Flavors, Colors, Fillers	Q.S

1. Active Pharmaceutical Ingredients [APIs]-

Generally 5% w/w to 30% w/w of active pharmaceutical ingredients can be incorporated in the buccal film. Water soluble APIs are present in the dissolved state in the buccal film or in the solid solution form. The water insoluble drugs are dispersed uniformly in the film. This involved the distribution of water

insoluble molecules in water miscible polymer, or the solubility of the drug can be enhanced by complexation with various cyclodextrins.

The use of micronized APIs will improve the texture of the film and also for better dissolution and uniformity in the buccal film. The buccal films are more advantageous in certain clinical situations where instantaneous release of the medicaments is necessary for prompt relief. Some of such of clinical situations includes cough, allergy, motion sickness, pain and other local oral manifestations.

2. Mucoadhesive Polymers-

Polymers with different characteristics have to be considered depending on the type of formulation. Different situations for buccal mucoadhesion are possible depending on the dosage form.

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 carboxy methyl cellulose [NaCMC]
- Hydroxyl propyl methylcellulose [HPMC]
- Hydroxy ethyl cellulose
- Hydroxyl propyl cellulose [HPC].

Hydrogels include anionic polymers like carbopol, polyacrylates, cationic polymers like chitosan and nonionic polymers like eudragit analogues [14].

3. Plasticizers-

Plasticizers are used in the concentration of 0-20% w/w of dry polymer. Plasticizer is an important ingredient of the film which improves the flexibility of the film and reduces the bitterness of the film by reducing the glass transition temp of the film. The selection of plasticizer depends upon the compatibility with the polymer and type of the solvent employed in the casting of film. Plasticizers should be carefully selected because improper use of the plasticizer affects the mechanical properties of the film.

Most commonly used plasticizers are –

- PEG400
- Propylene glycol
- Glycerol
- Castor oil

4. Penetration Enhancers-

Penetration enhancers are also the important excipients to be added in the buccal film formulation. These are required when a drug had to reach the systemic circulation to exert its action. These must be nonirritant and have a reversible effect. The epithelium should recover its barrier properties after the drug has been absorbed.

The most common classes of buccal penetration enhancers include-

Fatty acids that act by disrupting intercellular lipid packing, surfactant, bile salts and alcohols.

5. Taste Masking Agents-

Taste masking agents or taste masking methods should be used in the formulation of the APIs have bitter taste, as the bitter drugs makes the formulation unpalatable, especially for pediatric preparations. Thus, before incorporating the APIs in the buccal film, the taste needs to improve the palatability of the formulation, such as complexation technology, salting out technology, etc.

6. Sweetening Agents-

Sweeteners have become the important excipients for oral disintegrating drug delivery system. The sweet taste in the formulation is more important in case of pediatric population. Natural sweeteners, as well as artificial sweeteners, are used to improve the palatability of the mouth dissolving formulations. The natural sweeteners include sucrose, dextrose, fructose, glucose, liquid glucose and maltose. The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Artificial sweeteners should be used if the dosage form is meant for diabetic patients.

Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners, followed by acesulfame-K, sucralose, alitame and neotame, which come under the second generation artificial sweeteners.

7. Saliva Stimulating Agent-

Generally, acids which 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 that would aid in the faster disintegration of the rapid dissolving film formulation.

Examples of salivary stimulants-

- Citric acid
- Malic acid

- Lactic acid
- Ascorbic acid
- Tartaric acid

These agents are used alone or in combination between 2 to 6 % w/w of weight of the film.

8. Flavoring Agents-

The flavoring agents are very important in case of oral dissolving systems. The acceptance of the oral disintegrating formulation by a patient depends on the initialflavor quality, which is observed in first few seconds after the product has been consumed and the after taste of the formulation which last for at least about 10 min.

Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils, while vanilla, cocoa, coffee, chocolate, and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type.

The amount of flavor needed to mask the taste depends on the flavor type and its strength. Preferably, up to 10%w/w flavors are added in the buccal film formulation. To improve the flavor strength and to enhance the mouth feed effect of the product; cooling agents like monomethyl succinate can be added.

9. Coloring Agents-

To improve the elegant appearance of films, coloring agents are incorporated in the formulation.

