

**SIGNIFICANCE OF FAST DISSOLVING ORAL FILMS AND ITS  
NOVEL APPROACH TOWARDS DRUG DELIVERY—A REVIEW****S. Sudheer and Sk. Ershadul Haque\***

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**ABSTRACT**

Novel drug delivery system is one of the frontier areas of research towards achieving an innovative technique for drug administration which can improve drug safety, therapeutic efficacy, stability and self-life of an active drug. Over the past few decades, it is chosen as an important area of research to develop innovative methods for the health sector and pharmaceutical industries. Fast dissolving oral films (FDOFs) in the year of 1970 initiated as an alternative to the existing drug delivery system such as tablet, capsule, parenteral, syrup, emulsion, cream and ointment. FDOFs are one of the most popular drug delivery system due to its flexibility and comfort of use. These films have a potential to absorb the drug through oral buccal mucosa and directly enter to the systemic circulation by fast-pass metabolism.

These films have a potential to provide better drug utilization by delivering systemically through intra-gastric and sublingual. These films are gaining popularity due to rapid drug absorption and immediate onset of action within a few minutes of administration in buccal cavity. FDOFs are very convenient to pediatric, geriatric and bedridden patient who faces difficulty in swallow. FDOFs can be used for the treatment of common cold, mouth ulcer, cardiac problem, sore throat and allergic conditions etc. These films can be formulated by simple methods using several ingredients such as polymers, active medicaments, stabilizing agent, surfactants, sweetening agent, flavoring agent coloring agent and saliva stimulating agent. Evaluation of FDOFs can be done by checking several parameters such as thickness, folding endurance, tensile strength, percentage of elongation and disintegration test. Additionally, drug content and dissolution test are carried out to determine amount of active

drug present in the film. This review article shows all the details about formulation evaluation, packaging and marketed available product.

**KEYWORDS:** Fast dissolving oral films, buccal film, fast disintegration, novel drug delivery.

## INTRODUCTION

The oral rout is one of the oldest and popular rout of drug administration for all kind of medical treatment having advantages over other routes because ease of administration self-medication with accurate dose, painless ingestion, low cost of therapy and increase patient compliance. The oral rout is inconvenient to many patients specifically pediatric, geriatric and bedridden patient due to the difficulty in swallowing the medication such as tablets and hard gelatin capsules.<sup>[1]</sup> Most of the time patient avoids medication due to motion sickness, sudden episode of allergic attack or excess coughing and an unavailability of water. In order to satisfy these patients and fulfill the required demand, disintegrating agent and fast dissolving drug delivery systems (oral film) have been introduced to the market as an alternative to the conventional dosage forms.

Fast dissolving oral films are new in kind, an ultrathin strip (50-150 microns thick) of postage stamp size which is immediately dissolves in buccal cavity or in contact of tongue without water.<sup>[2]</sup> These quick dissolving oral films contain various polymers, bio adhesive substances and active drug for buccal delivery, known as mouth dissolving films<sup>[3]</sup> which can be provided in various packages convenient for use, especially by children and elders. FDOFs are also known as oral films, oral strips, oral dispersible film and mouth dissolving films which mainly contain hydrophilic polymers, disintegrating agent, active drug, saliva stimulating agent, plasticizer, sweetening agents, flavoring agents, coloring agents, thickening agents and stabilizers. FDOFs were introduced in the market as a mouth freshener, personal care products (dental strips and soap strips) whereas in United states and Europe introduced as a health care product such as breath strips, vitamins.<sup>[4]</sup> FDOFs are very thin film which can easily adhere to buccal cavity and hydrated by saliva to promote desired quick onset of action and local action such as sore throat, toothache, mouth ulcer and anesthetic action in mouth.<sup>[5-7]</sup> Few drugs which is very sensitive and unable to give through oral rout in the form of tablet, capsule and liquid formulation can be administered by oral films.<sup>[8]</sup> Drugs from the FDOFs absorbed either in normal way or from mouth, pharynx and esophagus as saliva moves from mouth to stomach or it follows hepatic fast pass metabolism.<sup>[9]</sup> FDOFs can able to resolve the

patient complain and fulfil the industrial need by improving solubility, biological half-life, stability, bioavailability and therapeutic efficacy of the drug. Today, fast dissolving oral films are a well proven and worldwide accepted technology for the systemic delivery of active pharmaceutical ingredients (APIs).

