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Review Article

A Review on Buccal Film: A Modern Expansion in Drug Delivery System

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Abstract

Objective: Main objective is to develop and characterize buccal films for low bioavailability drugs, which are suffering from presystemic metabolism. Now a day's extensive research is being carried out to improve efficacy, safety and patient compliance, for this there is a further need to design and develop advanced drug delivery systems. Development of buccal film is one of the challenges in the advanced drug delivery system. Buccal route is the best site for local as well as systemic administration of drugs, due to the physiological nature of buccal mucosa.

Method: Several methods such as solvent casting, hot melt extrusion, solid dispersion extrusion, rolling, spray technique and semi-solid casting methods are utilized to develop buccal films. All characterization parameters are discussed here with detailed procedure.

Result: This method serves as a best alternative. It has numerous advantages than other traditional types of drug delivery systems. Literature survey reveals that pulmonary, ocular, nasal, rectal, buccal, sublingual, vaginal, and transdermal routes are options for administration of drug having poor oral availability and extensive first pass metabolism but use of such alternative routes/drug delivery systems has limited success because of their inherent drawbacks.

Conclusion: Buccal films are suitable for delivery of low bioavailable drugs, which are suffering from first pass metabolism. Present review is focus on advantages, disadvantages, ideal characteristics for drug and excipients, compositions, formulation methods and evaluation parameters of buccal film.

Keywords: Orodispersible buccal films, Mucoadhesive buccal films, Drug selection for buccal films, Composition, Formulation methods, Evaluation Parameters.

INTRODUCTION

Oral route is the most convenient and preferred route for drug administration. This route is simple, non- invasive, and due to these it leads to high therapy compliance and patient acceptability.

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In market more than half of registered medicines are available as oral solid dosage forms. Oral solid dosage form consist advantages like accuracy in dose, relatively high stability, and they can be modified according to drug release profile in order to delay or fast the therapeutic effect. Instead of it there are many challenging problems with oral solid dosage form, like mostly when encountered in pediatric or geriatric populations there is difficulty in swallowing, and also in case of handicapped or bedridden patients. Also it involves little discomfort when administered large size tablets or capsules as well as problems such as irritation of the pharyngeal region, drug sticking to the throat mucosa, coughing or

chocking (Brniak et al., 2015; Yapar 2014). In case of biotechnologically produced drugs, due to their biological and physiochemical absorption and metabolism they are difficult to deliver through the conventional oral route. There are many drugs shows presystemic clearance extensive in liver when administered orally, which often leads to a lack of significant correlation between membrane permeability, bioavailability and absorption (Sudhakar et al., 2006). Delivery of drugs within oral cavity is classified into three categories:- a) Local delivery, desire drug delivered into oral cavity, b) Sublingual delivery, desired drug systematic delivered through the mucosal membranes lining the floor of the mouth, and c) Buccal delivery, delivery of the drug through the buccal mucosal lining of the oral cavity (Shojaei 1998). Among various transmucosal routes, buccal rout found more suitable for delivery of pharmaceutical agents. Buccal mucosa is suitable for administration of retentive dosage forms; it has good accessibility. It has direct approach to the systemic circulation through the internal jugular vein, it bypass drug form the hepatic first pass metabolism and provide high bioavailability to it. Other advantages includes painless administration, enzymatic activity is less, drug withdrawal is easier, suitable for drugs or excipients which mildly and reversibly damages or irritates the mucosa, addition of permeation enhancer or enzymes inhibitor or pH modifier in the formulations is possible. It's possible to design multidirectional or unidirectional release system for local or systemic action (Sudhakar et al., 2006). Different dosage forms like films, gels, tablets, ointment and patches can be used for administration of drug through the buccal mucosa (Singh et al., 2017). Buccal films are the most recently develops dosage form; our goal is to discuss the various approaches for buccal films in the systemic administration of orally less or in efficient drugs.

List of Abbreviations

Abbreviation	Full form
FDA	Food and Drug Administration
EMA	European Medicines Agency
ODF	Orodispersible film
MOF	Mucoadhesive oral film

Mucoadhesive Buccal Films

Buccal film can be defined as the postage stamp sized strips which contain water dissolving polymer to allows the dosage form to quick adhere, hydrate and dissolve when placed in the oral cavity or, on the tongue which give systemic drug delivery. Different terms can be found in the literature, for example, oral film, orally dissolving strip, wafer, flash release wafer, melt away film, quick dissolve film. The films are not melting but dissolving or at least disintegrating in saliva hence melt-away film and melting film are inappropriate terms. Therefore, the term buccal film, soluble or oral soluble film is preferred by the Food and Drug Administration (FDA), whereas the European Medicines Agency (EMA) is using orodispersible film (ODF) (Hoffmann et al., 2011).

