A NOVEL APPROACH FOR BUCCAL DRUG DELIVERY SYSTEM –
FAST DISSOLVING FILM

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1. ABSTRACT
Fast dissolving buccal film drug delivery system is an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms. It improve the efficacy of APIs by dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration. Oral films provide better drug utilization by avoiding the first pass metabolism, enhance drug bioavailability. There are so many methods to formulate fast dissolving film but solvent casting method is mostly preferred to formulate it, due to easy and low cost.

KEYWORDS – Fast dissolving buccal film, pediatric and geriatric patients.

2. INTRODUCTION
In the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms formulate the fast dissolving tablets by using superdisintigrants and hydrophilic ingredients which has the higher bioavailability, quick action and most patient compliance. Many FDTs are prepared by using the expensive lyophilisation process and sometimes difficult to carry, store and handle (fragility and friability also fear of chocking with fast dissolving tablet.

To eliminate the drawbacks of fast dissolving tablet a fast dissolving film can be placed. Fast dissolving films are very similar to ultra-thin strip of postage stamp in their shape, size and
thickness. Fast dissolving films are formulated using polymers, active pharmaceutical ingredients (API), plasticizers, saliva stimulating agents, sweeteners, flavors, preservatives and colors. Fast dissolving film is simply placed on the patient’s tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed.[1]

Fast dissolving drug delivery systems such as MDF are novel dosage forms that disintegrate or dissolve within the oral cavity. They have emerged as a convenient way of dosing medications, not only to special population groups with swallowing difficulties such as children and the elderly, but also to normal people. MDF are prepared using hydrophilic polymers that rapidly dissolve on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution on contact with saliva. MDF are typically designed for oral administration, with the user placing the strip on or under the tongue (sublingual) or along the inside of the cheek (buccal). These drug delivery options allow the medication to bypass the first pass metabolism, thereby increasing its bioavailability. As the strip dissolves, the drug can enter the blood stream primarily buccally and sublingually.[2]

Special features of fast dissolving films[3]

• Thin elegant film
• Available in various size and shapes
• Unobstructive
• Excellent mucoadhesion
• Fast disintegration
• Rapid release

Advantages[4,5]

1. Easy to swallow and Water is not required.
2. No risk of choking.
3. Ease in administration.
5. First pass metabolism is avoided
6. Taste masking
7. Enhanced stability
8. Rapid dissolution and absorption of drug, which may produce rapid onset of action.
9. Avoid hepatic first pass metabolism.

![Figure-1 Fast dissolving buccal film](image)

**Disadvantages**[^7,^8]

- a. Thermal degradation due to use of high temperature.
- b. Flow properties of the polymer are essential to processing.
- c. Limited number of available polymers.
- d. All excipients must be devoid of water or any other volatile solvent.
- e. Once placed at the absorption site & the dosage form should not be disturbed.
- f. The drug swallowed in saliva is lost.
- g. Properties like unpleasant taste or odour, irritability to the mucosa & stability at salivary pH possess limitations to the choice of drug.
- h. Only drugs with small dose can be administered.
- i. Eating and drinking may become restricted.

**Marketed Films**

**Table 1. List Of Marketed Fast Dissolving Films[^3]**

<table>
<thead>
<tr>
<th>S.N.</th>
<th>Products</th>
<th>Manufactured by</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dextromethorphan HBr (cough suppressant), Diphenhydramine Citrate (cough and cold), Breath Strips</td>
<td>MonoSolRx</td>
</tr>
<tr>
<td>2</td>
<td>Donepezil rapid dissolving films, Ondansatron rapid dissolving films</td>
<td>Labtec Pharma</td>
</tr>
<tr>
<td>3</td>
<td>Life-saving rotavirus vaccine to infants</td>
<td>Johns Hopkins undergraduate biomedical engineering students.</td>
</tr>
<tr>
<td>4</td>
<td>Methylcobalamin fast dissolving films, Diphenhydramine HCl fast dissolving films, Dextromethorphan fast</td>
<td>Hughes medical corporation</td>
</tr>
</tbody>
</table>
dissolving films, Folic Acid 1mg fast dissolving films, Caffeine fast dissolving films