#### **Advantages of FDOFs**

- Ease and safe administration
- soluble with saliva
- swallowing/chocking problem resolve
- Easily mask the test
- Increased stability
- Increase patient compliance.
- Improved hepatic first pass metabolism
- Increase bioavailability of drug
- Produce immediate local effect to mucosal cavity
- Accuracy of dose can be maintained as compare to liquid dosage form

#### **Disadvantages of FDOFs**

- Difficult to get drug uniformity
- Drug which is unstable in buccal pH not suitable for FDOFs form
- Taste masking should be required for bitter, nauseous and unpalatable drugs
- Bulk dose can't be provided
- Handle with care and special packaging equipment required
- Stability problem
- Restriction in intake of food and water immediately afterconsumption of FDOFs

#### **Special features of FDOFs**

- Uniform size having thin surface
- Special technique required for preparation
- Different shape and size can be made as per the requirement
- Easily adhere to the site of application
- Immediately disintegrate under favorable condition
- Quick release of medicaments due to more surface are
- Improved bioavailability
- Different flavors are available as per the test

- Completely dissolve in mouth cavity without any residue
- Should have good tensile strength and percentage of elongation
- Transportation is easy because films are more flexible and less fragile
- FDOFs can be taken without water
- Noncompliance could be minimized
- Reduce hepatic first pass effect and absorb to systemic circulation
- Convenient for pediatric, geriatric, bedridden and mentally ill patient
- Avoid swallowing and choking

### **Classification of FDOFs**

This is mainly divided into three different categories such as

- Flash release film
- Mucoadhesive melt film
- Mucoadhesive sustained release film

Mucoadhesive sustained release films are smaller in size (2-4 cm<sup>2</sup>) as compare to flash release films (2-8 cm<sup>2</sup>) and mucoadhesive melt films (2-7 cm<sup>2</sup>). Thickness of the flash release films (20-70 μm) is very less as compare to Mucoadhesive sustained release (50-250 μm) and mucoadhesive melt films (50-500 μm). Flash release films are single layer film applied on the tongue and dissolve within 60 second whereas single /multi-layer mucoadhesive melt films used in buccal cavity and dissolved within few minutes. Mucoadhesive sustained release films are available in multilayer form and absorb through buccal cavity within 8-10 hours.

### **Ideal characteristics of a drug incorporated in FDOFS**

The active drug which contain lower amount of dose can be easily incorporated in FDOFs. Different classes of drugs which can produce immediate onset of action is preferable for FDOFs such as omeprazole (antiulcer), salbutamol sulphate (anti-asthmatic), valdicoxib (NSAID), antitussives, expectorants, anti-histamines, sedative and hypnotics. An ideal drug should have

- Pleasant taste
- Low molecular weight
- Good solubility in saliva
- Should be unionized
- Good stability

### **Biopharmaceutical approach of FDOFs**

Biopharmaceutical factors should be considered for new drug delivery systems. In case of FDOFs disintegrate quickly and diffused drugs are absorbed through oral mucosa, mouth, pharynx and esophagus.<sup>[10]</sup> Drug distribution and drug action depends on rate of permeability to the targeted site, binding effect of drug to the specific site and its retention time in the body. There are few factors such as age, sex, severity of disease which can alter the pharmacodynamic action of a drug.

### **Excipients used in FDOFs**

#### **Water soluble polymers**

Hydrophilic polymers mostly used in the preparation of oral films which can easily disintegrate in saliva. Polymers used in the preparation contain 40%w/w of the film which provides toughness and good durability to the film during handling and transportation.<sup>[11,12]</sup> Polymers can be used in single or in combination form to satisfy the requirements of FDOFs. Polymer used for the preparation of FDOFs is hydroxyl propyl methyl cellulose, starch, chitosan, pectin, gelatin and carboxy methyl cellulose etc.