Advantages of Buccal films

Advantages of buccal film are as follows

- 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.
- Helpful for Pediatric and Geriatric people and also to the patients who are mentally retarded, disabled or non-cooperative they are ideal for travelers.
- Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- Fast onset of action achieved by the direct absorption through the oral mucosa and entrance into the systemic circulation.
- Able to give low dose with help of buccal films.
- Convenient for patients, no risk of chocking, no need of chewing, swallowing, or water for administration.
- Ease of transportation, handling of storage and consumer handling.
- Compatible for taste masking.

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- Good mouth feel and good stability.
- Accurate dosing compared to liquid dosage forms.
- Self administration is possible.
- Required less excipient.
- More economical.
- Do not form irritation at the site of application.
- Due to more flexibility buccal films may be preferred over buccal tablet (Hoffmann et al., 2011, Rao et al., 2013; Silva et al., 2015).

Disadvantages of Buccal films

Advantages of buccal film are as follows.

- Unable to give high dose by buccal film.
- Over hydration may lead to formation of slippery surface and structural integrity of the formulation may get disrupted by the hydration & swelling of the bio-adhesive polymer.
- Drinking and eating may become restricted.
- Hygroscopic in nature therefore need to store in dry place.
- Films are difficult to pack, for packaging of films requires equipments.
- Drug which irritate mucosa or have an unpleasant or bitter taste or an obnoxious odor cannot be administered by this route (Hoffmann et al., 2011; Rao et al., 2013; Silva et al., 2015; Vishwakarma 2017).

Ideal characteristics of drug candidate for buccal film

The incorporating drug should have low dose.

- Drugs undergoes extensive first pass metabolism are ideal drugs for buccal films.
- Drug should absorbed by passive diffusion mechanism.
- The pH of a drug should not be acidic.
- Drug should have a good stability in water and pH of saliva (6.2-7.6).
- Taste should be acceptable; otherwise taste masking has to be carried out.

Drug should have an ability to permeate oral mucosal tissue (Singh et al., 2017; Vishwakarma 2017).

Composition of Buccal film

Oral film are composed by film forming polymers, plasticizers, colorants, stabilizers, flavours and sweeteners for taste masking or improved palatability. For mucoadhesive oral film (MOF) it is necessary to include polymers that exhibit good adhesive properties to mucosal. Other important components are permeation enhancers that promote drug absorption. Regarding the design, MOF can be composed by several layers (multi-layer) or one layer (single-layer) considering the purpose of the formulation. Multilayer formulations ensure the unidirectional release of the drug towards the oral mucosa while with the single-layer film there is a multidirectional release of the drug. The presence of a backing layer reduces the diffusion of saliva into the following layers. Double-layer MOF consist of a mucoadhesive layer and a backing layer, while triple-layer MOF have an additional intermediate layer that works as a drug deposit and ensures its sustained or prolonged release (Silva et al., 2015). The composition of film is as shown in **Table No. I**

Table No I. Composition of film (Vishwakarma 2017**).**

Sr. No.	Components	Percentage Range (%)
1	Active pharmaceutical agent	5-30
2	Polymer	45
3	Saliva stimulating agent	2-6
4	Plasticizer	0-20
5	Sweetening agent	3-6
6	Surfactant	Quantity sufficient
7	Flavors, colors, fillers	Quantity sufficient

1. Active pharmaceutical agent

For the selection of API for formulation of buccal films, the API should follow the ideal characteristics of drug for buccal film highlighted above.

2. Polymers

Both natural and synthetic polymers which are able to adhere the mucosal surfaces are used for film casting. The use of appropriate polymer determines the various parameters such as thickness. Mucoadhesive strength, *in vitro* release and the residence time of the drug delivery device. Generally the polymers with high molecular weight are preferred because; they show effective release rate controlling properties. Some ideal properties of polymer for buccal drug delivery system are as follows:

- Nontoxic and nonirritant.
- Devoid of leachable impurities.
- Should not retard disintegration time of film.
- Tasteless i.e. should not impart any taste to film formulation.
- Should have good wetting and spread ability property.
- Should have sufficient peel, shear, and tensile strength.
- Readily available.
- Inexpensive.
- Sufficient shelf life.
- It should be compatible with the environment and drug.
- It should be inert.
- It should be adhere quickly with the mucus membrane.
- Adherence should be long lasting for required time.