MANUFACTURING METHODS:

The buccal film manufacturing process includes the following techniques.

1. Solvent casting technique[27, 28]:

The solvent casting method is widely preferred for the manufacture of buccal films. This process involves the following step:

- Water soluble ingredients firstly excipients are dissolved in water, then water soluble polymers are added to form homogenous viscous solution & lastly drug is added.
- Solution are stirred with the help of magnetic stirrer for 5 minutes to form a homogenous solution.
- Final casted in to the petri plate & dried at 40 temperature in hot air oven.
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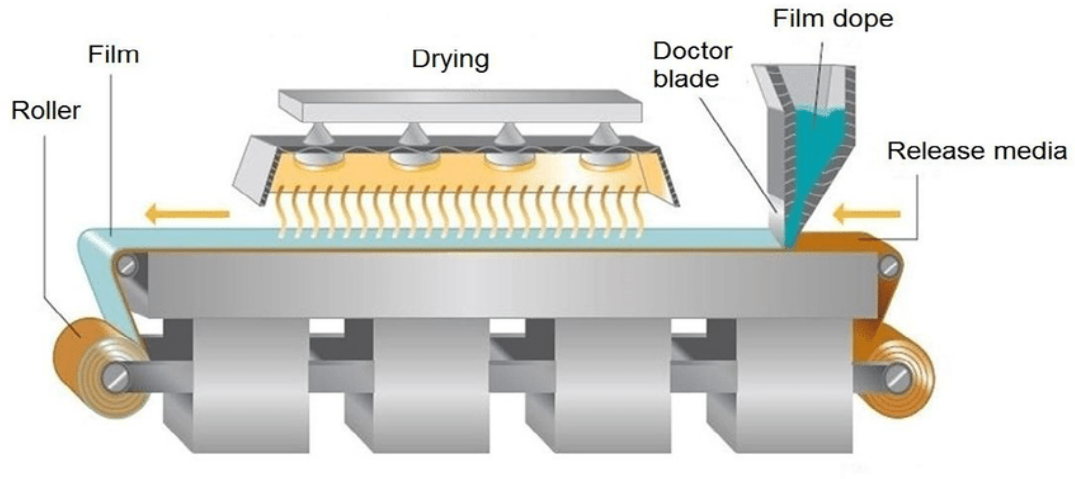

Fig.4: Solvent Casting process

2. Hot melt extrusion technique :

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 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 molted 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 temp 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 [15].

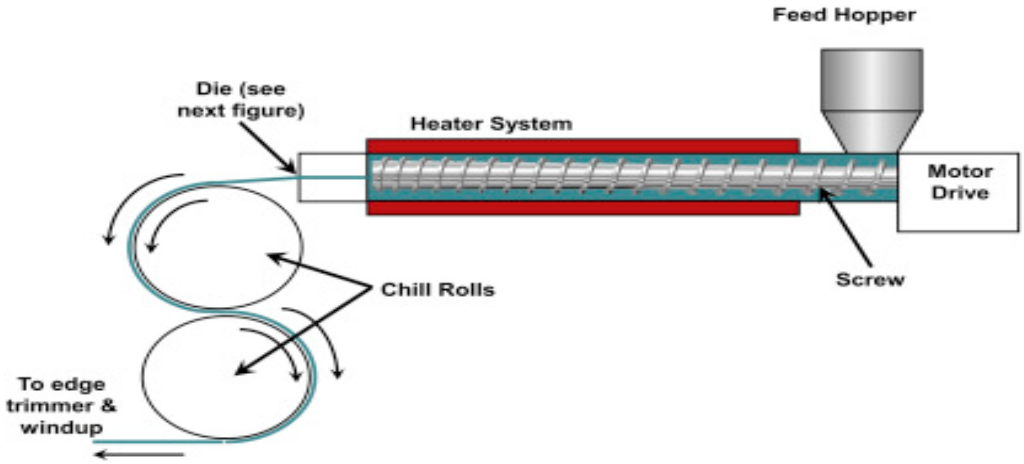

Fig.5: Hot Melt Extrusion Process

3. Rolling method:

A solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cute in to desired shapes and sizes. Other ingredients including active agent are dissolved in small portion of aqueous solvent using high shear processor. Water soluble hydrocolloid dissolved in water to form homogeneous viscous solution.