#### **Plasticizers**

The significance of plasticizers is to improve fragility and flexibility of the FDOFs. Plasticizers should have good compatibility with polymer and active drug and also enhance the therapeutic efficacy of the drug.<sup>[13]</sup> A good selection of plasticizer is mandatory for a stable and defect free films. Commonly used plasticizers are glycerol, dimethyl phthalate, dibutyl phthalate, polyethylene glycol, polyene glycol, acetyl citrate, castor oil etc.<sup>[14]</sup>

#### **Saliva stimulating agents**

Citric acid, tartaric acid, lactic acid, ascorbic acid and malic acid are considered as salivary stimulant which can help to liberate saliva for the faster disintegration of the FDOFs.<sup>[15]</sup> Water is required for most of the oral dosage forms but in case of FDOFs secretion of saliva can fulfil the demand of water and avoid the swallowing /chocking problem of patient.

#### **Surfactants**

Surfactants played a significant role in the preparation of FDOFs. Surfactants shows good wetting property, dispersion and solubility which is required for a FDOF to dissolve faster and produce immediate therapeutic effect. Frequently used surfactants are polaxamer 407, sodium lauryl sulfate, polyoxyethylene sorbitant, fatty acid and benzalkonium chloride etc.<sup>[16]</sup>

**Sweetening agent**

Drug shows bad taste like bitter, nauseous and unpalatable in nature to mask the bad taste sweetening agents are required to add in either alone or in combination form in the formulation at 3 to 6% w/w concentration.<sup>[17]</sup> They are mainly divided into two types such as natural and artificial sweeteners. Artificial sweeteners gained its popularity to meet the need of diabetic patient and less prone to growth of microorganism. Sucrose, fructose mannitol, sorbitol comes under natural sweeteners whereas acesulfame K, sucralose, alitame and neotame considered as artificial sweeteners.

**Cooling agents**

Cooling agents like WS3, WS23, spearmint and akin can be used with flavoring agent to mask the bad taste and flavor of the drug and make it palatable.

**Flavoring agents**

Different flavors are available in market depends upon individual liking. Collection of flavors depends on synthetic flavor oils and various parts of the plant such as leaves, flower and fruit. Amount need to be added in the formulation depends on the nature of active drug and the concentration of the flavoring agent.

**Coloring agents**

Coloring agents mainly used in FDOFs to make it attractive and distinguish them from other formulations of films. It can protect the films from the atmospheric condition. Titanium dioxide one of the approved coloring agents used in the formulation not more than 1% w/w in oral films.

**Preservatives and thickening agents**

Thickening agent played an important role to improve the viscosity of the solution whereas preservatives increase the stability and self-life of the film by avoiding microbial growth. It should be nontoxic and compatible with other added substances. Xanthan gum, acacia, tragacanth and sodium alginate commonly known as thickening agent but benzoic acid, sodium benzoate, methyl paraben and propyl-paraben chosen as preservatives.

**Preparation of FDOF'S**

Different methods are adopted for the preparation of fast dissolving oral films such as:

1. Solvent Casting Method

2. Hot-melt Extrusion Method
3. Semisolid Casting Method
4. Solid Dispersion Extrusion Method
5. Rolling Method

### **1. Solvent Casting Method**

In this method water soluble ingredients are dissolved to form a clear homogeneous solution and the active drug with excipients are dissolved in a solvent and prepared separately. Both the solution mixed and stirred to obtain a clear solution. Final solution is casted into a petri plate and dried at room temperature.

### **2. Hot-melt Extrusion Method**

Hot melt extrusion method is used for thermally stable drug and excipients. In this method drug is mixed with all other ingredients by using mortar and pestle in solid form. The extruder produces heat which melts the mixture and shaped them in films by the help of dies. The advantage of hot melt extrusion method is minimum product wastage, better content uniformity, an anhydrous process, absence of organic solvents.