Example of polymers used in films are-

Natural polymer: Pullulan, starch, glatin, pectin, sodium aginate, maltodextrins, polymerized rosin etc.

Synthetic polymer: Hydroxypropyl methylcellulose, sodium carboxymethlcellulose, polyethylemne oxide, hydroxypropyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, ethyl cellulose **(**Kumar et al., 2014; Salamat-Miller et al., 2005).

3. Saliva stimulating agent

The use of saliva stimulating agent is increases the rate of production of saliva. By stimulating saliva it help in quick disintegration and dissolution of the film. The agents which are most commonly used are citric acid, lactic acid, ascorbic acid, tartaric acid, malic acid sodium aurylsulphate (Siddiqui et al., 2011).

4. Plasticizers

Plasticizer provides good flexibility, enhances the folding endurance, reduces the brittleness, reduces the glass transition temperature and improves the film properties. Few examples of commonly used plasticizers are propylene glycol, PEG-600, PEG-400, glycerol, acetyltriethyl citrate glycerin, citrate ester, triacetin phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil etc (Fulzele et al., 2002).

5. Surfactants

Due to the cationic, anionic, nonionic and bile salts nature of the surfactants the perturbation with intercellular lipids on the mucosal surface happened which increases permeability of drugs. Commonly used surfactants are sodium lauryl sulphate, polyoxyethylene, cetyltrimethyl ammonium bromide polyoxyethylene-9-laurylether, 23-lauryl ether, benzalkonium chloride, Polyoxythylene-20-cetylether, cetylpyridinium chloride (Nair et al., 2013).

6. Sweetening, flavoring and coloring agent

Taste and color play an important role in the thin film technology. In case of pediatric population sweet taste of formulation is necessary. Both natural and artificial sweeteners are used to improve the taste of the film. Mannitol, aspartate, sorbitol, xylitol, polyols, glycyrrhizin, saccharin, cyclamate, malitol, isomalt, malitol, acesulfamepotasium are commonly used sweeteners in formulation of film. Flavors like lemon, peppermint, cinnamon, menthol,

wintergreen, vanilla, chocolate, coffee, orange are used for the formulation of film. To improve the appearance of films, coloring agents are incorporated in the formulation. Natural coloring agents like titaniumoxide, silicondioxide, zinc oxide and pigments such astitanium dioxide is incorporated for coloring (Madhavi et al., 2013).

Method of formulation of film

There are methods are used for the formulation of the film which are as follow

I. Solvent casting method
II. Hot melt extrusion
III. Solid Dispersion Extrusion
IV. Rolling method
V. Spray technique
VI. Semi-solid casting

I. Solvent casting method

It is a preferable, feasible and undoubtedly widely used method; the manufacturing process is straightforward and low cost for the preparation of buccal film. For solvent casting method it required polymers, excipients like flavoring agent, sweetening agent, colors and API. The film-forming polymers are mixed in a solvent in mixtures of water and organic solvents, or in pure water followed by the addition of all the excipients. To this solution finally the API is added. De-aeration of the coating mass is required to escape the bubble formation in to the liquid during mixing process which is achieved by continuous stirring and application of a vacuum. Then the final solution is poured onto petri plate and it allowed to dry overnight at room temperature or by providing high temperature at oven. After drying the films are cut into suitable size and shape. In industries before cutting the strips they are rolled and stored for a certain time which is called as 'rollstock'. A film is prone from the damaged that's why it should not be exposed for too long time. If possible, it should be cut and packed immediately after the preparation to keep its stability. Thickness, drying rate, content uniformity as well as morphology of the films is depends on the rheological properties of the polymeric mixture. Organic solvents could increases solubility as well as shorten drying time of the API but it is necessary to removed it at acceptable levels. Residual water content is necessary to obtained flexible films. Also high water content leads to tacky films. Also in solvent casting method the particle size can be a critical factor. Particles size greater than 250 µm can cause scratches on the surface of the film. There are several advantages of solvent casting method such as it is easy, having better physical properties, and excellent uniformity of thickness and low cost processing with the film. Limitations of this process are it requires polymers which are soluble in water or it is volatile in nature. In case of long time storage due to the evaporation or loss of the residual solvent, the percent elongation is decreases which form brittle film. Organic solvent causes a hazard to health and environment. Formation of films in commercial scale need to deal with many challenges regarding mixing speed heating, temperature could bring variability in consistency and quality of the film (Karki et al., 2016).