<table>
<thead>
<tr>
<th>Category</th>
<th>Amount (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>1-30</td>
</tr>
<tr>
<td>Polymer</td>
<td>40-50</td>
</tr>
<tr>
<td>Plasticizer</td>
<td>0-20</td>
</tr>
<tr>
<td>Surfactant</td>
<td>q.s</td>
</tr>
<tr>
<td>Saliva Stimulating agent</td>
<td>2-6</td>
</tr>
<tr>
<td>Sweetening agent</td>
<td>3-6</td>
</tr>
<tr>
<td>Flavoring agent</td>
<td>0-10</td>
</tr>
<tr>
<td>Coloring agent</td>
<td>q.s</td>
</tr>
<tr>
<td>Stabilizer or thickening agent</td>
<td>0-5</td>
</tr>
</tbody>
</table>

3. Formulation consideration

From the regulatory prospective all the excipients used in the formulation and development of oral films and they are regarded as safe and should be approved for use in oral pharmaceutical dosage forms. The area of oral thin films is 1-20cm² (depend on dose and drug loading containing drug).

Active Pharmaceutical agents

Active pharmaceutical substance can be from any class of pharmaceutically active substances that can be administered orally or through the buccal mucosa. It includes antiulcers, antiasthmatics, antitussive, antihistaminic, antiepileptic, expectorants, antianginal etc. For the effective formulation, dose of drug should be in mgs (less than 20 mg/day). Various categories of drugs such as antiemetic, neuroleptics, cardiovascular agents, analgesics, antiallergic, antiepileptic, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction, antialzheimers, expectorants and antitussive.
The ideal characteristics of a drug to be selected are as follows-
1. The drug should have pleasant taste.
2. The drug to be incorporated should have low dose generally less than 30mg.
3. The drugs with smaller and moderate molecular weight should be preferable.
4. The drug has should be stable and soluble in water as well as in saliva.
5. It should be partially unionized at the pH of oral cavity.
6. It should have the ability to permeate oral mucosal tissue.[9]

Water soluble polymers
Water-soluble polymers are used as film formers. The use of film forming polymers in dissolvable films has attracted considerable attention in medical and nutraceutical application. The water-soluble polymers achieve rapid disintegration, good mouth feel and mechanical properties to the films. The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer film bases.[9]

Some of the water soluble polymers used as film former are HPMC E-3 and K-3, Methyl celluloseA-3, A-6andA-15, Pullulan, Carboxymethylcellulose cekol 30, PVPK-90, Pectin, Gelatin, SodiumAlginate, Hydroxypropylcellulose, Polyvinylalcohol, Maltodextrins and eudragit, Polymerized rosin is a novel film forming polymer.

Ideal properties of the polymers used in the oral film
1. Polymers should be non toxic and non- irritant
2. It should be non- bitter
3. Polymers should be tasteless
4. It should be devoid of leachable impurities
5. It should be inexpensive and readily available
6. It should not be an obstacle in the disintegration time
7. It should have good wetting and spreadibility property
8. It should exhibit sufficient peel, shear and tensile strength
9. It should have sufficient shelf life
10. It should not cause secondary infection in the oral cavity[10].

Plasticizers
Plasticizer is a vital ingredient of the MDF formulation. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the
casting of film. It helps to improve the flexibility of the film and reduces the brittleness of the film. Plasticizer significantly improves the film properties by reducing the glass transition temperature of the polymer in the range of 40-60°C for non-aqueous solvent system and below 75°C for aqueous system. Typically the plasticizers are used in the concentration of 0-20% w/w of dry polymer weight. Mechanical property is plasticizers concentration dependent only. It is also reported that the use of certain plasticizers may also affect absorption rate of the drug. The plasticizer employed should impart the permanent flexibility to the film and it depends upon volatile nature plasticizer and the type of interaction with the polymer. Cellulosic hydrophilic polymers were easily plasticized with hydroxyl containing plasticizers like PEG, propylene glycol, glycerols, polyols. In contrast, less hydrophilic cellulosic polymers were plasticized with esters of citric acid and phthalic acid. Glycerol acts as a better plasticizer for polyvinyl alcohol while diethylene glycol can be used for both hypromellose as well as polyvinyl alcohol films.

Surfactants
Surfactants act as solubilizing or wetting or dispersing agent in formulation so that the film is getting dissolved within seconds and release active agent quickly. Some of the commonly used surfactants are sodium lauryl sulphate, benzalkonium chloride, tweens etc. One of the most important surfactant is poloxamer 407 that is used as solubilizing, wetting or dispersing agent.

Colours
A full range of colours is available, including FD&C colours, EU Colours, Natural Colours and custom Pantone-matched colours.

Saliva stimulating agents
Saliva stimulating agents Increases the saliva production rate, aids in faster disintegration of OTF Conc.- 2 -6 % w/w Examples citric acid , malic acid, lactic acid, ascorbic acid, tartaric acid. Flavoring agents may be selected from syn. Flavor oils, oleoresins, from plant parts. Amount depends on the flavor type and strength important flavors: peppermint, cinnamon, nutmeg, vanilla, cocoa, coffee, chocolate, citrus, apple, cherry, raspberry, pineapple.