### **3. Semisolid Casting Method**

This method is used to prepare acid insoluble polymers by dissolving polymers in water. Prepared solution is added to an acid insoluble polymer with plasticizer to obtain a gel mass. Heat controlled drums are used for further preparation of films.

### **4. Solid Dispersion Extrusion Method**

The dispersion of one or more ingredient takes place in an inert carrier and dissolved in suitable solvent. Then the solution transfer into hydrophilic polymer solution. Dies are used to prepare required shaped films.

### **5. Rolling Method**

In this method polymer and other additives are mixed with suitable solvent except drug. Then add required amount of drug to the prepared mixture and mixed well to obtain uniform matrix. Then specific amount of uniform mixture passed through the roller to obtain films. Films are dried for further use.

### **Evaluation of FDOF's**

To evaluate fast dissolving oral films following tests are performed-

- ❖ Weightvariation test of film
- ❖ Thickness of film
- ❖ Surface pH
- ❖ Surface roughness
- ❖ Tack tests/ Dryness
- ❖ Folding Endurance
- ❖ Mechanical properties
- ❖ Morphology study
- ❖ Transparency
- ❖ Contact Angle
- ❖ Swelling property
- ❖ Percent of moisture uptake
- ❖ Percent of moisture content
- ❖ Linear Expansion Coefficient in Water
- ❖ Drug content uniformity
- ❖ In-vitro Disintegration test
- ❖ In-vitro dissolution study
- ❖ Ex-vivo permeation studies through porcine oral mucosa
- ❖ Stability studies

### **Weightvariation test of film**

Randomly selected three films from each group have been taken and weighed individually and determine the average weight. All films should have similar weight without much variation ensure that films contain same amount of drug and excipients in each film containing uniform thickness.<sup>[18]</sup>

### **Thickness of the film**

Randomly selected film has been taken for thickness measurement by using screw gauge or Vernier caliper. Thickness is directly related to uniformity of dose in the film, determined by measuring every corner of each film.<sup>[19]</sup>

### **Surface pH of the film**

Film immersed in distilled water for 1h and measure the pH of the water by using pH meter or pH paper which determine the pH of the formulated film.<sup>[20]</sup> Change in pH can leads to irritation and incompatible to mucous membrane of oral cavity.

**Surface analysis of the film**

Surface analysis of formulated films can be done under scanning electron microscope (SEM), electron microscope at different magnification range to determine the smooth and roughness of the film surface.

**Tack tests/ Dryness of the film**

Tack test can determine the adhesive property of the prepared film with the surface. To determine the dryness of the film eight different properties have been identified such as set to touch, dust free, tack free, dry to touch, dry hard, dry to handle, dry to recoat and dry print free, used to paint the films.<sup>[19]</sup>

**Folding Endurance of the film**

It can be done manually by the help of a forcep. Folding of film can be done in a repeated manner at any corner of the film till it break. This will give the value of the folding endurance.<sup>[12]</sup> This test should be performed with randomly selected three films from each group and the mean should be calculated.

**Mechanical Properties of the film**

To determine the mechanical strength of the film, tensile strength, tear resistance, young's modulus and percentage of elongation should be performed.

**Tensile strength**

Universal testing machine (UTM) is used to determine the weight required to break the film and also measure the elasticity of the film. Tensile strength can be calculated by following formula mention below.<sup>[21]</sup>

$$\text{Tensile Strength} = \frac{\text{Break force}}{WT(1 + \frac{\Delta L}{L})}$$

Where W= width, T= thickness, L= length of the film and  $\Delta L$  is the elongation at break.