II. Hot melt extrusion

This method is especially useful when no organic solvent system is required. Heating process is used to incorporate polymer in to a film. Under high temperature a mixture of API, polymer and all the excipients is extruded to form a homogenous mass, this homogenous mass then used for casting the film. Due to use of high temperature only thermo labile substances are used in this process. The dry state API is blend and filled in the hopper then it transport for heating process, the formed extruded molten mass is used to cast film. In this process casting and drying are the critical steps. The advantages of hot melt extrusion are: this process is continuous, no organic solvents are needed, fewer operation units, wastage of product is minimum, scale up is possible, this is an anhydrous process, mixer of drug carrier need a short residence time and temperature, give content uniformity, increased bioavailability of poorly soluble API and excipients used, low cost is needed for this process and the disadvantages are it is a thermal process which affect on drug and polymer

stability, flow properties of polymer affect on formulation, very few polymers are suitable for this process (Panda et al., 2012).

III. Solid Dispersion Extrusion

Solid dispersion method involves the incorporation of drug in to the melted polymer solution. For these firstly the drug is dissolved in a suitable liquid solvent and then drug loaded solution is incorporated in to melted polymeric solution. The drug or the solvent used to dissolve drug should not miscible with melt polymer. Finally the prepared solid dispersions are shaped into films by using dies **(**Vishwakarma 2017).

IV. Rolling method

For this method the solution or suspension of polymer and API is used for a preparation of film. The suspension or solution which is used should have specific rheological properties. Water or mixture of water and alcohol should used as the solvent for these process. For the formulation of film the prepared solution or suspension directly subjected to the roller. The film is dried on the roller and cut in to desired size and shape (Bala et al., 2013).

V. Spray technique

For film casting the polymer, API, and all the excipients are dissolved in suitable solvent to form a clear solution. This prepared solution is spread or coated on carrier material then dried and peeled off to get a film. Examples of different carrier materials used are glass, polyethylene film of non-siliconized Kraft paper or teflon sheet (Irfan et al., 2016).

VI. Semi-solid casting

This method is more preferable when acid insoluble polymer is used. In this method to the water soluble polymeric solution acid insoluble polymeric solution is added and then to this solution plasticizer is added to form a gel like solution. This gel like solution is used for film casting with the help of ribbons using heat controlled drums. The thickness of the casted films should be within the range of 0.015 - 0.05 µm. The ratio of the acid insoluble polymer to film forming polymer should be 1:4. The water soluble polymeric solution is prepared in water and acid insoluble polymeric solution is prepared in ammonium or sodium hydroxide. Examples of acid insoluble polymers are cellulose acetate phthalate and cellulose acetate butyrate (Bala et al., 2013; Mahajan et al., 2011).

Evaluation Parameters

Usually following evaluation parameters are performed on the formulated buccal films.

1. Thickness
2. Disintegration time
3. Drug content
4. Folding endurance
5. Mechanical properties of buccal film
6. Surface pH
7. Percentage moisture absorption
8. *In vitro* drug release study

1. Thickness

Thickness of the prepared films will be measured by digital Vernier caliper and the mean average should be taken. The required thickness for buccal films should be in the range of 50 to 1000 µm (Dangre et al., 2019; Karki et al., 2016).

2. Disintegration time

Disintegration time is a time at which film begins to collapse when brought into contact with water. For these test film of desired size place in a Petri dish containing water and note the time required to break down the film. Disintegrating test apparatus is used for this study. Disintegration time for oral fast disintegrating strips is 5 – 30 sec (Bala et al., 2013).

3. Drug Content

The method of drug content is different for the different API, which is described in standard pharmacopoeia. Content uniformity is needed for buccal films as per other dosage forms (Dixit and Puthli 2009).

4. Folding endurance

The flexibility of the buccal films is depends on folding endurance. The films are folded at 180° angle repeatedly to the same plane up to it breaks or the films are folded to 300 times without breaking. The number of times the film is folded without breaking is called as the folding endurance value. Mechanical strength of a film is directly proportional to a folding endurance.

Therefore higher folding endurance value more the mechanical strength of a film (Li et al., 2017).

5. Mechanical properties of buccal film

Texture analyzer is used for determination of the mechanical properties of a buccal film which is based on the ASTM D882 method. Tensile strength is defined as the maximum stress required for break the film. The tensile strength is calculated by using following equation: Eq.1

$$\text{Tensile strength} = \frac{\text{Force at failure}}{\text{Cross section area of the film}} \times 100$$

The elongation at break is a measurement of the maximum deformation the film can undergo before tearing apart and is calculated using Eq. 2

$$\text{Elongation at break} = \frac{\text{Increase in length at break}}{\text{Initial film length}} \times 100$$

In general, elongation increases with increasing concentration of plasticizers (Morales et al., 2012).