Flavour
Flavouring agent are those ingredients which impart flavour to any of the formulation. The perception of flavour varies from individual to individual ethnicity and personal liking.
Any US-FDA approved flavour can be added to the formulation according to the choice of the individuals of different age groups. The flavours liking changes with the age as geriatric population like mint or orange flavour while young generation like fruit, raspberry, strawberry flavor.[10] Flavouring agent should be compatible with the drug and other excipients. Flavouring agents are selected depend on their flavour impart in first few seconds and its after taste. Upto 10% of the flavouring agent can be added to the oral strip formulation. Flavouring agent can be extracted from different part of the plant like leaves, flower, fruit, bark, and seeds.[12]

4. METHODS OF PREPARATION
One or more of the following process can be used to manufacture the fast dissolving films
1) Solvent casting
2) Semisolid casting
3) Hot melt extrusion
4) Rolling methods

1) Solvent casting method
Fast dissolving buccal films are preferably formulated using the solvent casting method, whereby the water soluble ingredients are dissolved to form a clear viscous solution and the drug along with other excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate and dried.[13]

![Figure-2 Solvent Casting Method](image)

2) Semisolid Casting
In this method, solution of water soluble film forming polymer is mixed to solution of acid insoluble polymer to form homogenous viscous solution (e.g. cellulose acetate phthalate and cellulose acetate butyrate). After sonication, it is coated on non-treated casting film. On
drying the thickness of the film should be about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4. [14]

3) Hot Melt Extrusion
In this method the polymers which have low molecular weight and low viscosity are preferred. Drug is mixed with the carrier in the solid form so that granular material is formed. These granules are then dried and then introduced into the extruder. The speed of the screw should be around 15rpm so that the granules reside inside the extruder for about 3-4min. The processing temperatures should be 80°C (zone 1), 115°C (zone 2), 100°C (zone 3), and 65°C (zone 4). The extrudate (T= 65°C) then pressed into a cylindrical calendar to obtain a film. [12]

![Figure-3 Hot Melt Extrusion Method](image)

4) Rolling Method
In 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 cutted 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 hydrocolloids dissolved in water to form homogenous viscous solution. [14]

![Figure- 4 Three roll coating unit](image)
5) Solid dispersion extrusion

The term solid dispersions refer to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers. Drug is dissolved in a suitable liquid solvent. Then solution is incorporated into the melt of polyethylene glycol, obtainable below 70°C. Finally, the solid dispersions are shaped into the films by means of dies.\footnote{15}

5. TECHNOLOGIES

1) SOLULEAVES™ technology is used to produce a range of oral delivery films that can incorporate active ingredients, colours and flavours. SOLULEAVES™ films can be designed to dissolve rapidly on contact with saliva, quickly releasing the active ingredients and flavours. This quality makes edible films an excellent delivery method for a large range of products requiring fast release in the mouth. For pharmaceutical uses this method of administration is especially useful for paediatric or elderly patients who may have difficulty swallowing traditional tablets or capsules. The delivery system can be used for the cough/cold, gastrointestinal and pain therapeutic areas as well as delivering nutritional products. SOLULEAVES™ films can also be designed to adhere to mucous membranes and to release the active ingredient slowly over 15 minutes.

2) WAFERTAB™ is a drug delivery system that incorporates pharmaceutical actives into an ingestible filmstrip. The system provides rapid dissolution and release of actives when the strip comes into contact with saliva in the mouth. The WAFERTAB™ filmstrip can be flavoured for additionally improved taste masking. The active ingredient is precisely dosed and integrated into the body of a pre-manufactured XGEL™ film, thus preventing exposure to unnecessary heat and moisture and potentially enhancing product stability. The WAFERTAB™ system lends itself to many possibilities for innovative product design, enabling multiple films with different actives to be bonded together. WAFERTAB™ can be prepared in a variety of shapes and sizes and is an ideal method for delivery of medicines, which require fast release, or for use by patients who have difficulty swallowing.\footnote{3}