**Tear resistance**

This is also known as the ultimate resistance to rupture the film. A slow rate of loading 51mm is used to measure the force required to tear the film.<sup>[22]</sup>

### Young's modulus

Young's modulus or elastic modulus used to determine the stiffness of the film by the application of stress over strain which leads to elastic deformation calculated as

$$\text{Youngs modulus} = \frac{\text{force at corresponding strain}}{\text{Cross sectional area(mm}^2)} \times \frac{1}{\text{Corresponding strain}}$$

### Percent Elongation

Deformation of film from its original position by the application of stress determines the elongation percentage.<sup>[23]</sup> Plasticizer played an important role to increase elongation percentage.

$$\% \text{ Elongation} = \frac{L}{L_0} \times 100$$

Where L is Increase in the film length and  $L_0$  is Initial length of the film.

### Morphology Studyof the film

Scanning electron microscope (SEM) and electron microscope used to determine surface morphology of the film.<sup>[24]</sup>

### Transparencyof the film

Transparency of the film can be determined by using UV Visible spectrophotometer. Selected film is cut as per the size of the sample holder and placed inside the UV Visible spectrophotometer.<sup>[25]</sup> The transparency of the film is calculated as per the formula mentioned below

$$\text{Transparency} = (\log T_{600})/b = - \epsilon c$$

Where  $T_{600}$  is the transmittance at 600 nm, b is the film thickness (mm) and c is concentration.

### Contact Angle

It can be determined by placing a drop of water on the surface of the film at room temperature usinggoniometer (AB Lorentz and Wetter, Germany) apparatus. Images of water droplet recorded up to 10 seconds and analyzed the image by using software reveal the contact angle. If contact angle is less than  $90^\circ$  it considered as good wetting agent.<sup>[26]</sup>

**Swelling index of the film**

Each film sample is weighed and placed under simulated saliva solution. Every interval of time the sample was removed and weighed till a constant weight obtained. Increase in the weight of the film at specific interval of time gives the swelling index of the film.<sup>[27]</sup> Degree of swelling property can be calculated by using this formula:

$$\text{Swelling index} = \frac{(W_t - W_0)}{W_0}$$

Where  $W_t$  is the weight of the film at time "t" and  $W_0$  = weight of the film at  $t = 0$ .

**Percentage of moisture uptake by the film**

Previously weighed film kept it inside the humidity chamber at a particular temperature and relative humidity. The film is reweighed at suitable interval of time till there is no further change in weight and calculates the percentage of moisture uptake by the following formula.<sup>[28]</sup>

$$\% \text{ of moisture uptake} = \frac{(\text{Final weight} - \text{Initial weight})}{\text{Initial weight}} \times 100$$

**Linear Expansion Coefficient of the film in water**

The expansion of thin film can be determined by immersing film into the water and the size of the length has been measured at different interval of time.<sup>[29]</sup> The expansion coefficient of the film calculated by the formula mention below:

$$L \% = \frac{L_1 \times L_0}{L_0} \times 100$$

$L_0$  is the initial length of the film,  $L_1$  is the change in length at different interval of time.

**Drug content uniformity of the film**

Standard procedure has been followed as per Indian pharmacopoeia (IP) to find out the drug content of the prepared individual film. The limit should be in the range of 85-115%.

**In-vitro Disintegration test of the film**

This test will determine the time taken for a film to tear, rupture or break down from any part with the contact of water using disintegrating apparatus. The release of active drug depends on the strength of the film.

**In-vitro Dissolution test of the film**

Dissolution medium is required to perform the test. Basket and paddle type dissolution apparatus is available. As per IP revolution per minute (RPM), temperature ( $37 \pm 0.5$ ) must be set before start the test. Every interval of time 5ml solution should be pipette out from the container and a fresh solution of same buffer should be added. Collected solution after suitable dilution measure under UV Visible spectrophotometer and note the absorbance.<sup>[30]</sup>

**Ex-vivo permeation studies of the film**

Franz diffusion cell was considered for the permeation study. Buccal pouch of a freshly sacrificed pig was collected from a slaughter house. Further the collected buccal mucosa was excised and trimmed to form uniformity and washed with phosphate buffer pH 6.4 for further use. The mucosa has been fixed properly in between donor and receptor compartment. The receptor compartment contains 200ml of (pH 7.4) phosphate buffer and temperature was maintained at  $37 \pm 0.5^\circ\text{C}$  with 50 rpm. Buccal film of 2X2 cm dimension was placed on the mucosal surface of the membrane, previously moistened simulated saliva. Sample collection was done at suitable interval of time by replacing with same amount of fresh solution. Collected sample after suitable dilution measured under UV Visible spectrophotometer and calculate the percentage of drug release.