6. Surface pH

Each film was wetted with sufficient amount of double distilled water and then allowed to equilibrate for 30 min in petri-plate. The pH electrode was brought into contact with the surface of wet film and pH was digitally displayed by pH meter (Dangre et al., 2019; Nair et al., 2013).

7. Percentage Moisture Absorption

In desiccators containing 200 mL saturated solution of potassium chloride, the patches were placed for 3 days which give relative humidity of 84%. The patches were weighed after removing from desiccators. The percent moisture absorption of each patch was calculated according to the Eq.3 (Hanif et al., 2014).

$$\text{Percentage moisture uptake} = \frac{\text{Final Weight - Initial Weigh}}{\text{Final Weight}}$$

8. *In vitro* drug release study

Standard basket or paddle type dissolution apparatus described in any of the pharmacopoeia is used to perform the *in vitro* drug release study. On the basis of sink conditions and highest dose of the API, the dissolution medium will be selected. Many times in paddle type dissolution apparatus, dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium (Irfan et al., 2016).

According to literature review formulation and evaluation of buccal films containing following API are well reported.

Table No. II. Literature survey or work completed on buccal films

Sr. No.	API Name	Reference
1.	Lignocaine	Brook et al., 1989
2.	Teracycline	Minabe et al., 1989
3.	Buprenorphine	Guo 1994
4.	Chorhexidine	Jones and Medlicott 1995
5.	Oxytocin	Li et al., 1996
6.	Isosorbide dinitrate	Nozakiet al., 1996
7.	Ethylcellulose-Polyethylene Glycol	Samuelov et al., 1978
8.	Peptides	Li et al., 1998
9.	Eudragit	Wong et al., 1998
10.	Clorhexidine Gluconate	Snel et al., 1999
11.	Thiocolchicoside	Artusi et al., 2002
12.	Miconazole nitrate	Nafee et al., 2003
13.	Acyclovir	Rossi et al., 2003

14.	Ibuprofen	Perioli et al., 2004
15.	Salbutamol Sulphate	Mashru et al., 2005
16.	Toluidine blue O	Donnelly et al., 2006
17.	Propranolol hydrochlorid	Patel et al., 2007
18.	Carvedilol	Vishnu et al., 2007
19.	Triclosan	Dinge and Nagarsenker 2008
20.	Clotrimazole	Singh et al., 2008
21.	Maltodextrin	Cilurzo et al., 2008
22.	Glipizide	Semalty et al; 2008
23.	Verapamil HCL	Deshmane et al., 2009
24.	Prochlorperazine	Nishimura et al., 2009
25.	Methotrexate	Chaudhari et al., 2010
26.	Miconazole	Rasool and Khan 2010
27.	Dicyclomine	Tomar et al., 2012
28.	Simvastatin	Mishra et al., 2012
29.	Rosuvastatin	Gajula et al., 2013
30.	Carbamazepine	Govindasamy et al., 2013
31.	Cetirizine Hydrochloride	Mishra and Amin 2013
32.	Diltiazem	Manhar and Suresh 2013
33.	Tromethamin	Sandhya et al., 2013
34.	Loratidine	Kumaria et al., 2014
35.	Lidocaine hydrochloride	Preis et al., 2014
36.	Prednisolone	kumria et al., 2014
37.	Gliencamide	Najafi et al., 2014
38.	Ergotamine Tartrate and Caffeine Anhydrous	Jelvehgari et al., 2015
39.	Ciprofloxacin	Wu et al., 2015
40.	Simvastatin	Maghraby et al., 2015
41.	Nystatin	Gajdosova et al., 2016
42.	Ondansetron	Trastullo et al., 2016
43.	Fentanyl	Jones 2016
44.	Zaleplon	Farag et al., 2017
45.	Rizatriptan benzoate	Salehi and Boddohi 2017
46.	Palonosetron	Nair et al., 2018
47.	Sodium cromoglycate	Sabry 2018

Conclusion

A good number of researcher's are continuously contributing around the world in the development and characterization of mucoadhesive buccal films. This review is an effort to summarize the literature work done till date and to demonstrate the future pathway of mucoadhesive buccal films. Due to consumer friendly nature, many of the pharmaceutical companies are switching their products toward buccal films. Buccal films also provide good platform for the patients who have difficulty in swallowing conventional or traditional oral dosage forms such as pediatric, geriatric and psychiatric patients with dysphagia. For future pharmaceuticals, nutraceuticals as well as cosmeceuticals, this buccal drug delivery system provide good platform.

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