3) FOAMBURST™ is a special variant of the SOLULEAVES™ technology where an inert gas is passed into the film during production. This results in a film with a honeycombed structure, which dissolves rapidly giving a novel mouth sensation. FOAMBURST™ has attracted interest from food and confectionary manufacturers as a means of carrying and releasing flavours.
4) XGEL™ film is at the heart of Meldex International's intellectual property, used in all its film systems and its ingestible dosage delivery technologies. XGEL™ film provides unique product benefits for healthcare and pharmaceutical products: it is non-animal-derived, approved on religious grounds and is suitable for vegetarians; the film is GMO free and continuous production processing provides an economic and competitive manufacturing platform. XGEL™ film can be taste masked, coloured, layered, and capable of being enteric properties whilst also having the ability to incorporate active pharmaceutical ingredients. The XGEL™ film systems can be made to encapsulate any oral dosage form, and can be soluble in either cold or hot water. XGEL™ film is comprised of a range of different water-soluble polymers, specifically optimised for the intended use. All of the XGEL ingredients are well known and generally regarded as safe.\textsuperscript{[15]}

6. EVALUATION PARAMETER OF FAST DISSOLVING FILM

Weight Variation
For evaluation of film weight, three films of every formulation is selected randomly and individual weight of each 1x1cm patch was taken on digital balance. The average weight was calculated.\textsuperscript{[16]}

Film thickness
Thickness of the film is measured by using screw gauge with a least count of 0.01 mm at different places on the film. The thickness of the film was measured at three different places and the average of thickness is measured.\textsuperscript{[16]}

Surface pH
For determination of surface pH three films of each formulation is allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of films and allowing equilibrate for 1 min. A mean of three reading is recorded.\textsuperscript{[17]}

Folding endurance
Folding endurance of the film is determined by repeatedly folding one film at the same place till it broke, which was considered satisfactory to reveal good films properties. The number of times of films could be folded at the same place without breaking gave the value of the folding endurance. This test was done on randomly selected three films from each formulation.\textsuperscript{[18]}
Drug content uniformity

This parameter was determined by dissolving film of 1 × 1 cm diameter containing drug in 50 ml simulated salivary fluid with occasional shaking. Filtration was carried out to remove insoluble residue, 1 ml of the filtrate was diluted to 10 ml with simulated salivary fluid (pH 6.8). The absorbance was measured at specified nm using an UV spectrophotometer. The experiments were carried out in triplicate for the films of all formulations.\textsuperscript{[18,19]}

In-vitro dissolution studies

Dissolution study was carried out in USP basket type apparatus using the stimulated salivary fluid (pH 6.8) as a dissolution medium at 50 rotations per minute. 10 ml aliquots were withdrawn at one minute time intervals and same amount of fresh dissolution medium was added. The aliquots were assayed for drug content at specified wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated.\textsuperscript{[20]}

Moisture absorption

The moisture absorption study of films was done at a relative humidity of 75% for a period of three days. The low moisture uptake by all the formulations was observed at 75% relative humidity. The low moisture uptake by all the buccal films can help to retard any hydrolytic degradation, and films will remain stable.\textsuperscript{[21]}

Swelling Studies

The degree of swelling is determined in phosphate buffer pH 6.8. All batches have good swelling properties which remain hydrated for longer time. All formulations were swelled within 10 min and which delayed the swelling after 2 h i.e. constant weight of the buccal patch is seen. It is highlighted that swelling properties are important when film integrity is evaluated.\textsuperscript{[22]}

Percent Elongation at Break

For the determination of percentage elongation of the film formulations, the distance between the tensile grips of the tensile strength testing machine was measured before and after the fracture of the film and calculated the % elongation of patch by using the following formula:

\[
\text{% Elongation at break} = \frac{\text{Increase in length}}{\text{Initial length}} \times 100
\]

Then the percentage elongation of the films was computed with the help of the formula given below.\textsuperscript{[23]}
Dispersion test
A strip equivalent to 5mg of drug placed in 200ml of 6.8pH phosphate buffer and was stirred for 3 minutes. The resulting solution was passed through sieve number 22. The film is said to be passed the dispersion test only when no residue is left on the sieve.[24]

In vitro residence/mucoadhesion time
The in vitro adhesion time of films was evaluated by assessing the time for the patch to detach from goat buccal mucosa in a well stirred beaker filled with 500 mL phosphate buffer pH 6.8 at 37 °C. The mucosal membrane was fixed on the side of the beaker with cyanoacrylate glue. The patch was attached to the membrane by applying light force with finger tip for 60 sec. The beaker was then magnetically stirred at an approximate rate of 150 rpm to simulate buccal and saliva movement. The time necessary for complete erosion or detachment of the films from the mucosal membrane was taken as an indication of the in vitro adhesion time.[24,25]