**Stability Studies of the film**

Stability study determines the effect of temperature and humidity on the buccal film. Randomly selected film from each group stored under humidity chamber at  $45^\circ\text{C}$  temperature with 75% humidity. The buccal films were collected at 90 days and 180 days interval and subjected for disintegration and dissolution test.<sup>[31]</sup>

**Packaging of the film**

Packaging is one of the most important stage for the finished pharmaceutical products which can provide exceptional care during transportation and product stability. Different types of packaging options are available for FDOFs. Generally aluminum pouch is used as a packaging material for the buccal films.

**Ideal characteristics of a packaging material**

- It should provide good protection against environmental conditions.
- It should be inert and non-toxic
- It should have good compatibility with the dose

- Materials should be approved by FDA
- It should be tamper resistant and provide good stability to the dose
- It should not interfere the color, odor and taste of the product

Materials generally used for the packing of the buccal films are discussed below.

### Foil, papers and plastic pouches

The pouches mainly considered for the packaging should be temper resistance and give protection against environmental factors such as temperature and humidity. Deliquescent and hygroscopic drug in the form of film should be given extra care or double rap to protect from the environment. Flexibility of pouches has shown an added advantage towards filling and sealing of films horizontally and vertically.

### Aluminum pouch

The significance of the pouch is to give protection to the product by blocking of gas and moisture. The presence of moisture may lead to the growth of microorganism and degradation of the film. Special care should be taken to avoid such kind of complication by providing lamination on to the packing materials. Aluminum pouch is inert and chemically compatible to most of the drugs, could be a good selection for a packing material.

### Blister cards

The blister having two components first cavity which holds the product and the second one is lid used for sealing the blister. Generally plastic is used for the cavity and aluminum used as a lid for sealing.<sup>[2]</sup> A soft sheet of blister passes through thermoplastic resin and vacuum draying to form molded cavity for the film. These molded sheets are further used in the packaging machine to pack thin films. If light sensitive drug is used for the preparation of the film umber colored cavity should be provided with proper labeling.

**Table 1: List of commercially available FDOF's.**<sup>[32]</sup>

Sl. No.	Brand Name	API	Use	Manufacturer
1.	KlonopinWafers	Clonazepam	Treatment ofAnxiety	Solvay Pharmaceuticals
2	Listerine CoolMint Pocket Packs	Cool mint	Mouth Fresheners	Pfizer, Inc
3	Sudafed PE	Phenylephrine	Relieving Congestion	Wolters Kluwer Health, Inc.
4	Suppress®.	Menthol	Cough Suppressants	InnoZen®, Inc
5	Theraflu	Dextromethorphan HBr	Cough Suppressant	Novartis

		(15 mg)		
6	Orajel	Menthol/pectin	Mouth ulcer	Del
7	Gas-X	Simethicone	Anti-Foaming	Novartis
8	Subozone®	Buprenorphine-hydrochloride + Naloxone	Narcotic Opioid Antagonist	Reckitt - Benckiser Pharmaceutical

## CONCLUSION

The current review concluded that FDOFS bypass the hepatic first pass metabolism to increase better bioavailability which leads to enhance the therapeutic efficacy of the drug. The oral route is one of the most popular and convenient route for ease of administration of FDOFS to increase patient compliance. FDOFS is very convenient for the patient such as pediatric, geriatric and aged person who have swallowing issue of conventional dosage form. These films could be a good alternative for emergency cases (Cardiac, allergy, asthma) where quick drug release and fast onset of action of a dose can save life of a patient. Recent development in pharmaceutical technology mainly focused on the new formulations and designing. The strong market acceptance and patient demand for FDOFS technology gradually increasing for further development of a most accurate and acceptable form of dose.

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