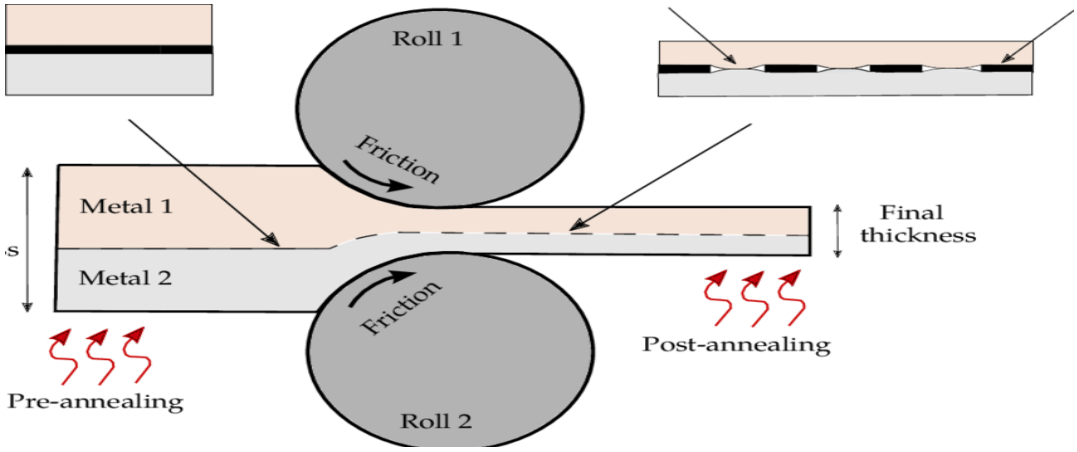

Fig.6: Rolling method

EVALUATION OF BUCCAL FILMS

The buccal films are evaluated by following evaluation parameters,

1) Weight and Thickness of the Film -

For evaluation of film weight, 3 films of every formulation are taken and weighed individually on a digital balance. The average weights are calculated. Similarly, 3 films of each formulation were taken and the film thickness is to be measured using micrometer screw gauge at 3 different places, and the mean value is to be calculated.

2) Surface pH of films-

For determination of surface pH, 3 films of each formulation are allowed to swell for 2 hr on the surface of an agar plate. The surface pH is to be measured by using a pH paper placed on the surface of the swollen patch. A mean of 3 readings is to be recorded.

3) Swelling Index [17, 19]

After determination of the original film weight and diameter, the samples are allowed to swell on the surface of agar plate kept in an incubator maintained at 37$\pm$ 0.2^{0}C. Weight of the films (n=3) is determined at different time intervals (1-5hr). The % swelling, %S is to be calculated using the following equation:

$$\textbf{Percent swelling [\%S]} = [X_t\text{-}X_0 / X_0] \times 100$$

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

X_o = the initial film weight at zero time

4) Folding Endurance -

3 films of each formulation of required size are cut by using sharp blade. Folding endurance us to be determined by repeatedly folding the film atthe same place,till it is broken. The number of times, the film could be folded at the same place without breaking gives the value of folding endurance.

5) Moisture Content -

The prepared films are to be weighed individually and kept in a desiccators containing calcium chloride at RT for 24 hr. The films are to be weighed again after a specified interval, until they show a constant weight. The percent moisture content is to be calculated by using following formula;

% moisture content = [Initial weight–Final weight / Initial weight] x 100

6) In-vitro residence time[18]-

The *in vitro* residence time is determined using IP disintegration apparatus using 900ml of the disintegration medium maintaining at 37$\pm$ 2^{0}C. The segment of rat intestinal mucosa, each of 3 cm length, are to be glued to the surface of a glass slab, which is then vertically attached to the apparatus. 3 mucoadhesive buccal films of each formulation are hydrated on one surface and the hydrated surface is brought into contact with the mucosal membrane. The glass slab is vertically fixed to the apparatus and allowed to move up and down. The film is completely immersed in the buffer solution at the lowest point, and is out at the highest point. The time required for complete erosion or detachment of the film from the mucosal surface is to be recorded.

7) Drug content uniformity-

3 film units (each of 20 mm diameters) of each formulation has to be taken in separate 100ml volumetric flask, 100ml of solvent has to be added and continuously stirred for 24hr. The solutions have to be filtered, diluted and suitably and analyzed at specified nm in UV spectrophotometer. The average of drug content of 3 films has to be taken as final reading [20].