Tensile Strength
Tensile strength of the buccal films was determined by using universal strength testing machine. The sensitivity of the machine is one gram. It consists of 2 load cell grips. The lower one is fixed and upper one is movable as shown in the figure. The test patch of specific size is fixed between these cell grips and force was gradually applied, till the patch breaks. The tensile strength of the patch was taken directly from the dial reading.[26]

Percentage Moisture content
The buccal patches is weighed accurately and kept in desiccators containing anhydrous calcium chloride. After three days, the patches were taken out and weighed. The moisture content (%) was determined by the formula.[26]

\[
\% \text{ Moisture content} = \frac{\text{Initial weight} – \text{Final weight} \times 100}{\text{Initial weight}}
\]

Effect of temperature and humidity
Effect of temperature and humidity of optimization formulation was carried out for one month at 40 °C ± 2 °C, 75 % ± 5% RH maintained in environmental stability chamber. The patches were wrapped in aluminium foil and exposed to the said conditions. Samples were evaluated at 0, 7, 14, 21 and 28 days for the parameters as
a) Appearance  
b) Surface pH  
c) Folding endurance  
d) Drug release (%)\cite{27,28}

7. PACKAGING OF FAST DISSOLVING FILM

In the pharmaceutical industry it is vital that the package selected adequately preserve the integrity of the product. Expensive packaging, specific processing, and special care are required during manufacturing and storage to protect the dosage of other fast dissolving dosage forms. A variety of packaging options are available for fast dissolving films. Single packaging is mandatory for films, which are pharmaceutical products; an aluminum pouch is the most commonly used packaging format. APR- Labtec has developed the Rapid card, a proprietary and patented packaging system, which is specially designed for the Rapid films. The rapid card has same size as a credit card and holds three raid films on each side. Every dose can be taken out individually.

The material selected must have the following characteristics

- They must protect the preparation from environmental conditions.
- They must be FDA approved.
- They must meet applicable tamper-resistant requirement.
- They must be non-toxic.
- They must not be reactive with the product.
- They must not impart to the product tastes or odors.

Foil, paper or plastic pouches

The flexible pouch is a packaging concept capable of providing not only a package that is temper-resistance, but also by the proper selection of material, a package with a high degree of environmental protection. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling, or sealing equipment. The pouches can be single pouches or aluminum pouches.

Single pouch and Aluminum pouch

Soluble film drug delivery pouch is a peelable pouch for “quick dissolve” soluble films with high barrier properties. The pouch is transparent for product display. Using a 2 structure combination allows for one side to be clear and the other to use a cost-effective foil
lamination. The foil lamination has essentially zero transmission of both gas and moisture. The package provides a flexible thin film alternative for nutriceutical and pharmaceutical product, and the lid stock, which is the material that seals to the blister. The blister package is formed by heat –softening a sheet of thermoplastic resin and vacuum-drawing the softened sheet of plastic into a contoured mold. After cooling the sheet is released from the mold and proceeds to the filling station of the packaging machine. The semi –rigid blister previously formed is filled with the product and lidded with the heat sealable backing material. The film selection should be based upon the degree of protection required. Generally the lid stock is made of aluminum foil. The material used to form the cavity is typically a plastic, which can be designed to protect the dosage form from moisture.

**Barrier Films**

Many drug preparations are extremely sensitive to moisture and therefore require high barrier films. Several materials may be used to provide moisture protection such as Polychlorotrifluoroethylene (PCTFE) film, Polypropylene. Polypropylene does not stress crack under any conditions. It is an excellent gas and vapour barrier. Lack of clarity is still a drawback. applications. The single dose pouch provides both product and dosage protection. Aluminum pouch is the most commonly used pouch.[25]

**8. CONCLUSION**

Fast dissolving buccal film drug delivery system is an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience in difficulties of swallowing traditional oral solid dosage forms. There are so many methods to formulate fast dissolving film but solvent casting method is mostly preferred to formulate it, due to easy and low cost. Many type of polymer and other excipients are available that increase the effect of the drugs, most suitable polymer for fast dissolving film are HPMC E4, HPMC E10, HPMC E15, etc. These polymer are dissolve in saliva pH, easy to fabricate. All other additive should be analytical grade and don’t show any type of interaction with drugs. Different formulation technique are also available, in this WAFERTAB™ is mostly use due to rapid dissolution & release of the drugs. These also prevent exposure to unnecessary heat and moisture and potentially enhancing product stability. Fast dissolving film should be pass all evaluation parameter like drug content, surface pH, swelling index, weight variation etc. Packaging and storage condition also effect the drug stability so proper storage condition should be preferred.
9. REFERENCES