8) Surface characterization studies -

The scanning electron photomicrograph of the film is taken at 6000X magnification. The prepared film containing drug is examined for clear and colorless surface. The photomicrographs of the film with the drug and the blank film are compared, and are examined whether the drug is distributed uniformly throughout the film in an amorphous form.

9) In-Vitro Dissolution Studies -

Dissolution studies are carried out for all the formulation, employing USP dissolution apparatus at 37$\pm$ 0.5^{0}C, rotated at constant speed of 50 rpm using 900ml of dissolution medium. A sample of drug film is used in each test. An aliquot of the sample is periodically withdrawn at suitable time interval and the volume is replaced with fresh dissolution medium. The sample is analyzed spectrophotometrically at specified nm.

10) Organoleptic Evaluation -

The prepared buccal film should possess the desired features of sweetness and flavor, which is acceptable to a large mass of population. Controlled human taste panels are used for psychophysical evaluation of the product. In-vitro methods of utilizing taste sensors, specially designed electronic tongue measurement devices can be used for this purpose.

11) Packaging -

Many options are available for buccal films packing, such as single pouch, blister card with multiple units, multiple-unit dispenser and continuous roller dispenser. Single packaging is mandatory for films. An aluminum pouch is the most commonly used packaging system. There are some patented packaging systems for oral films. Labtec company has patented packaging technology called rapid card and Amcor Flexibilities Company has patented Core-peel technology.

12) Ex-vivo Permeation studies-

The modified Franz diffusion cell is use for permeation studies. It consists of two compartments, one is donor compartment and another is receptor compartment of 18ml capacity and having 0.785 cm^2 effective diffusion area. The receptor compartment was covered with water jacket to maintain 37^{0}C.

The porcine or rabbit buccal mucosa can be used for these studies. The buccal mucosa is carefully separated from fat and muscles using scalpel. The buccal epithelium is isolated from the underlying tissue. The buccal epithelium was used within 2 hrs. upon removal. The separated buccal epithelium is mounted between two chambers and receptor chamber is filled with PBS pH 7.4. The buccal epithelium is allowed to stabilize for the period of 1 hr. After stabilization of buccal epithelium, the film is kept on buccal epithelium and periodically samples are withdrawn and some fresh volume is replaced. The aliquots are analyzed spectrophotometrically.

FLEXIBILTIY IN FORMULATION OF BUCCAL FILMS

There is wide range of flexibility in developing the buccal films. The main benefits of buccal film formulation includes that many of the eligible APIs can be formulated as buccal films and many of the physical properties can be altered, such as material composition, films dissolution rates and API absorption rates. The formulation of buccal films includes film forming polymers and other additives.
Formulators can design the films to release the drug immediately in seconds as immediate drug release formulations, or to deliver the dose over a period of hours as controlled release formulations by modifying the combination of film-forming polymers and film thickness. The buccal mucosal area, as it has an expanse of smooth and relatively immobile surface, the area is well suited for placement of retentive device and appears to be acceptable to the patient. The anatomical features of buccal mucosa make it as an appropriate site for prolonged systemic delivery of drugs. The buccal 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. Buccal film formulation is more feasible drug delivery method even for the systemic delivery of orally inefficient drugs, and it is as an attractive alternative for the delivery of protein and peptide drug molecules.

APPLICATIONS

- Multilayer drug film construction is possible, which 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 acts as gastro retentive dosage forms, in which the dissolution of the films could be triggered by the pH or enzyme secretions of gastro intestinal tract, and could be potentially used to treat gastro intestinal disorders.

CONCLUSION

The present review concludes that the buccal film is the most accurate and acceptable dosage form, which bypasses the hepatic first pass effect and shows good bioavailability. This is the most promising and innovative technology, which is useful to all the age groups, specifically pediatric, geriatric patients and also to the patients with swallowing difficulties. Buccal films can replace the conventional dosage forms, including fast disintegrating tablets due to its advantages over the conventional dosage forms, and they can be manufactured with low cost. This technology provides a good tool for maintenance of drug therapeutic value, as well as pharmcoeconomic value.

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